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Prognostic and clinicopathological value of MUC1 expression in colorectal cancer

A meta-analysis

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Abstract

Background: Accumulating evidence supports the overexpression of mucin 1 (MUC1) in colorectal cancer (CRC), but the value of elevated MUC1 expression remains controversial. Here, we evaluated the prognostic and clinicopathological value of MUC1 expression in CRC.

Materials and methods: The Web of Science, PubMed, Embase, Cochrane Library, and Wanfang databases, as well as the China Biology Medicine disc (CBMdisc) and China National Knowledge Infrastructure (CNKI) were searched for studies on MUC1 expression and prognosis of CRC through July 20, 2018. The pooled relative risks (RRs) and hazard ratios (HRs) with 95% confidence intervals (95% CIs) were calculated to evaluate the prognostic and clinicopathological value of MUC1 expression in CRC. The Revman version 5.3 package and STATA, version 12 were employed for pooled analysis and analysis of publication bias.

Results: This meta-analysis included 16 published studies. The combined analysis showed that CRC patients with high MUC1 expression had a worse clinical outcome in overall survival (OS) (HR = 1.51, 95% CI = 1.30–1.75, $P < .00001$). In addition, high MUC1 expression was associated with higher TNM stage (RR = 1.44, 95% CI = 1.17–1.77, $P = .0007$), greater depth of invasion (RR = 1.30, 95% CI = 1.10–1.53, $P = .002$), and lymph node metastasis (RR = 1.47, 95% CI = 1.20–1.80, $P = .0002$) of CRC. However, the elevated MUC1 expression was not related to disease-free survival/recurrence-free survival (DFS/RFS) (HR = 1.51, 95% CI = 0.78–2.89, $P = .22$), histological grade (RR = 1.15, 95% CI = 0.96–1.38, $P = .12$), gender (RR = 0.95; 95% CI = 0.83–1.08, $P = .44$), tumor size (RR = 1.11, 95% CI = 0.85–1.44, $P = .44$), tumor site (RR = 1.01, 95% CI = 0.88–1.16, $P = .84$), or mucinous component (RR = 0.83, 95% CI = 0.60–1.14, $P = .24$) in CRC.

Conclusion: Our findings indicated that high MUC1 expression represents a marker of poor prognosis in CRC. Meanwhile, elevated MUC1 expression was associated with advanced TNM stage, greater depth of invasion, and lymph node metastasis.

Abbreviations: CI = confidence interval, CRC =colorectal cancer, DFS = disease-free survival, HR = hazard ratio, MUC1 = mucin 1, RFS = recurrence-free survival, RR = relative risk.

Keywords: clinicopathologia, colorectal cancer, meta-analysis, micin-1, prognosis

1. Introduction

Colorectal cancer (CRC) is a frequently diagnosed cancer worldwide.[1] In addition, CRC is the most common cause of cancer-related death.[2,3] Studies have shown that only 40% of CRC cases are diagnosed at an early stage.[4] Although surgery is the primary means of treating cancer, 30% to 40% of patients have metastatic disease that cannot be treated by surgery.[5] In addition, patients with CRC have a high risk of recurrence.[3,6]

The classic tumor, node, and metastasis (TNM) staging system were considered to be the most standard prognostic parameter, providing a basis for CRC treatment.[7] However, the TNM system does not reflect the inherent biological heterogeneity of CRC, and about 50% of recently diagnosed cases will progress to metastatic cancer.[8,4] There are no suitable markers for predicting the progression, metastasis, and response to treatment of CRC.[9] Thus, it is necessary to find better biomarkers for predicting the outcome of CRC.

The mucin family members are high-molecular-weight glycosylated proteins[10] that form a barrier to protect the epithelial cells.[11–13] To date, about 20 human mucins have been identified and categorized into secreted gel-forming mucins and transmembrane mucins according to their structure and function.[14] Among them, MUC1 has a heavily glycosylated extracellular domain. It is normally expressed in secretory epithelial cells and hematopoietic cells,[15] but abnormally overexpressed in lung cancer, pancreatic tumors, prostate cancer, epithelial ovarian tumors, breast cancer, and colon cancers.[13,16–20] MUC1, as a master regulator of the metabolic program, facilitates metabolic alterations to help tumor cells survive and proliferate.[21] MUC1 activates antiapoptotic proteins and induces drug resistance via upregulation of multidrug resistance genes in the treatment and development of CRC.[22,23] These observations identify MUC1 as an attractive marker for the diagnosis, immunotherapy, and prognosis of cancer.[24,25]

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Currently, the association between MUC1 expression and malignancy has been indicated in many reports.[26–56] In CRC, MUC1 as a novel biomarker is highly expressed. However, Research findings regarding MUC1 expression and the prognosis of CRC are still conflicting, with some studies indicating that high MUC1 expression is a potential predictor of poor outcome in CRC patients[56–59] and other studies reporting contradictory evidence.[37,51,60] Thus, the prognostic value of MUC1 expression remains inconclusive. This quantitative meta-analysis aimed to determine the correlation of MUC1 with prognosis and clinicopathological features in CRC.

2. Methods

This meta-analysis was based on Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline (File S1). Our meta-analysis was based on previously published studies and does not contain any studies with human or animal subjects, thus no ethical approval and patient consent were required.

2.1. Search strategy

The PubMed, Web of Science, Embase, Cochrane Library, Wanfang databases as well as the China Biology Medicine disc (CBMdisc) and China National Knowledge Infrastructure (CNKI) were searched for studies on MUC1 expression and its prognostic value in CRC through July 20, 2018. All studies were analyzed to explore the association between MUC1 level and CRC prognosis. The primary terms used for literature retrieval included (CRC or colorectal neoplasms or colorectal cancer or colorectal carcinoma or colon cancer or rectal cancer) and (mucin 1 [MUC1]) and (survival or outcome or prognosis or prognostic factor) (File S2). To obtain additional eligible studies, conference summaries and references cited in these papers were surveyed. All literature searches were conducted by 2 independent reviewers.

2.2. Inclusion and exclusion criteria

Inclusion criteria:

(1) the patients were diagnosed with CRC according to pathological findings;
(2) clinicopathological parameters, MUC1 expression, and survival rate were investigated;
(3) values of relative risk (RR) and/or hazard ratio (HR) with 95% confidence interval (CI) were calculated; and
(4) publication in English or Chinese.

Exclusion criteria:

(1) repeated publication of data or poor quality data, lacking raw data, or presenting incomplete information; and
(2) review articles, case reports, conference abstracts, commentary, or letters to editors. The most recent paper was selected when several studies were published on the same trial.

2.3. Data extraction and quality assessment

All search results were screened and extracted by 2 authors (Chao Li and Tao Liu), and cases of inconsistency and disagreement were submitted to a third investigator (Libin Yin) for further review. The following information, including author, country, time of publication, number of patients, methods, antibodies, cut-off for MUC1 expression, mean or median age, follow-up time, and pathological outcome were systematically obtained from the charts and article contents. For studies providing HRs, we extracted data directly. We obtained the necessary data by using Engauge Digitizer, version 4.1 when patients' survival data were provided in the form of a Kaplan–Meier curve. Furthermore, the quality of the studies was assessed by 2 independent authors according to the Newcastle Ottawa Scale (NOS).[61] NOS score ranges from 0 to 9 and studies with a NOS score of 7 or more were considered to be high-quality studies.

2.4. Statistical analysis

HRs (95% CIs) were used to evaluate the relationship between MUC1 expression and survival (OS and disease-free survival [DFS]/recurrence-free survival [RFS]). An observed $HR > 1$ suggested a worse prognosis in patients with high MUC1 expression and an $HR \leq 1$ indicated a better prognosis. The association between MUC1 expression and the clinicopathological status of CRC, including gender, tumor size, tumor site, mucinous expression, histological grade, TNM stage, depth of invasion, and lymph node metastasis were assessed using RRs and 95% CIs. We assessed the heterogeneity among studies by calculating relevant P values and I^2 values. If the I^2 was $>50\%$, indicating the presence of heterogeneity in studies, a random effects model was applied in the pooled analysis. Otherwise, a fixed effects model was selected.[62,63] The potential for publication bias was assessed using Begg funnel plots and the Egger linear regression test, in which a P value $<.05$ was considered to indicate significant potential publication bias. Sensitivity analysis was performed to investigate the robustness of the results. The meta-regression analysis was searched for the sources of heterogeneity.

Meta-analyses were performed using Review Manager 5.3 software (Cochrane Collaboration, Copenhagen, Denmark) and STATA, version 12.0 (Stata Corporation, College Station, TX). The significance of pooled data was further tested, and $P < .05$ was considered statistically significant.

3. Results

3.1. Study selection

We retrieved 462 articles through the initial database searches. Among them, 82 duplicates were retrieved. After rough screening of the titles and abstracts of all studies, 380 articles were further excluded according to the predefined criteria. Thirty articles were excluded after full review of the remaining 46 articles, due to the following reasons: review article (6) and no study endpoint (24). Finally, 16 eligible studies involving 2614 patients were included.[48,50,55,56–59,64–72]Figure 1 details the selection process.

3.2. Patients' characteristics

A total of 6 countries' studies were included in this meta-analysis, with sample sizes ranging from 35 to 403. The mean age of patients in the 16 articles ranged from 52.88 to 72.00 years old, and the follow-up ranged from 36 to 116 months (shown in Table 1). The MUC1 expression was detected by immunohistochemical (IHC) staining using different anti-MUC1 monoclonal antibodies, including clone MA695, clone KL-6, clone HMFG-2, clone DF3, clone NCL-MUC1, Dako EnVision system detection kit, and clone ZM-0391, which impacted the rate of positive MUC1 expression. The cut-off values for IHC evaluation applied

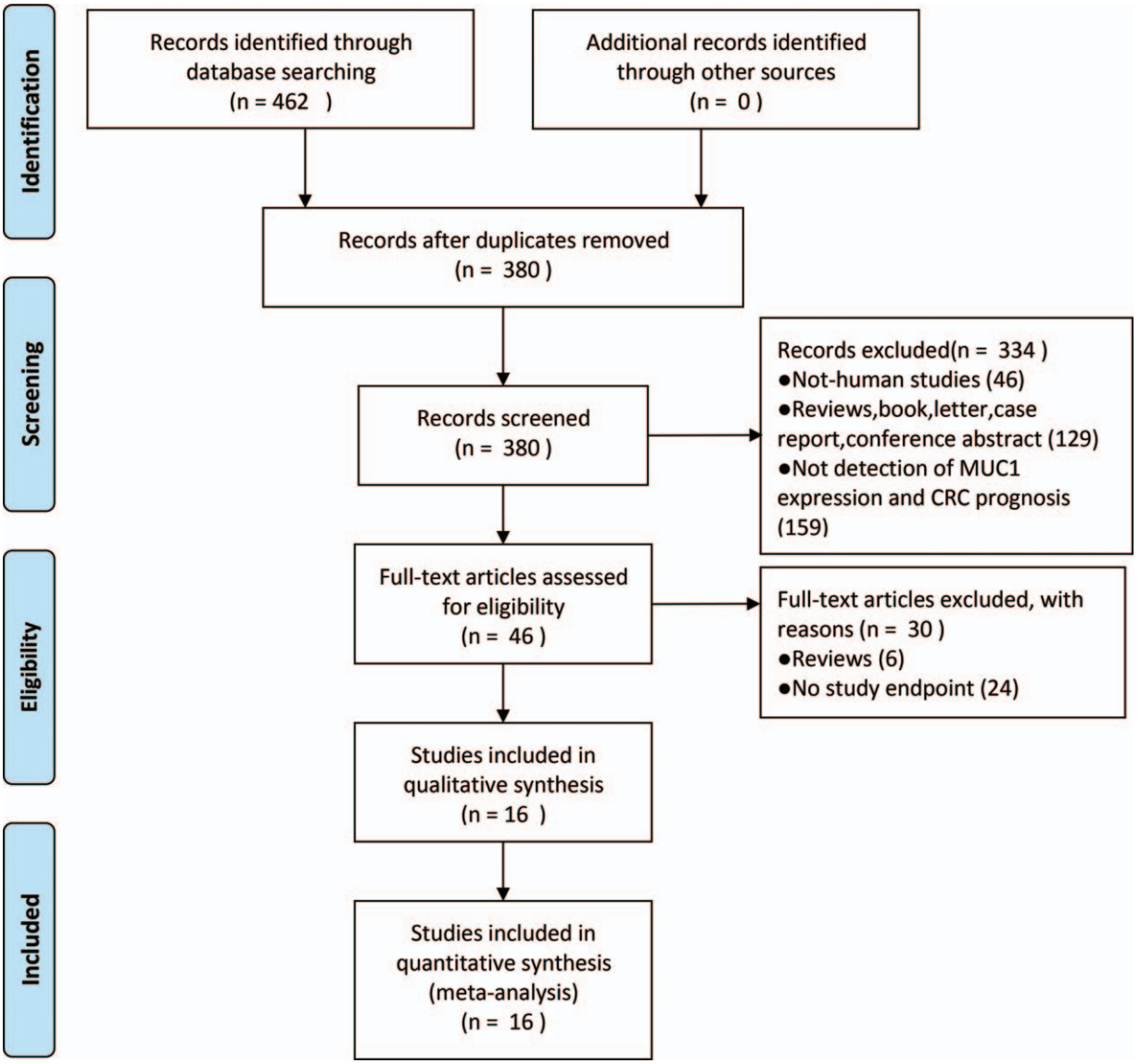

Figure 1. Flow diagram outlining the identification of retrieved publications.

in the studies were not consistent, ranging from 0% to 35% according to the positive cell percentage. All the clinicopathological parameters showed a significant association with the expression of MUC1 in CRC. According to the qualities assessed with the NOS score (Table S1), all studies were of high quality.

3.3. Outcomes

3.3.1. MUC1 and survival in CRC. Fifteen studies provided data on overall survival (OS). Figure 2 shows the forest plot from the analysis of OS. The results showed that, compared with the group with lower MUC1 expression, the OS was worse in higher MUC1 expression group (HR = 1.51, 95% CI = 1.30–1.75, $P < .00001$). A fixed effects model was used in view of small heterogeneity ($P = .69$, $I^2 = 0\%$). In addition, the DFS/RFS among CRC patients was reported in 4 studies. The combination of HRs suggested that positive MUC1 expression was not associated with DFS/RFS in CRC (HR = 1.51, 95% CI = 0.78–2.89, $P = .22$, Fig. S1, http://links.lww.com/MD/C854). A random-effects model was applied due to significant heterogeneity ($P = .01$, $I^2 = 72\%$) between the studies.

3.3.2. MUC1 and CRC TNM stage. Twelve articles were analyzed for the association between MUC1 expression and CRC TNM state. Pooled analysis showed significant heterogeneity among these studies ($P < .00001$, $I^2 = 81\%$), and thus a random effects model was used. Further analysis showed MUC1 overexpression was associated with TNM stage (III/IV vs I/II: RR = 1.44, 95% CI = 1.17–1.77, $P = .0007$; Fig. 3). This suggests that MUC1 expression is closely related to the clinicopathological parameters of CRC.

3.3.3. MUC1 and CRC invasion. Eleven studies on the depth of invasion showed that the pooled RR (positive vs negative) was 1.30 (95% CI = 1.10–1.53, $P = .002$). A random effects model was applied ($P = .02$, $I^2 = 53\%$, Fig. 4).

3.3.4. MUC1 and CRC lymph node metastasis. Eleven articles reported lymph node metastasis, and a significant relationship

Table 1

Main characteristics of the included publications.

Publication	Year	Country	Patient number	Antibody	Cut-off (low/high expression)	Method	Outcome	TNM stage	Mean age, yr	Mean follow-up, mounts	NOS score
Baldus	2000	Germany	264	NCL-MUC1	PP >5%	IHC	OS	I-IV	64.80	>60	8
Baldus	2004	Germany	205	HMFG-2	PP >3	IHC	OS	I-IV	64.96	NR	7
Betge	2016	Germany	381	Ma695	PP >0%	IHC	OS/DFS	I-IV	68.50	>60	8
Diaz	2018	Spain	96	DE detection kit	PP >0%	IHC	DFS	0-IV	65.90	NR	8
Duncan	2007	UK	403	Ma695	PP ≥30%	IHC	OS	0-IV	72.00	116	8
Hiraga	1998	Japan	100	KL-6	PP >30%	IHC	OS	II-IV	62.70	80	8
Khanh	2013	Japan	206	Ma695	PP ≥5%	IHC	OS/RFS	I-IV	NR	>60	8
Kimura	2000	Japan	110	KL-6	PP ≥30%	IHC	OS	II-IV	63.10	>84	7
Lu	2014	China	60	Ma695	PP >5%	IHC	OS	I-IV	52.88	>60	8
Manne	2000	USA	166	DF3	PP >25% IRS ≥0.5	IHC	OS	I-IV	65.31	>72	8
Perez	2008	Brazil	35	Ma695	PP >10%	IHC	OS/DFS	I-IV	62.20	>36	7
Wang	2016	China	81	ZM-0391	IRS >1	IHC	OS	I-IV	63.50	>60	8
Xu	2010	China	77	KL-6	PP >10%	IHC	OS	I-IV	64.90	NR	8
You	2006	China	203	Ma695	IRS ≥2	IHC	OS	I-IV	NR	111.9	8
Yu	2007	China	150	Ma695	IRS ≥2	IHC	OS	I-IV	57.50	>60	8
Zhang	2008	Japan	77	KL-6	SI(positive)	IHC	OS	I-IV	64.90	NR	8

DE = Dako EnVision system detection kit, DFS = disease-free survival, IHC = immunohistochemistry, IRS = immunoreactive score, NOS score = Newcastle–Ottawa, NR = not reported, OS = overall survival, PP = positive cell percentage, RFS = recurrence-free survival, SI = staining intensity.

was revealed between MUC1 expression and lymph node metastasis in CRC (HR = 1.47, 95% CI = 1.20–1.80, $P = .0002$, Fig. 5). The random effects model was applied because the heterogeneity was obvious among these studies ($P < .00001$, $I^2 = 77\%$).

3.3.5. MUC1 and CRC clinicopathological features. Elevated MUC1 was not significantly associated with histological grade (3 vs 1/2: RR = 1.15, 95% CI = 0.96–1.38, $P = .12$, Fig. S2, http://links.lww.com/MD/C854), gender (female vs male: RR = 0.95, 95% CI = 0.83–1.08, $P = .44$, Fig. S3, http://links.lww.com/MD/C854), tumor size (small vs large: RR = 1.11, 95% CI = 0.85–1.44, $P = .44$, Fig. S4, http://links.lww.com/MD/C854), tumor site (rectum vs colon: RR = 1.01, 95% CI = 0.88–1.16, $P = .84$, Fig. S5, http://links.lww.com/MD/C854), and mucinous component (≥50% vs <50%: RR = 0.83, 95% CI = 0.60–1.14, $P = .24$, Fig. S6, http://links.lww.com/MD/C854).

3.4. Publication bias

Begg funnel plots and Egger linear regression test were used to evaluate the publication bias in our meta-analysis. No evidence of publication bias was found for OS ($P = .553$, 0.219; Fig. S7A, http://links.lww.com/MD/C854), DFS/RFS ($P = .308$, 0.336; Fig. S7B, http://links.lww.com/MD/C854). We also performed Begg test and Egger test for clinicopathological features (Fig. S8, S9, http://links.lww.com/MD/C854) and found no evidence of publication bias.

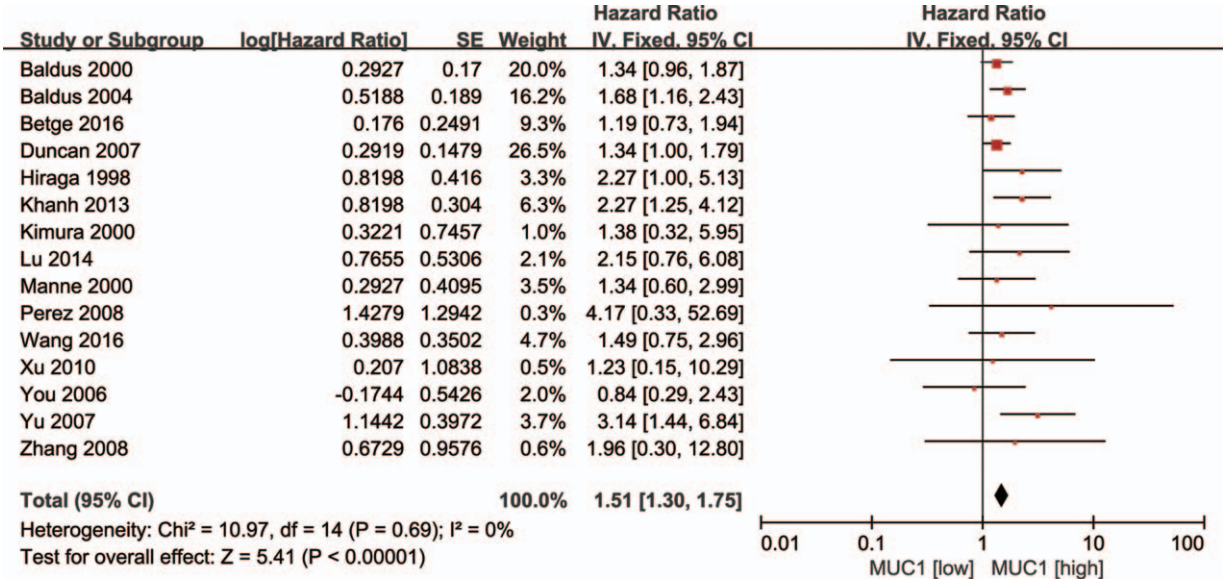

Figure 2. Forest plots of HRs for MUC1 expression and colorectal cancer OS. HRs = hazard ratios, MUC1 = mucin 1, OS = overall survival.

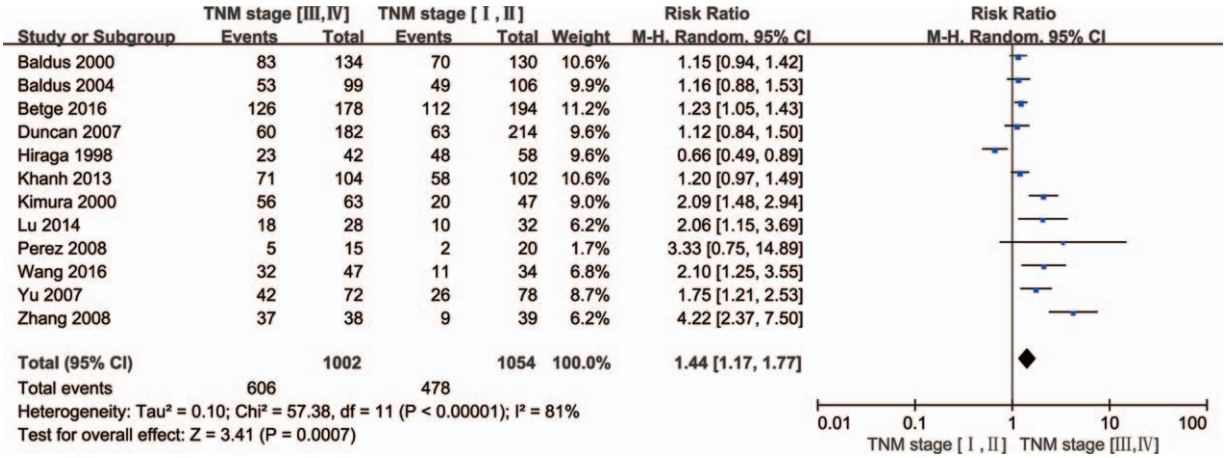

Figure 3. Forest plots of RRs for MUC1 expression and TNM stage in CRC. CRC = colorectal cancer, MUC1 = mucin 1, RRs = relative risks, TNM = tumor, node, and metastasis.

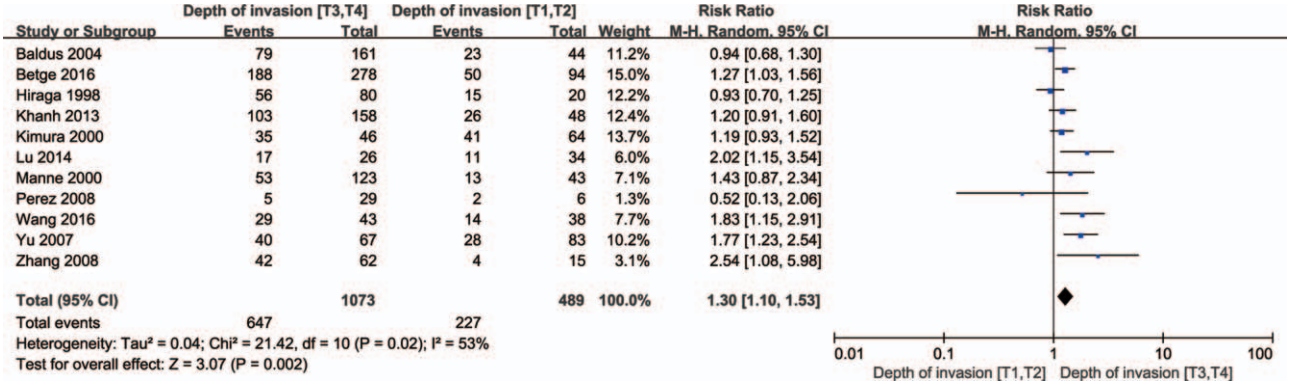

Figure 4. Forest plots of RRs for MUC1 expression and depth of invasion in CRC. CRC = colorectal cancer, MUC1 = mucin 1, RRs = relative risks.

3.5. Sensitivity analysis

Sensitivity analysis was applied to test the robustness of the results by omitting each single study. The results suggested no significant changes in the pooled HRs for OS (Fig. S10A, http://links.lww.com/MD/C854). However, for DFS/RFS (Fig. S10B, http://links.lww.com/MD/C854), the results are not reliable, probably because an article[72] uses antibodies that are different from other articles.[50,56,57] The data were robust and reasonable in the sensitivity analysis for clinicopathological status (Fig. S11, http://links.lww.com/MD/C854, S12, http://links.lww.com/MD/C854).

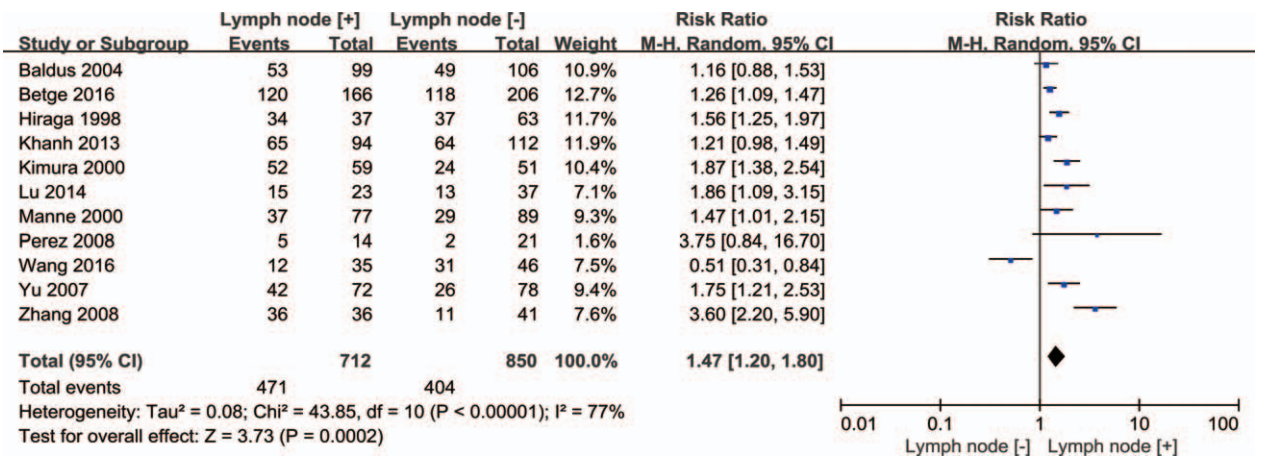

Figure 5. Forest plots of RRs for MUC1 expression and lymph node metastasis in CRC. CRC = colorectal cancer, MUC1 = mucin 1, RRs = relative risks.

Table 2

Meta-regression analysis for OS.

Covariates	Multivariable analysis		
	Coefficient	SE	*P* value
Year	−0.005	0.022	.823
Country	0.074	0.078	.368
Antibody	−0.026	0.124	.837
Cut-off of MUC1	0.02 0	0.159	.903

MUC1 = mucin 1, OS = overall survival.

3.6. Meta-regression analysis

Table 2 shows the results of a meta-regression analysis. None of the covariates listed including year ($P = .823$), country ($P = .368$), antibody ($P = .837$), and cut-off ($P = .903$) contributed to the heterogeneity in our study. Due to insufficient observations, meta-regression analysis for DFS/RFS and tumor size were not performed. In addition, none of the above covariates led to inconsistencies in the clinicopathological characteristics (Table, S2, http://links.lww.com/MD/C854).

4. Discussion

Evidence suggests that MUC1 is highly expressed in CRC tissues and MUC1 plays roles in the development and progression of CRC. However, its prognostic value in CRC is still inconclusive. Previous research has reported the prognostic significance of MUC1 in various human epithelial cancers, gastric cancer, and cholangiocarcinoma, but not in CRC.[73–75] Zeng et al[76] demonstrated a correlation between MUC1 expression and CRC metastasis; however, they did not study the prognostic value of MUC1 expression in CRC. This is the first comprehensive meta-analysis assessing and systematically reviewing the correlation of MUC1 expression with CRC prognosis and clinicopathological characteristics based on published studies.

The present meta-analysis showed that MUC1 expression in CRC tissue was strongly related to worse OS, and HR for OS was 1.51 (95% CI = 1.30–1.75, $P < .00001$). Furthermore, an elevated MUC1 expression level did not contribute to reduced DFS/RFS (HR = 1.51, 95% CI = 0.78–2.89, $P = .22$) compared with that in the lower MUC1 expression group. The possible mechanisms may be that MUC1, a ligand of cell adhesion molecules, induces circulating tumor cells (CTCs) to conglutinate at endothelial cells, and CTCs are then transported to distant sites to establish secondary tumors.[77] Furthermore, MUC1 can induce the expression of multiple growth factors that play roles in the survival and proliferation of tumor cells and induce the production of the proangiogenic factors that promote the formation of new blood vessels in tumor tissues.[78–83] In addition, MUC1 also promotes epithelial-mesenchymal transition (EMT) and cell invasion.[84] Thus, the above results and mechanisms indicate that MUC1 is a promising protein target in future clinical trials and can serve as a novel, valuable biomarker for predicting survival in CRC. To date, several anti-MUC1 monoclonal antibodies have entered into preclinical studies, including PankoMab-GEX, AS1402 antibody, BrevaRex, mAb-AR20.5, and muHMFG1 labeled with Yttrium-90.[85–89] However, a MUC1 antibody has not been marketed yet. However, the MUC1 expression level did not contribute to improved OS (HR = 1.51, 95% CI = 0.78–2.89, $P = .22$). The reason may be that the number of studies included is small. If we exclude studies[72] that affect stability, the results indicated that elevated MUC1 was strongly related to worse DFS/RFS.

As clinicopathological features are closely correlated with the prognosis of CRC patients, our study investigated the relationship between MUC1 expression and its features in CRC. Previous evidence supports that MUC1 expression is significantly associated with advanced TNM stage (III/IV) in CRC.[56–59] Likewise, some studies have reported that MUC1 expression is significantly and strongly correlated with advanced tumor grade, depth of invasion, and lymph node involvement.[59,66,67,69,90] In our meta-analysis, elevated MUC1 was associated with advanced TNM stage (RR = 1.44), depth of invasion (RR = 1.30), and lymph node involvement (RR = 1.42), but no significant association was found with other clinicopathological characteristics, including histological grade, gender, tumor size, tumor site, and mucinous component. According to TNM stage, advanced TNM stage, lymph node metastasis, and lymphatic invasion are predictors of poor prognosis in CRC. These studies also demonstrated that high expression of MUC1 indicates a poor prognosis in CRC.

In clinical work, high expression of MUC1 in colorectal tumor tissue may contribute to the diagnosis of CRC and help in the assessments of predicted survival and risk of recurrence. For patients with tumors overexpressing MUC1 in an early stage, it is worthwhile to perform a more detailed examination to find the existing small transition, especially for those without signs of metastasis or symptoms. Because CRC patients with high MUC1 expression have a higher risk of metastasis, the expression level of MUC1 is important for guiding the development of treatment plans. In addition, detection of MUC1 expression in CRC by immunohistochemical methods may be important for being able to determine a treatment strategy in clinical situations.

We acknowledge that there are some limitations in this study. First, the type of CRC, antibody, cut-off expression, detection method, and treatment regimen varied among included studies, which increased the heterogeneity and affected the stability of the results. Second, 16 studies were included for meta-analysis, and the case numbers in each were relatively small, which may cause bias due to variation. Third, some of the original articles did not provide HRs, which were then extracted from the Kaplan–Meier curves, potentially affecting the robustness of the results. Finally, because the current prognosis of patients with CRC is improved through regular treatment and follow-up, the role of MUC1 as a prognostic marker is weakened. Thus, more updated studies are required to confirm our findings.

Taken together, our findings indicate that high expression of MUC1 predicts a poor prognosis and survival outcome in CRC. Meanwhile, high expression of MUC1 correlates with TNM stage, depth of invasion, and lymph node metastasis, but not with histological grade, gender, tumor size, tumor site, and mucinous component. These findings indicate MUC1 expression is a promising prognostic factor for CRC and may serve as a novel, valuable biomarker of CRC.

Author contributions

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Funding acquisition: Lei Wang.
Investigation: Chao Li, Tao Liu, Libin Yin.
Methodology: Chao Li.
Project administration: Lei Wang.

Resources: Chao Li.
Software: Didi Zuo, Yuyang Lin.
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Validation: Chao Li, Libin Yin.
Visualization: Lei Wang.
Writing - original draft: Chao Li.
Writing - review & editing: Lei Wang.
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