

Prognostic Significance of Mucin Antigen MUC1 in Various Human Epithelial Cancers

A Meta-Analysis

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Abstract: Accumulating evidence indicates that mucin antigen MUC1 plays a fundamental role in the initiation and progression of several types of epithelial carcinomas. However, whether the expression of MUC1 on tumor cells is associated with patients' survival remains controversial.

Medline/PubMed, EMBASE, the Cochrane Library, Chinese National Knowledge Infrastructure (CNKI) databases, and Grey literature were searched up to 15 August 2015 for eligible studies of the association between the MUC1 expression and overall survival (OS) in various epithelial cancers. The hazard ratio (HR) and its 95% confidence interval (CI) were calculated from the included studies. Moreover, the odds ratio (OR) was also extracted to evaluate the association between the clinicopathological parameters of participants and MUC1 expression.

A total of 3425 patients covering 23 studies were included in the analysis. The pooled results showed that positive MUC1 staining was a negative predictor of OS ($HR_{FEM} = 1.98, 95\% CI_{FEM}: 1.76-2.22, P_{FEM} = 0.479$; $HR_{REM} = 2.16, 95\% CI_{REM}: 1.58-2.94, P_{REM} = 0.355$) in various epithelial carcinomas. Subgroup analysis revealed that the increased MUC1 expression was significantly associated with poor OS in patients with gastric cancer ($HR_{FEM} = 2.12, 95\% CI_{FEM}: 1.75-2.57, P_{FEM} = 0.359$; $HR_{REM} = 1.89, 95\% CI_{REM}: 1.05-3.41, P_{REM} = 0.238$), colorectal cancer ($HR_{FEM} = 1.73, 95\% CI_{FEM}: 1.41-2.13, P_{FEM} = 0.048$; $HR_{REM} = 2.00, 95\% CI_{REM}: 1.46-2.73, P_{REM} = 0.019$), cholangiocarcinoma ($HR_{FEM} = 2.52, 95\% CI_{FEM}: 1.42-4.49, P_{FEM} = 0.252$; $HR_{REM} = 2.34, 95\% CI_{REM}: 1.30-4.22, P_{REM} = 0.244$), and nonsmall cell lung cancer (NSCLC) ($HR_{FEM} = 2.14, 95\% CI_{FEM}: 1.46-3.14, P_{FEM} = 0.591$; $HR_{REM} = 2.81, 95\% CI_{REM}: 1.40-5.64, P_{REM} = 0.280$). In addition, MUC1 overexpression was more likely to be found in colorectal cancer patients with an advanced TNM stage ($OR_{REM} = 1.55, 95\% CI_{REM}: 1.06-2.27, P_{REM} = 0.187$) and in gastric cancer patients with positive lymph node metastasis ($OR_{REM} = 2.37, 95\% CI_{REM}: 1.19-4.73, P_{REM} = 0.004$) and intestinal-type classification ($OR_{REM} = 2.34, 95\% CI_{REM}: 1.59-3.45, P_{REM} = 0.767$).

Our findings provide evidence that MUC1 detection has a prognostic value in patients with epithelial-originated cancers, especially in NSCLC and gastrointestinal cancers.

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Abbreviations: BC = breast cancer, CC = cholangiocarcinoma, CI = confidence interval, CRC = colorectal cancer, EMT = epithelial to mesenchymal transition, FEM = fixed effect model, GBC = gallbladder carcinoma, GC = gastric carcinoma, HR = hazard ratio, MAB = monoclonal antibody, MOOSE = Meta-Analysis of Observational Studies in Epidemiology group, MUC1 = mucin 1, NOS = Newcastle–Ottawa Scale, NSCLC = nonsmall cell lung cancer, OR = odds ratio, OS = overall survival, OSC = oral squamous cell carcinoma, PC = pancreatic cancer, REM = random effect model, SGMEC = salivary gland mucoepidermoid carcinoma, UCC = uterine cervical carcinoma.

INTRODUCTION

Cancer is currently the second leading cause of death in the United States and is a major public health problem worldwide. In 2015, ~1658,370 new cases will be diagnosed with cancer, with an estimated 589,430 deaths.¹ Although cancer death rates have been declining for the past 2 decades, there are no suitable biomarkers for predicting tumor progression, tumor metastasis, and response to treatment.² Thus, it is still a great need to detect better predictors for clinical application, especially for predicting the outcome of cancer patients.

Mucins are a family of highly glycosylated proteins with a basic structure consisting of a variable number of tandem repeats rich in serine, threonine, and proline. Biochemically, mucins comprise a large gene family of ~20 molecules, which can broadly be divided into secreted and membrane-associated mucins. Among them, Mucin 1 (MUC1), a transmembrane glycoprotein that is normally expressed at the basal level in human epithelial cells to provide a protective barrier for the epithelial cells,³ has been the focus of research. In neoplastic cells, MUC1 expression can be upregulated to stimulate tumor cell proliferation and also suppress apoptosis, which supports a role for MUC1 in tumor progression.⁴ In addition, it has been reported that MUC1 could reduce the cell–cell adhesion to the extracellular matrix,⁵ which would lead to an increased invasive and metastatic capability of tumor cells. In vivo experiment of transgenic mice demonstrated that overexpression of MUC1 in mouse mammary tissue results in spontaneous mammary gland carcinoma.⁶ Furthermore, MUC1 in tumor cells is aberrantly glycosylated, which resulted in overexpression of several novel tumor-associated carbohydrate structures such as Tn antigen, T antigen, and sialyl-Tn antigen, suggesting a possible prognostic role in diverse kinds of human cancers.⁷ Taken together, MUC1 may play a role in tumorigenesis, progression, and metastasis

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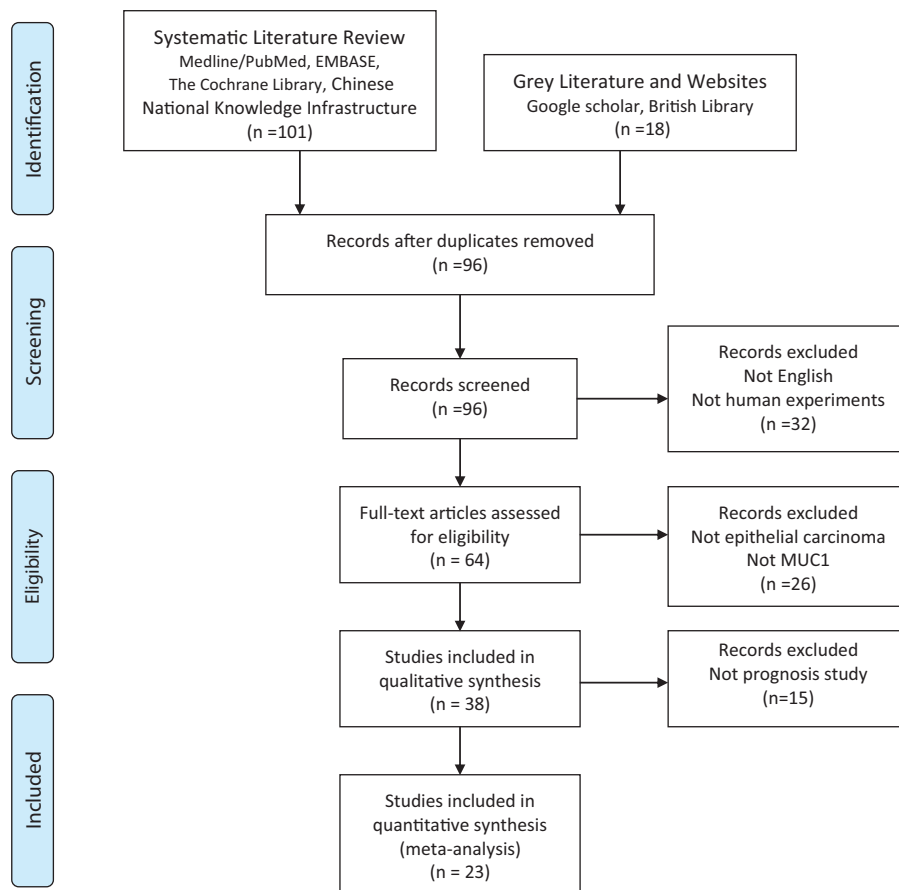


FIGURE 1. PRISMA flowchart of the literature search.

and thus may serve as a potential prognostic factor of epithelial-originated cancer.

Moreover, some researchers have investigated MUC1 expression by immunohistochemical (IHC) staining in several human epithelial malignancies including gastric,⁸ colorectal,⁹ pancreatic,¹⁰ breast,¹¹ endometrial,¹² lung,¹³ bladder,¹⁴ and renal cell cancers.¹⁵ However, its prognostic role in cancers is still under debate. In this study, we aimed to perform an up-to-date meta-analysis to reveal the prognostic value of MUC1 in various human epithelial carcinomas.

METHOD

Search Strategy

We searched several international databases including Medline/PubMed, EMBASE, the Cochrane Library, and Chinese National Knowledge Infrastructure (CNKI) databases up to 15 August 2015. The key terms used for literature retrieval included “Mucin1” or “MUC1” or “Episialin” and “cancer” or “carcinoma” or “tumor” or “neoplasm” and “survival” or “outcome” or “prognosis.” To obtain additional relevant manuscripts, conference summaries and reference lists missed in the retrieval were identified. We even contacted the corresponding authors to get additional information if necessary. All procedures were approved by the Ethics Committee for human experiments of Capital Medical University.

Selection Criteria

Studies were selected if they met the following criteria: (a) they focused on epithelial cancers; (b) all selected cancer patients were pathologically confirmed; (c) the expression level of MUC1 was tested by immunohistochemistry staining; and (d) correlation between MUC1, clinicopathological features, and overall survival was described.

Articles were excluded from the analyses based on the following criteria: (a) non-English papers; (b) nonhuman experiments; (c) review articles, case reports, or letters; (d) duplicate publication; and (e) insufficient data to report the hazard ratios (HR) and 95% confidence interval (95% CI), or the Kaplan–Meier curve could not be extracted.

Data Extraction

All relevant data were screened and extracted by 2 independent investigators (FX and GSF). The quality of the selected articles was assessed according to the Newcastle–Ottawa Scale (NOS).¹⁵ The information including author, year of publication, country, patient number, cancer type, the cut-off value, over-expression rates of MUC1, antibody for MUC1 staining, hazard ratio, and follow-up time was recorded for each study. To get the HRs and their 95%CI that were not reported in the articles, we digitized and extracted the data from the Kaplan–Meier curves using the software designed by Jayne F Tierney and Matthew R Sydes.¹⁶ To reach a consensus, any disagreement on a conflicting study was resolved by full discussion.

TABLE 1. Characteristics of Included Studies for Meta-Analyses

Authors (ref)	Year	Number of Patients	Country	Cancer Type	Cut-Off (Positive/High Expression)	Antibody For MUC1 Staining	HR For OS (95%CI)	Follow-Up (Months)	P Value
Mcguckin ²⁰	1995	171	Australia	BC	> 75% (103)	MAB Clone BC2	Survival curve 1.80 (0.97–3.33)	NA	<0.05
Guddo ²¹	1998	93	Greece	NSCLC	>25% (40)	MAB Clone 214D4	Survival curve 2.35 (1.00–5.52)	62 (45–74)	0.007
Baldus ²²	1998	128	Germany	GC	>5% (78)	MAB Clone HMF2G-2	Survival curve 1.74 (1.09–2.75)	>60	0.040
Utsunomiya ²³	1998	136	Japan	GC	>5% (75)	MAB Clone DF3	Survival curve 1.78 (1.14–2.78)	NA	<0.01
Higashi ²⁴	1999	39	Japan	CC	>5% (23)	MAB Clone DF3	Survival curve 2.72 (1.08–6.87)	NA	<0.05
Matsumura ²⁵	2001	50	Japan	CC	>5% (38)	MAB Clone HMPV	Reported 4.21 (1.93–14.07)	NA	0.0011
Lee ²⁶	2001	300	Korea	GC	>20% (73)	MAB Clone NCL-MUC1	Survival curve 2.62 (1.87–3.67)	42 (1–60)	0.001
Baldus ²⁷	2002	243	Germany	CR	>35% (79)	MAB Clone HMF2G-2	Survival curve 2.25 (1.60–3.16)	>60	<0.0001
Akyurek ²⁸	2002	143	Turkey	GC	>50% (82)	MAB Clone NCL-MUC1	Survival curve 1.93 (1.21–3.08)	30 (2–80)	0.04
Wang ²⁹	2003	76	China	GC	>5% (49)	MAB Clone VU-4H5	Survival curve 5.13 (1.76–14.91)	30 (1–58)	0.0081
Nagal ³⁰	2006	62	Japan	NSCLC	NA	MAB Clone DF3	Reported 4.73 (1.00–22.3)	NA	0.049
Duncan ³¹	2007	462	UK	CR	>30% (148)	MAB Clone NCL-MUC1	Reported 1.339 (1.002–1.790)	75	0.048
Woenckhaus ³²	2008	125	Germany	NSCLC	>5% (96)	MAB Clone MA695	Survival curve 1.46 (0.65–3.31)	NA	0.03
Togami ³³	2008	52	Japan	UCC	>5% (31)	MAB Clone DF3	Survival curve 2.69 (0.66–27.34)	NA	0.08
Park ³⁴	2009	85	Korea	CC	>10% (56)	MAB Clone MA695	Reported 1.211 (0.403–3.640)	NA	0.733
Ando ³⁵	2009	102	Japan	GC	>10% (44)	MAB Clone Ma552	Reported 0.92 (0.18–4.70)	NA	0.906
Westgaard ³⁶	2009	63	Norway	PC	>40% (18)	MAB Clone MA695	Reported 2.02 (1.02–3.98)	>60	0.043
Retterspitz ³⁷	2010	94	Germany	GC	>35% (75)	MAB Clone HMF2G-2	Reported 2.074 (1.153–3.671)	>65	0.046
Situ ³⁸	2011	178	China	NSCLC	NA (114)	MAB Clone-0581	Reported 2.212 (1.295–3.777)	NA	0.004
Kim ³⁹	2012	54	Korea	GBC	Score \geq 4 (44)	MAB Clone VU-4H5	Survival curve 1.13 (0.38–3.38)	31.9(1–126.6)	0.747
Hamada ⁴⁰	2012	206	Japan	OSCC	>5% (80)	MAB Clone DF3	Reported 2.09 (1.04–4.29)	61(1–206)	0.04
Khanh ⁴¹	2013	206	Japan	CR	>25% (129)	MAB Clone MA695	Reported 2.27 (1.25–4.13)	>60	0.007
Liu ⁴²	2014	357	China	SGMEC	>5%(246)	NA	Reported 2.175 (1.263–3.745)	32.8(10–106)	0.0051

BC = breast cancer, CC = cholangiocarcinoma, CI = confidence interval, CRC = colorectal cancer, GBC = gallbladder carcinoma, GC = gastric carcinoma, HR = hazard ratio, MAB = monoclonal antibody, MUC1 = mucin 1, NA = not available, NSCLC = nonsmall cell lung cancer, OS = overall survival, OSCC = oral squamous cell carcinoma, PC = pancreatic cancer, SGMEC = salivary gland mucoepidermoid carcinoma, UCC = uterine cervical carcinoma.

Statistical Analysis

The statistical analysis was performed according to the guidelines proposed by the Meta-Analysis of Observational Studies in Epidemiology group (MOOSE).¹⁷ Hazard ratio with 95% CI was calculated using Stata SE12.0 (Stata Corporation, TX). The heterogeneity among studies was measured using the *Q* and *I*² tests. A probability value of *P* < 0.1 and *I*² ≥ 50% indicated the existence of significant heterogeneity.¹⁸ Both the fixed-effect model (FEM) and random-effect model (REM) were used to estimate the association between MUC1 expression and OS.¹⁹ The potential for publication bias was assessed using Begg's funnel plot and the Egger linear regression test. *P* value < 0.05 was considered statistically significant. All *P* values are 2-tailed.

RESULTS

Search Results

The initial search returned a total of 119 manuscripts. After screening the titles and abstracts, 96 irrelevant articles were excluded according to the search strategy above. As a result, a total of 23 studies were included in our meta-analysis. The detailed screening process was shown in Figure 1. All of these enrolled studies comprehensively assessed the expression of MUC1 and the OS rate.

Study Selection and Characteristics

All features of the 23 eligible studies are listed in Table 1.^{20–42} Among them, participants in 14 studies were Asian and in the other 9 were Caucasian. Our study focused on 10 types of epithelial malignancies, including breast cancer (BC), cholangiocarcinoma (CC), uterine cervical carcinoma (UCC), colorectal cancer (CRC), oral squamous cell

carcinoma (OSCC), gastric carcinoma (GC), gallbladder carcinoma (GBC), nonsmall cell lung cancer (NSCLC), pancreatic cancer (PC), and salivary gland mucoepidermoid carcinoma (SGMEC). The cut-off values of IHC evaluation applied in the studies were not consistent ranging from 5% to 75%. Regarding different anti-MUC1 monoclonal antibodies, 3 studies used clone HMFG-2, 5 for clone DF3, 3 for clone NCL-MUC1, 2 for clone VU-4H5, 4 for clone MA695, and 6 focused on others. Hazard ratios with their 95% CIs were extracted from the graphical survival plots in 12 studies and reported directly in 11 studies, 15 of which calculated HRs by the multivariate analysis and 8 via univariable analysis. In all studies, none of the patients received neo-adjuvant radio- or chemotherapy prior to surgery.

Correlation of MUC1 Expression With Prognosis

As shown in Table 2, we found that elevated MUC1 predicted a poor outcome (HR_{FEM} = 1.98, 95% CI_{FEM}: 1.76–2.22, *P*_{FEM} = 0.479; HR_{FEM} = 2.16, 95% CI_{FEM}: 1.58–2.94, *P*_{FEM} = 0.355) for 23 studies evaluating OS (Figs. 2 and 3). Regarding diverse cancer types, subgroup analyses using a fixed effect model showed that increased MUC1 predicted an unfavorable prognosis in gastric cancer (HR_{FEM} = 2.12, 95%CI_{FEM}: 1.75–2.57, *P*_{FEM} = 0.359), colorectal cancer (HR_{FEM} = 1.73, 95%CI_{FEM}: 1.41–2.13, *P*_{FEM} = 0.048), cholangiocarcinoma (HR_{FEM} = 2.52, 95% CI_{FEM}: 1.42–4.49, *P*_{FEM} = 0.252), and nonsmall cell lung cancer (HR_{FEM} = 2.14, 95% CI_{FEM}: 1.46–3.14, *P*_{FEM} = 0.591). When ethnicity was considered, results revealed that positive MUC1 expression indicating poor OS was found both in Asian people (HR_{FEM} = 2.28, 95%CI_{FEM}: 1.90–2.72, *P*_{FEM} = 0.683) and Caucasian populations (HR_{FEM} = 1.77, 95%CI_{FEM}: 1.51–2.07, *P*_{FEM} = 0.678). When performing subgroup analyses stratified by the analysis method, it is found that increased MUC1 was a

TABLE 2. Meta Analysis Results

Outcome	Variables	Number of Studies	Number of Patients	HR _{FEM} (95% CI _{FEM})	<i>P</i> _{FEM}	HR _{REM} (95% CI _{REM})	<i>P</i> _{REM}
OS	ALL	23	3425	1.98 (1.76–2.22)	0.479	2.16 (1.58–2.94)	0.355
	Cancer type						
	NSCLC	4	458	2.14 (1.46–3.14)	0.591	2.81 (1.40–5.64)	0.280
	GC	7	979	2.12 (1.75–2.57)	0.359	1.89 (1.05–3.41)	0.238
	CC	3	174	2.52 (1.42–4.49)	0.252	2.34 (1.30–4.22)	0.244
	CRC	3	911	1.73 (1.41–2.13)	0.048	2.00 (1.46–2.73)	0.019
	Others	6	903	1.95 (1.45–2.63)	0.931	1.98 (1.00–3.92)	0.930
	Ethnicity						
	Asian	14	1903	2.28 (1.90–2.72)	0.638	2.27 (1.50–3.46)	0.638
	Caucasian	9	1522	1.77 (1.51–2.07)	0.572	1.88 (1.47–2.40)	0.509
	Analysis method						
	Univariable	8	1023	2.05 (1.70–2.47)	0.694	2.03 (1.10–3.75)	0.694
	Multivariable	15	2402	2.00 (1.67–2.39)	0.271	2.22 (1.57–3.16)	0.127
	Antibody-catalog						
	Clone HMFG-2	3	465	2.06 (1.61–2.64)	0.680	2.00 (1.48–2.69)	0.660
	Clone DF3	5	495	2.07 (1.48–2.89)	0.747	2.96 (1.34–6.52)	0.177
	Clone NCL-MUC1	3	905	1.81 (1.48–2.21)	0.012	1.92 (1.52–2.44)	0.010
Clone VU-4H5	2	130	2.45 (1.14–5.26)	0.052	2.39 (1.11–5.13)	0.052	
Clone MA695	4	479	1.86 (1.29–2.70)	0.704	1.59 (1.00–2.55)	0.552	
Others	6	951	2.18 (1.64–2.90)	0.675	1.87 (1.05–3.32)	0.510	

CC = cholangiocarcinoma, CI = confidence interval, CRC = colorectal cancer, FEM = fixed effect model, GC = gastric carcinoma, HR = hazard ratio, MUC1 = mucin 1, NSCLC = nonsmall cell lung cancer, OS = overall survival, carcinoma REM = random effect model.

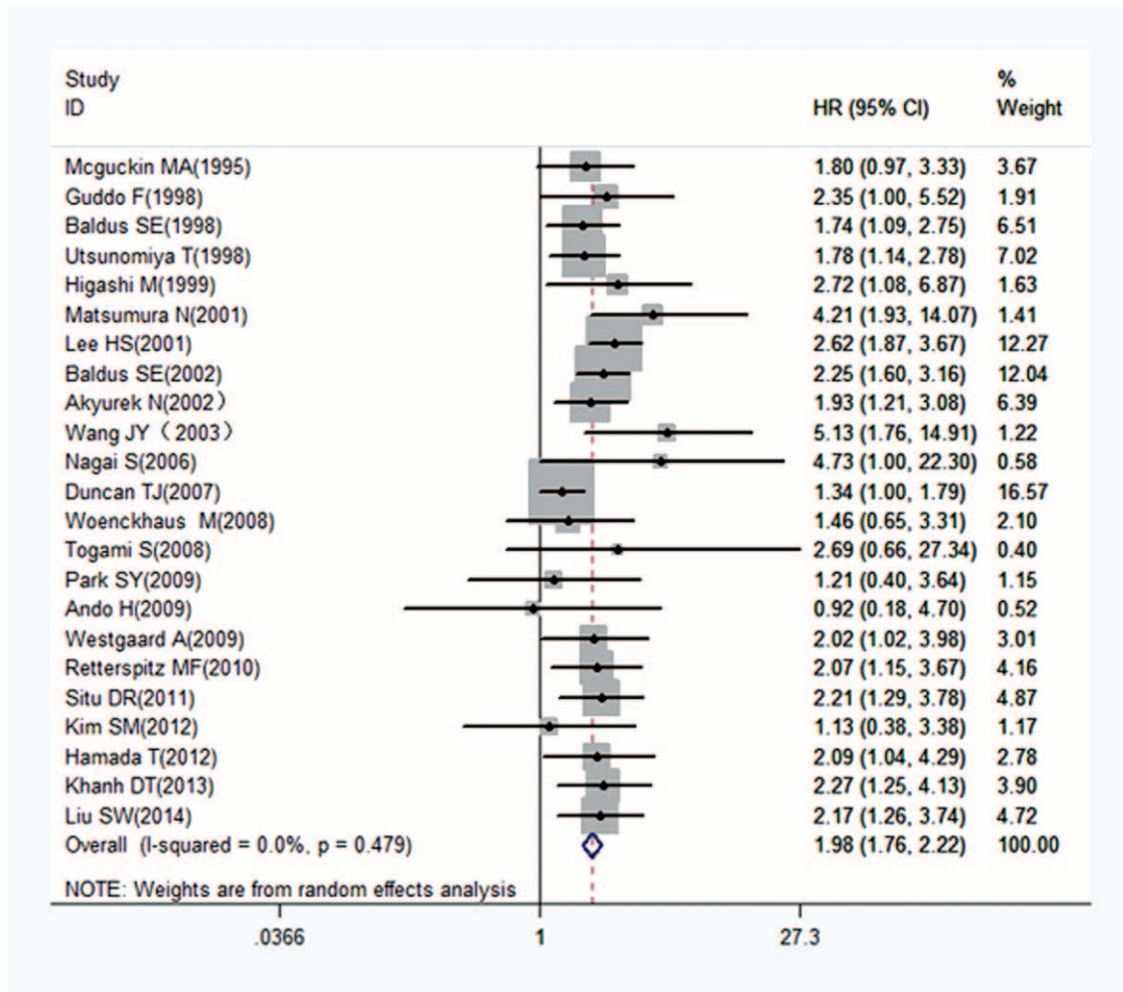


FIGURE 2. Forest plots of studies evaluating hazard ratios (HRs) of MUC1 for overall survival with a fixed effect model. HRs = hazard ratios, MUC1 = mucin 1.

negative predictor for OS both by univariable analysis ($HR_{FEM} = 2.05$, $95\%CI_{FEM}: 1.70-2.47$, $P_{FEM} = 0.694$) and multivariable analysis ($HR_{FEM} = 2.00$, $95\%CI_{FEM}: 1.67-2.39$, $P_{FEM} = 0.271$). Considering different anti-MUC1 monoclonal antibodies, MUC1 was a negative prognostic marker for the data applying clone HMFG-2 ($HR_{FEM} = 2.06$, $95\%CI_{FEM}: 1.61-2.64$, $P_{FEM} = 0.680$), clone DF3 ($HR_{FEM} = 2.07$, $95\%CI_{FEM}: 1.48-2.89$, $P_{FEM} = 0.747$), clone NCL-MUC1 ($HR_{FEM} = 1.81$, $95\%CI_{FEM}: 1.48-2.21$, $P_{FEM} = 0.012$), clone VU-4H5 ($HR_{FEM} = 2.45$, $95\%CI_{FEM}: 1.14-5.26$, $P_{FEM} = 0.052$), clone MA695 ($HR_{FEM} = 1.86$, $95\%CI_{FEM}: 1.29-2.70$, $P_{FEM} = 0.704$), and other antibodies ($HR_{FEM} = 2.18$, $95\%CI_{FEM}: 1.64-2.90$, $P_{FEM} = 0.675$). Furthermore, subgroup analyses utilizing the random effect model showed consistent results in Table 2.

Correlation of MUC1 Expression With Clinicopathological Features

The relationship between elevated MUC1 and clinicopathological parameters (reported in at least 3 studies) was explored with a random effect model in colorectal cancer and gastric cancer. As shown in Figure 4, increased MUC1 was

found to be significantly associated with positive lymph node metastasis and intestinal-type classification but not with advanced TNM stage in gastric cancer. In addition, MUC1 overexpression was more likely to be found in colorectal cancer patients with an advanced TNM stage. However, no significant relationship was detected between MUC1 overexpression and clinical characteristics in other epithelial cancers due to limited studies.

Heterogeneity

To explore the potential source of heterogeneity among studies, “metareg” STATA command was conducted utilizing variables as year of publication, ethnicity (Asian vs Caucasian), cancer type, and analysis method (univariable vs multivariable). The results showed that no variable included in the meta-regression contributed to the heterogeneity.

Sensitivity Analysis

The selected studies were sequentially removed to investigate whether any single study could have an influence on the

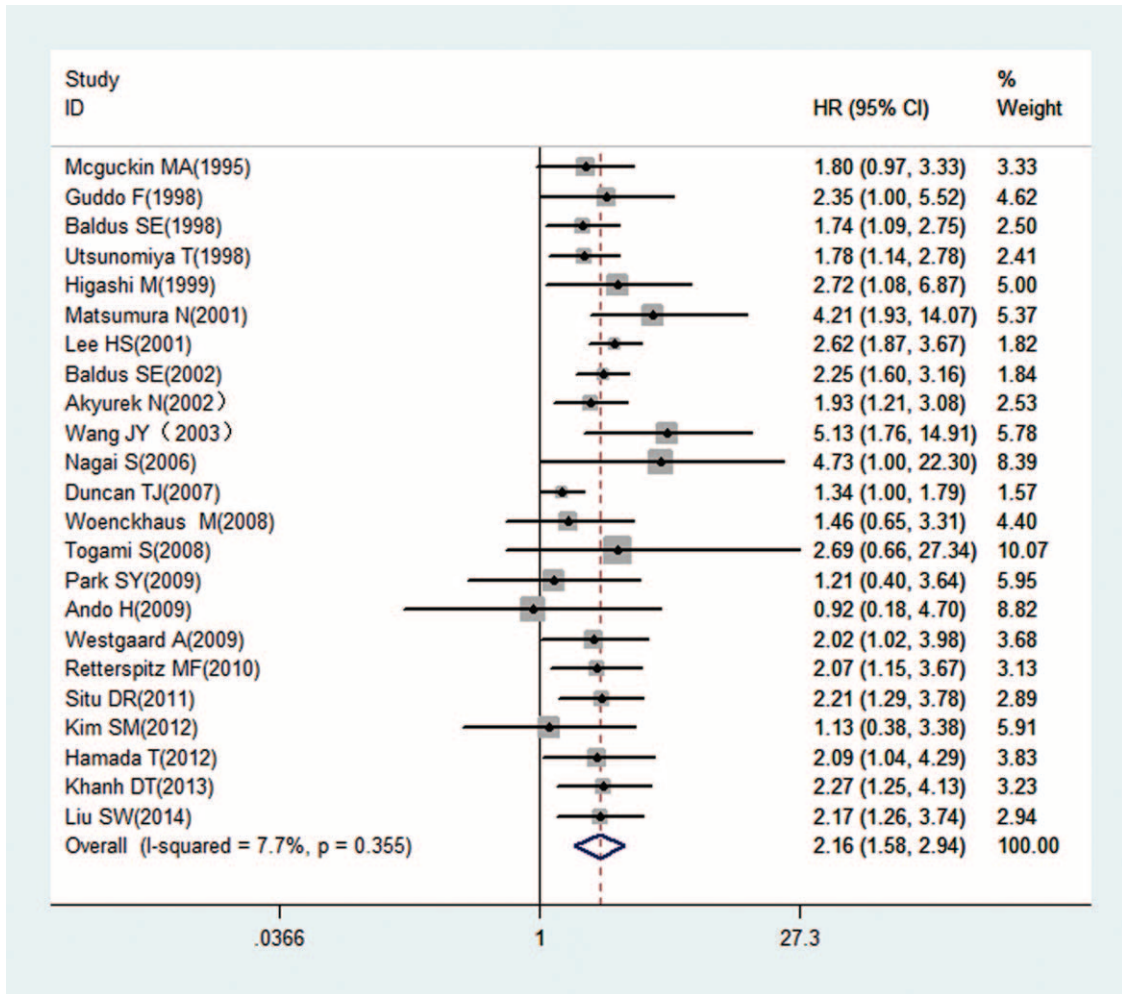


FIGURE 3. Forest plots of studies evaluating hazard ratios (HRs) of MUC1 for overall survival with a random effect model. HRs = hazard ratios, MUC1 = mucin 1.

pooled results. As shown in Figure 5, the stable pooled HRs was found to be not significantly affected by each individual study.

Publication Bias

Bgger’s funnel plot (Fig. 6) was almost symmetric and the P value of Egger’s linear regression test was 0.296. Thus, no evidence for publication bias in this meta-analysis was found.

DISCUSSION

To date, the relationship between MUC1 expression and the outcome of tumor sufferers remains inconclusive. Our current study chiefly concerned with the prognostic role of MUC1 in epithelial-originated cancer. To the best of our knowledge, it is the first meta-analysis to investigate the prognostic role of MUC1 in various human epithelial cancers. We found that positive/higher MUC1 expression significantly predicted poorer OS compared with negative/lower MUC1 expression. The pooled results indicated that MUC1 might act as a reliable biomarker in predicting clinical outcomes of human epithelial cancers.

The mechanisms responsible for the above association derived the following interpretations. As a common feature of epithelial-originated tumors, overexpression of MUC1 is caused by the genetic and transcriptional levels of gene expression control and by a loss of post-transcriptional regulation. Amplification of the MUC1 gene locus (1q21) has been observed in breast cancer cells.⁴³ Through associations with various transcription factors (STAT3, NF-κB, p53, and β-catenin), MUC1 could upregulate its own promoter activity.⁴⁴ Moreover, MUC1 overexpression is regulated post-transcriptionally through microRNA-125b targeting the 3’ untranslated region (UTR) of MUC1 mRNA in breast cancer cells.⁴⁵ Several studies have indicated that MUC1 plays a critical role in tumor invasion and metastasis. On one hand, MUC1 involves in the biological process of epithelial to mesenchymal transition (EMT) by repressing E-cadherin expression and upregulating expression of several EMT inducers,⁴⁶ by which tumor cells acquire their invasive potential. On the other hand, the binding of MUC1 to adhesion molecules expressed on endothelial cells, such as selectin-like molecules might eventually contribute to the hematogenous metastatic spread.⁴⁷ Such mechanisms

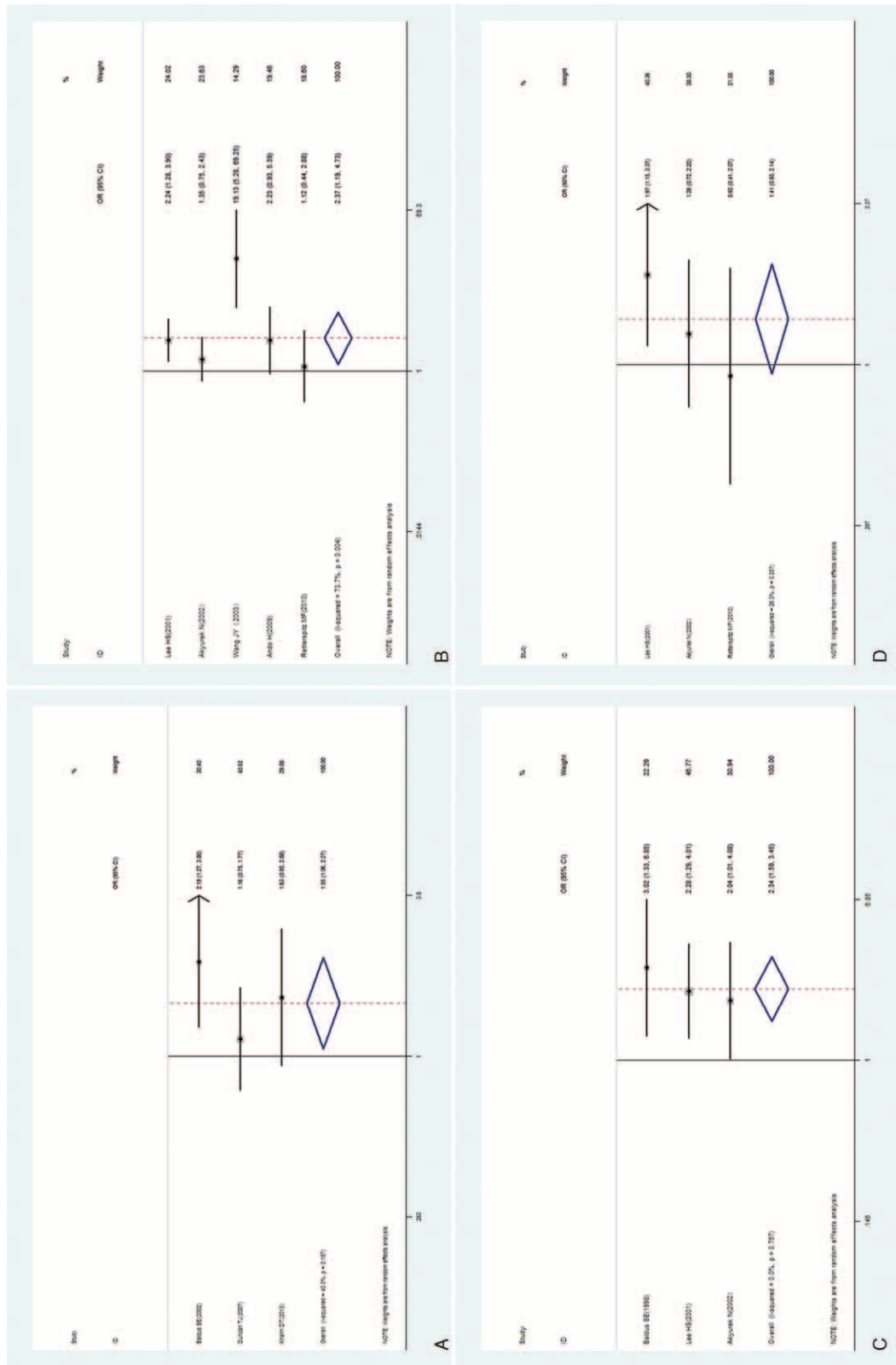


FIGURE 4. Forest plots of studies evaluating the association between MUC1 and clinical parameters in CRC and GC with a random effect model. (A) Tumor node metastasis (TNM) stage (advanced vs early) in CRC; (B) lymph node metastasis (present vs absent) in GC; (C) Lauren classification (intestinal-type vs diffuse-type) in GC; (D) TNM stage (advanced vs early) in GC. CRC = colorectal cancer, GC = gastric carcinoma, MUC1 = mucin 1.

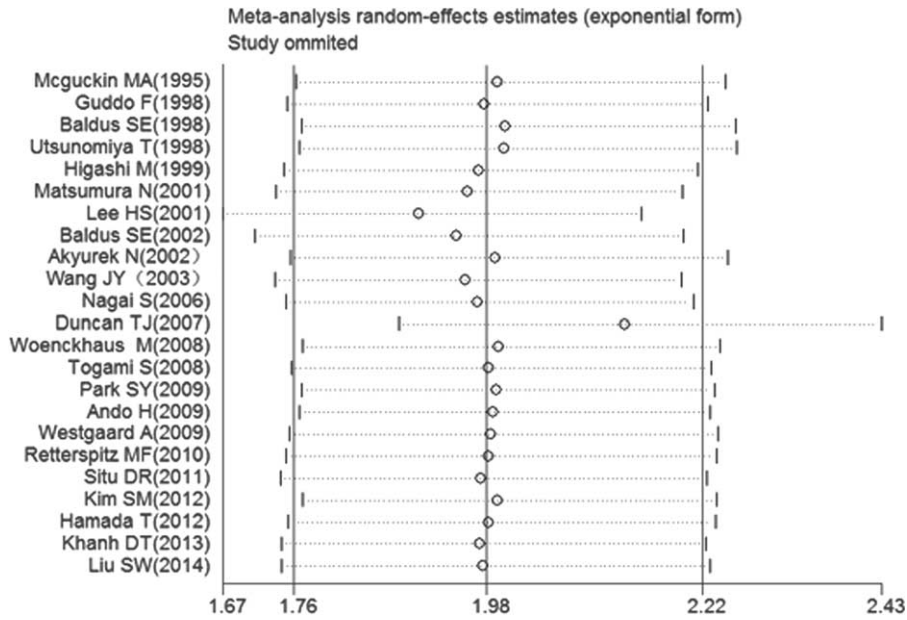


FIGURE 5. Effect of individual studies on the pooled HR for MUC1 and OS of patients. HR = hazard ratio, MUC1 = mucin 1, OS = overall survival.

explained the clinical findings that MUC1 overexpression leads to tumor metastasis and poor prognosis in human epithelial cancers.

Subgroup analyses revealed that worse OS with high MUC1 could be found in many cancers, such as gastric cancer, colorectal cancer, cholangiocarcinoma, and NSCLC regardless of different analysis strategies and antibodies. Compared with Caucasian people, increased MUC1 expression was more significantly associated with poor OS in Asian population ($HR_{FEM} = 2.28$, 95% CI_{FEM} : 1.90–2.72, $P_{FEM} = 0.683$; $HR_{REM} = 2.27$, 95% CI_{REM} : 1.50–3.46, $P_{REM} = 0.638$). Further, considering different

cut-off values, follow-up time, and antibodies, meta-regression was performed to investigate the source of heterogeneity. However, none of the variables listed above contributed to the heterogeneity in our meta-analysis. Additionally, when the clinicopathological features were considered, MUC1 overexpression was more likely to be found in colorectal cancer patients with an advanced TNM stage and in gastric cancer patients with positive lymph node metastasis and intestinal-type classification. To date, most immunotherapy approaches targeting MUC1 have been administered to >1200 patients in clinical trials. As a notable example, synthetic vaccine ImMucin successfully completed a

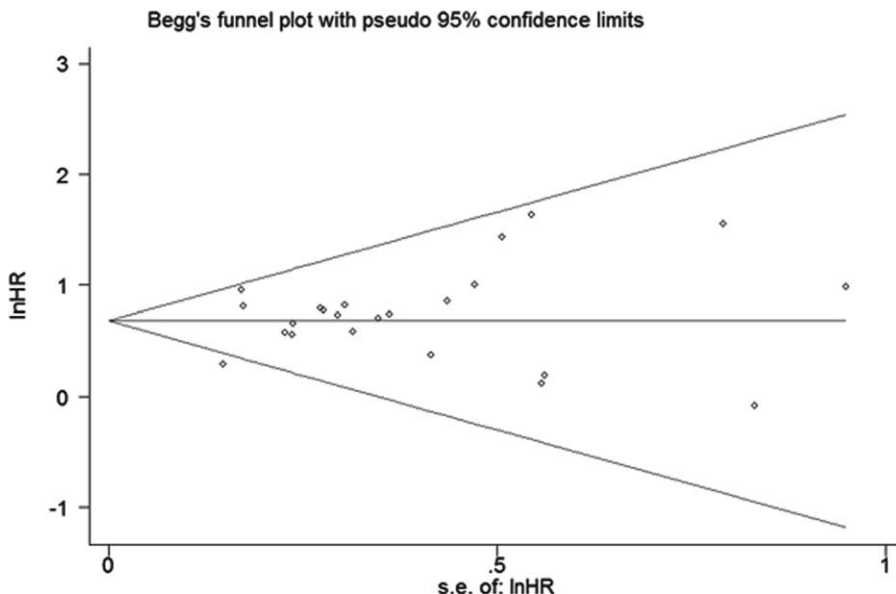


FIGURE 6. Begg's funnel plots for all of the included studies reported with OS. OS = overall survival.

Phase I/II clinical trial in multiple myeloma patients.⁴⁸ Recently, Stimuvax has been developed and has completed a Phase III trial in patients with IIIA/B NSCLC. However, few anti-MUC1 immunotherapy trials were explored in gastrointestinal cancers during 1996 to 2012. Our results suggest that anti-MUC1 immunotherapy might be preferentially carried out on patients with gastrointestinal cancers in future clinical trials.

Although our results are promising, there are several limitations of this study need to be carefully taken into account. First, as a novel prognostic marker in malignancies, MUC1 just loomed in recent years and nearly half of the sample size was relatively small. Second, all of the selected studies measured MUC1 expression by IHC, the distinct antibodies used, the protocol of staining, the different cut-off values, and the method of scoring might account for the high variability in the frequencies reported by different authors. In addition, although triple subsets of MUC1 threshold values revealed the similar results, a baseline referring to MUC1 overexpression should be set up. Third, few studies explored the association of patient prognosis and circulating MUC1 (also known as CA15–3) expression, which might be more acceptable than tissue markers because they can be assayed before surgery and be monitored throughout the life. Finally, due to the lack of appropriate data, most studies included in this meta-analysis focused on gastrointestinal neoplasms and NSCLC. In the future, studies with more types of cancers and larger sample size are needed to present more convincing results of the clinical relevance and precise molecular explanation for the abnormal expression of MUC1.

In conclusion, the current evidence first shows that an elevated MUC1 is a negative predictor for survival in epithelial-originated cancers, especially in NSCLC and gastrointestinal tumors.

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