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Prognostic Value of Mismatch Repair Genes for Patients With Colorectal Cancer: Meta-Analysis

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Abstract

DNA mismatch repair was proposed to play a pivotal role in the development and prognosis of colorectal cancer. However, the prognostic value of mismatch repair on colorectal cancer is still unknown. The PubMed, EMBASE, and Cochrane Central Register of Controlled Trials databases were searched. The articles about mismatch repair (including hMLH1, hMSH2, hMSH3, hMSH6, hPMSH1, and hPMSH2) deficiency for the prognosis of patients with colorectal cancer were included in the study. The hazard ratio and its 95% confidence interval were used to measure the impact of mismatch repair deficiency on survival time. Twenty-one articles were included. The combined hazard ratio for mismatch repair deficiency on overall survival was 0.59 (95% confidence interval: 0.50-0.69) and that on disease-free survival was 0.57 (95% confidence interval: 0.43-0.75). In subgroup analysis, there were a significant association between overall survival and mismatch repair deficiency in Asian studies (hazard ratio: 0.67; 95% confidence interval: 0.50-0.91) and Western studies (hazard ratio: 0.56; 95% confidence interval: 0.46-0.67). For disease-free survival, the hazard ratios in Asian studies and Western studies were 0.55 (95% confidence interval: 0.38-0.81) and 0.62 (95% confidence interval: 0.50-0.78), respectively. Our meta-analysis indicated that mismatch repair could be used to evaluate the prognosis of patients with colorectal cancer.

Keywords

DNA mismatch repair (MMR), prognosis, colorectal cancer, meta-analysis, overall survival, disease-free survival

Abbreviations

CI, confidence interval; CRC, colorectal cancer; DNA, deoxyribonucleic acid; DFS, disease-free survival; HR, hazard ratio; IHC, immunohistochemistry; MMR, mismatch repair; MSI, microsatellite instability; OS, overall survival; PCR, polymerase chain reaction; TS, thymidylate synthase.

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Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in males and the second in females, with an estimated 1.4 million cases and 693 900 deaths occurring in 2012.[1] Molecular markers for the biological behavior and prognosis of CRC were extensively studied; among these markers, DNA mismatch repair (MMR) was proposed to play a pivotal role in the development and prognosis of CRC.[2]

Approximately 10% to 20% of sporadic CRC is associated with impaired function of DNA MMR genes.[3] Mismatch repair

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genes encode corresponding enzymes that can recognize and repair mismatched base pairs during DNA replication. Deficient MMR leads to genetic instability and accounts for the accumulation of widespread alterations in the length of short repeated DNA sequences, known as microsatellite instability (MSI). The accelerating accumulation of gene mutations in proto-oncogenes and cancer suppressor genes because of aberrant MMR can affect the proliferation of normal cells and promote the development of carcinoma.[4-6] A meta-analysis by Guastadisegni, including 31 eligible studies reporting survival in 12 782 patients with CRC, showed that MSI predicted favorable prognosis, with both longer overall survival (OS) and disease-free survival (DFS).[7] However, the detection of MSI by polymerase chain reaction (PCR) in 5 highly monomorphic mononucleotidic microsatellite markers (BAT26, BAT25, NR21, NR24, NR27) is complex and costly, limiting its application in the clinic. Currently, different MMR genes (hMLH1, hMSH2, hMSH3, hMSH6, hPMSH1, and hPMSH2) have been identified to cause the development of MSI.[8] The hMLH1 and hMSH2 account for more than 90% of MSI development. Thus, their relationship with the development and prognosis of CRC has been extensively studied.[9-18] However, the results were controversial. Thus, the aim of this meta-analysis is to identify the association between deficient MMR and the prognosis of CRC.

Materials and Methods

Search Strategy

A meta-analysis was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[19] Two reviewers (JTH and XLC) independently searched the following databases from their inceptions to June 1st, 2017: PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials. The search terms included the following:

1. "colorectal cancer" OR "colon cancer" OR "rectal cancer"
2. "mismatch repair gene" OR "hMLH1" OR "hMSH2" OR "hMSH3" OR "hMSH6" OR "hPMSH1" OR "hPMSH2" OR MMR
3. "prognosis" OR "prognoses" OR "prognostic" OR "predictive" OR "biomarker" OR "marker" OR "survival" OR "survive" OR "Cox" OR "Logrank" OR "Kaplan-Meier"

The search was not limited by language. The potentially relevant studies were manually reviewed in the relevant systematic reviews and meta-analysis. The relevant studies were also obtained by searching Google scholar with the search terms "colorectal cancer, colon cancer, or rectal cancer," "mismatch repair gene," and "prognosis, predictive, or survive."

Inclusion Criteria

The inclusion criteria included the following: (1) patients who were diagnosed with primary CRC (including colon cancer, or rectal cancer) were included. Patients exhibiting different clinical stages, histological types, or treatment methods were all included; (2) the expression of MMR genes was measured using PCR, immunohistochemistry (IHC), or enzyme-linked immunosorbent assay in the CRC tissue; (3) the association between MMR with patient prognosis was investigated, and the hazard ratio (HR), its 95% confidence interval (CI), or the relevant information were provided; and (4) a full paper was published. When the same team reported several studies from the same patients, the most recent study was included. Studies published in the abstract were excluded.

Study Selection

The same studies from the different databases were identified. The titles and abstracts were read for eligibility by 2 of the 3 authors (DJZ, PRL, or LZC). The full texts of potentially eligible studies were retrieved and reviewed independently by 2 authors (HBL and DJZ). Any disagreements were recorded and resolved by consensus under the guidance of another author (XLC).

Data Collection

The data in the eligible studies were extracted by 2 authors (JTH and DJZ). The study information (the first author, the year of publication), study participants (the type of patients, gender, mean age, and sample size), the characteristics of treatment (surgery, chemotherapy, radiotherapy), the characteristics of MMR (gene subtype, test sample, test content, test method), and the prognostic outcomes of interest (OS, DFS, and/or relapse-free survival) were extracted. If the relevant data were not reported in the study, the item was recorded as "NR (not reported)."

Data Analysis

The MMR genes were classified as either "deficiency" (weak or negative) or "proficiency" (strong or positive). If the HRs and their 95% CI were reported explicitly in the study, the data were collected. If these data were not reported explicitly, they were calculated from the available numerical data or survival curves using the methods reported by Tierney *et al*.[20] The meta-analysis was conducted according to 2 types of indexes, OS, and DFS.

To measure the impact of deficient MMR on survival time, the combined HR and its 95% CI were calculated. The heterogeneity of the individual HR was calculated with a χ^2 test. The heterogeneity test with the inconsistency index (I^2) statistic and Q statistic was performed. For the Q statistic, a P value of less than 0.1 was considered representative of statistically significant heterogeneity. The I^2 is the proportion of total variation contributed by between-study variation. An I^2 index of approximately 25% was considered to demonstrate low levels of

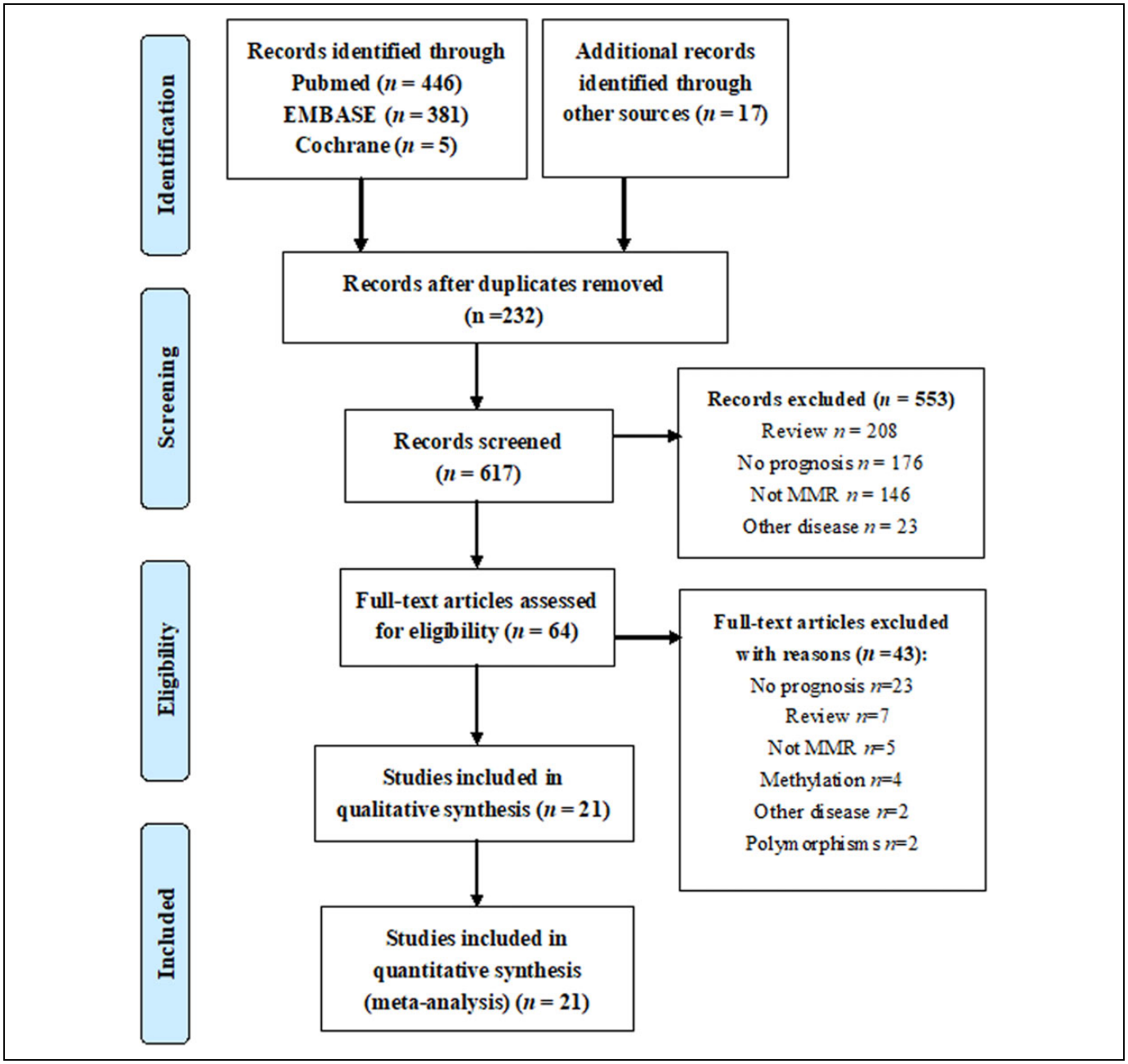

Figure 1. Flow chart of the search strategy.

heterogeneity, 50% was considered medium, and 75% was considered high. The sensitivity analysis were conducted by reestimating the pooled HR and omitting each study in turn to investigate the influence of each individual study on the overall meta-analysis summary estimate. Furthermore, subgroup analysis based on geographical regions (Asia, West [Europe and America]), different subtypes of gene (MMR, hMSH2, hMLH1), and different methods for detection of MMR (IHC, PCR) were performed to clarify the source of heterogeneity. In addition, the heterogeneity of the effect was discovered using meta-regression, including country, type of patient, sample size ($\leq$200, and >200), test content, analysis method, subtype of gene, and therapy methods as covariates. Heterogeneity was defined as a $P \leq .05$. An observed HR >1 implied a worse prognosis in the high expression of MMR compared to the low expression of MMR. Publication bias and small study effects were assessed by Begg test and Egger test, with $P < .05$ considered to show significant publication bias. All of the calculations were performed by STATA version 12.0.

Results

The Characteristics of the Studies

A total of 849 studies met the inclusion criteria (Figure 1), of which 232 studies were excluded for duplicates, and 553 studies

Table 1. The Main Characteristics of the Included Studies.

Author	Year of Publication	Country	Time	Patients	Sample Size	Male	Mean of Age (range)	Stage	Surgery Treatment	Chemotherapy	Radiotherapy	Median Follow-Up Month (Range)
Bendardaf R	2008	Finland	1996-2003	CRC	73	46	57.9 (NR)	II-IV	Partial	All	No patient	32.6 (NR)
Cawkwell L	1999	UK	NR	CRC	101	NR	>50 (NR)	NR	NR	NR	NR	60.0 (NR)
Huh JW	2016	Korea	NR	Rectal cancer	209	136	56 (27-81)	II, III	All	All	All	44 (2-87)
Ide T	2008	Japan	1999-2005	CRC	94	60	68.2 (40-87)	I-IV	All	All	NR	26.1 (NR)
Jansson A	2003	Sweden	1972-1996	CRC	301	NR	70 (34-94)	I-IV	All	NR	NR	NR (NR)
Jensen LH	2007	Denmark	NR	CRC	28	13	61 (49-74)	III-IV	NR	All	NR	12.2 (6.7-20.2)
Jensen SA	2009	Denmark	1996-2003	CRC	340	159	NR (NR)	II-IV	NR	All	NR	6.1 (4.1-11.3)
Langner E	2010	Poland	NR	CRC	75	45	NR (NR)	I-IV	All	NR	NR	NR (NR)
Lanza G	2006	Italy	1986-1995	CRC	718	359	65 (27-85)	II, III	Partial	Most	Partial	90.5 (63-144)
Ma J	2015	China	2008-2011	Colon cancer	184	111	NR (NR)	NR	NR	All	NR	17.6 (7-36)
Park JW	2010	Korea	2001-2003	CRC	318	191	60.5 (27-87)	I-IV	All	Partial	NR	24.0 (NR)
Pu C	2015	China	2005-2008	CRC	327	201	NR (NR)	I-IV	NR	Partial	NR	24.0 (NR)
Rau B	2003	Germany	1993-1999	CRC	66	41	59 (39-74)	NR	NR	All	All	39.3 (11.3-83.4)
Russo A	2009	Italy	NR	CRC	526	288	48 (20-88)	I-IV	NR	NR	NR	64 (6-383)
Sinicrope FA	2006	USA	NR	Colon cancer	528	274	NR (NR)	II, III	NR	All	NR	NR (NR)
Smyth EF	2004	UK	1995-1998	Colon cancer	111	NR	72 (3990)	I-IV	All	NR	NR	NR (NR)
Sun Z	2014	China	2009-2012	CRC	404	233	NR (NR)	I-IV	NR	NR	NR	>36 (NR)
Wang H	2014	China	2005-2008	CRC	327	201	58.7 (2581)	I-IV	NR	NR	NR	60.0 (NR)
Wang JB	2016	China	2011-2012	Colon cancer	90	58	NR (NR)	II, III	All	Partial	NR	27 (5-35)
Wang Y	2014	China	NR	CRC	433	254	58.6 (2482)	I-IV	All	Partial	Partial	52 (1-87)
Wu HW	2013	China	2004-2006	CRC	87	56	59 (35-82)	I-III	All	NR	NR	60.0 (NR)

Abbreviations: CRC, colorectal cancer; NR, not report.

Table 2. The Gene and Results of the Included Studies.

Author	Subtypes of Gene	Test Sample	Test Content	Test Method	Analysis Method	Survival Type
Bendardaf R	MMR	Tissue	Protein	IHC	Univariate	DFS
Cawkwell L	MMR	Tissue	Protein	IHC	Univariate	OS
Huh JW	hMSH2	Tissue	Protein	IHC	Multivariate	DFS
Ide T	hMLH1	Tissue	mRNA	PCR	Univariate	DFS
Jansson A	hMSH2	Tissue	Protein	IHC	Univariate	OS
Jensen LH	hMSH2	Tissue	RNA	PCR	Univariate	OS
Jensen SA	MMR	Tissue	Protein	IHC	Multivariate	OS, RFS
Langner E	hMSH2	Tissue	RNA	PCR	Univariate	OS
Lanza G	MMR	Tissue	Protein	IHC	Multivariate	OS
Ma J	MMR	Tissue	Protein	IHC	Multivariate	OS, DFS
Park JW	MMR	Tissue	Protein	IHC	Multivariate	OS
Pu C	hMLH1	Tissue	Protein	IHC	Multivariate	DFS
Rau B	hMSH2	Tissue	Protein	IHC	Univariate	OS, DFS
Russo A	MMR	Blood	mRNA	PCR	Multivariate	OS
Sinicrope FA	MMR	Tissue	Protein	IHC	Univariate	OS, DFS
Smyth EF	hMLH1	Tissue	Protein	IHC	Multivariate	OS
Sun Z	MMR	Tissue	Protein	IHC	Univariate	DFS
Wang H	hMSH2	Tissue	Protein	IHC	Multivariate	OS
Wang JB	MMR*	Tissue	Protein	IHC	Univariate	OS
Wang Y	MMR	Blood	DNA	PCR	Multivariate	OS
Wu HW	hMSH2	Tissue	Protein	IHC	Multivariate	DFS

Abbreviations: DFS, disease-free survival; DNA, deoxyribonucleic acid; IHC, immunohistochemistry; MMR, contain hMLH1, hMSH2; MMR*, contain hMLH1, hMSH2, hMSH6, and hPMS2; mRNA, messenger RNA; Multivariate, multivariate survival analysis; OS, overall survival; PCR, polymerase chain reaction; RFS, recurrence-free survival (which was used as DFS); RNA, ribonucleic acid; Univariate, univariate survival analysis.

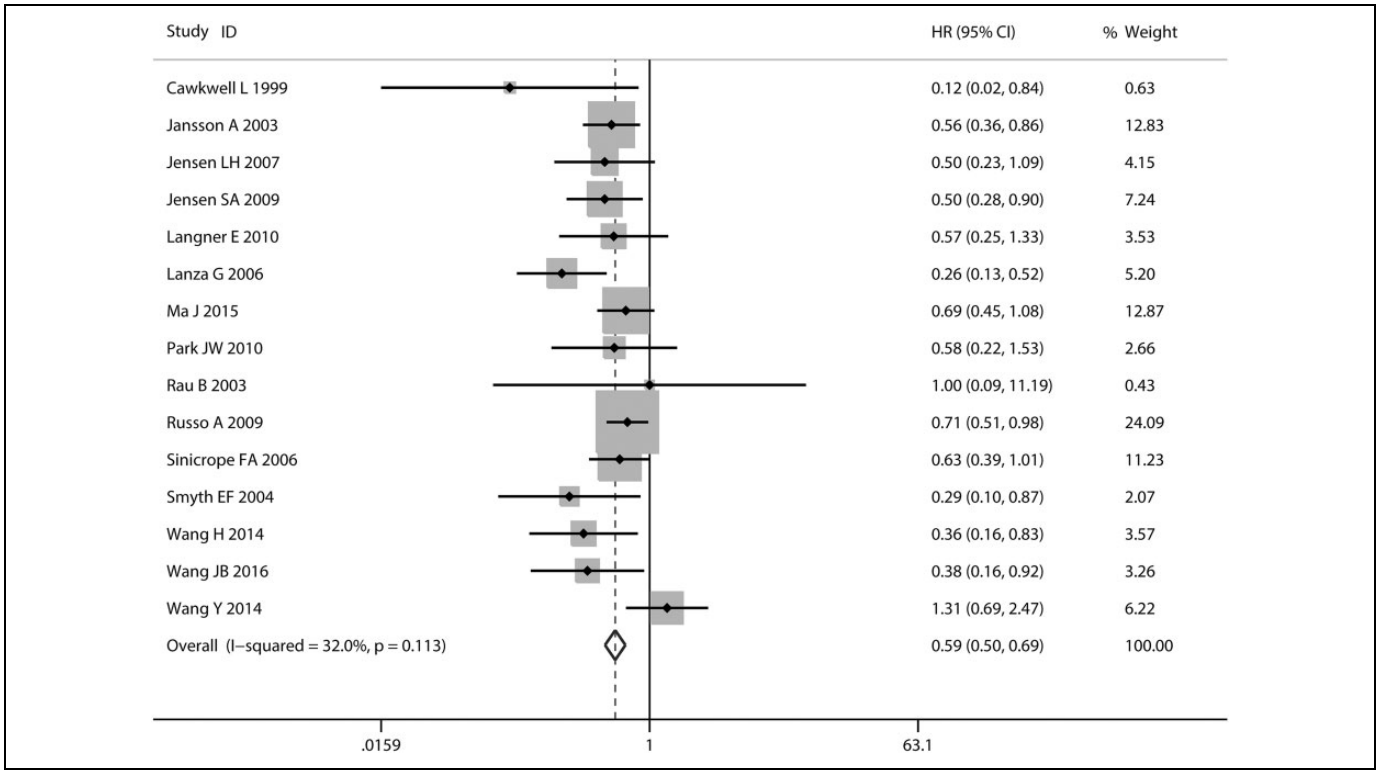

Figure 2. Forest plot for the association between MMR expression and OS in CRC.
CRC indicates colorectal cancer; MMR, mismatch repair; OS, overall survival.

were excluded by reviewing the titles and abstracts. The full texts of the remaining 64 studies were obtained for review. Eventually, 21 studies were included in the meta-analysis.[9-18,21-31]

The characteristics of the included studies are shown in Table 1. Twenty-one studies contained a total of 5340 patients with CRC. All the studies were published from 1999 to 2016.

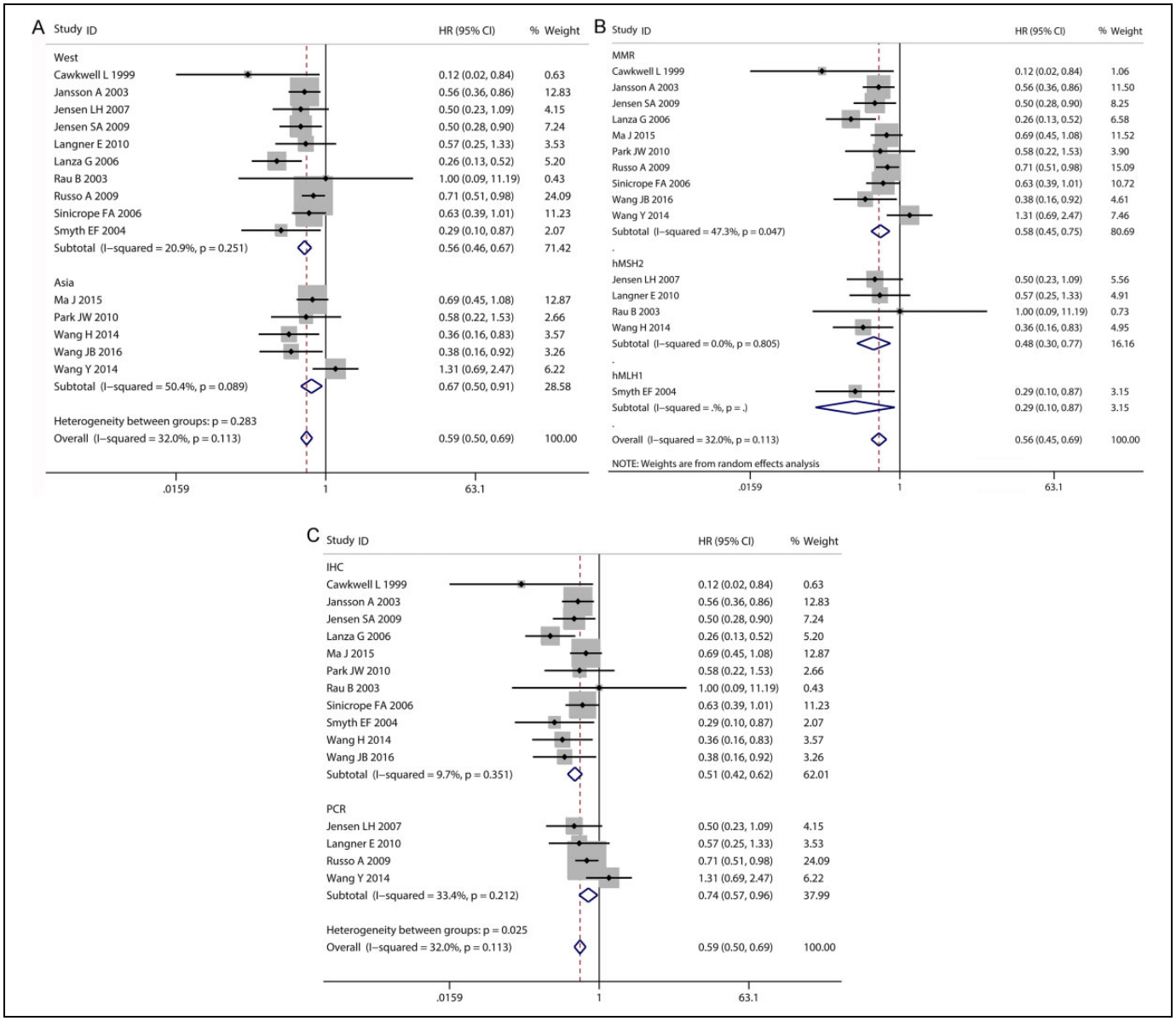

Figure 3. Subgroup analysis for the association between MMR expression and OS in CRC. A, different geographical regions (Asia, west); (B) different subtypes of gene (MMR, hMSH2, hMLH1); (C) different methods for detection of MMR (immunohistochemistry [IHC], polymerase chain reaction [PCR]). CRC indicates colorectal cancer; MMR, mismatch repair; OS, overall survival.

Of the 21 studies, 15 studies reported OS and 10 reported DFS (Table 2).

Meta-Analysis for OS

Fifteen studies of MMR for OS in patients with CRC were included in the meta-analysis. There was no significant heterogeneity across 15 studies with OS ($I^2 = 32.0\%$, $P = 0.113$; Figure 2). The combined HR of the 15 studies was 0.59 (95% CI: 0.50-0.69; Figure 2). Mismatch ratio was significantly associated with improved prognosis in Asian studies (HR: 0.67; 95% CI: 0.50-0.91; Figure 3) and western studies (HR: 0.56; 95% CI: 0.46-0.67; Figure 3). The HR was 0.58 (95% CI: 0.45-0.75) for MMR as a marker in 10 studies, 0.29 (95% CI: 0.10-0.87) for hMLH1 as a marker in one study, and 0.48 (95% CI: 0.30-0.77) for hMSH2 as a marker in 4 studies (Table 3; Figure 3). When the subgroups were analyzed based on the test method, the combined HRs for IHC and PCR were 0.51 (95% CI: 0.42-0.62) and 0.74 (95% CI: 0.57-0.96), respectively (Figure 3).

Meta-Analysis for DFS

In a pooled analysis of 10 DFS studies, deficient MMR was associated with a better prognosis for CRC (HR: 0.62; 95% CI: 0.44-0.88; Figure 4). There was significant heterogeneity across 10 studies with DFS ($I^2 = 66.5\%$, $P = .001$). A meta-regression was performed to explore the source of

Table 3. The Results of the Meta-Analysis.

	Number of Studies	Patients	HR (95% CI)	Heterogeneity (I^2, P)
Overall survival				
All	15	4146	0.59 (0.50-0.69)	32.0%, 0.113
Asian	5	1352	0.67 (0.50-0.91)	50.4%, 0.089
Western	10	2794	0.56 (0.46-0.67)	20.9%, 0.251
Gene				
MMR	10	3539	0.58 (0.45-0.75)[a]	47.3%, 0.047
hMSH2	4	496	0.48 (0.30-0.77)	0.0%, 0.805
hMLH1	1	111	0.29 (0.10-0.87)	NR
Test method				
IHC	11	3084	0.51 (0.42-0.62)	9.7%, 0.351
PCR	4	1062	0.74 (0.57-0.96)	33.4%, 0.212
Disease-free survival				
All	10	2312	0.62 (0.44-0.88)	66.5%, 0.001
All[b]	9	2239	0.57 (0.43-0.75)	48.0%, 0.052
Asian	6	1305	0.62 (0.50-0.78)[a]	61.9%, 0.022
Western	3	934	0.55 (0.38-0.81)	0.0%, 0.373
Gene				
MMR	4	1456	0.61 (0.47-0.79)	0.0%, 0.493
hMLH1	2	421	0.32 (0.17-0.58)[a]	79.2%, 0.028
hMSH2	3	362	0.72 (0.52-1.00)	25.5%, 0.261
Test method				
IHC	8	2145	0.62 (0.51-0.76)	5.3%, 0.389
PCR	1	94	0.06 (0.01-0.30)	NR

Abbreviations: IHC, immunohistochemistry; NR: not report; MMR, mismatch repair; PCR, polymerase chain reaction.
[a]Results from random-effect model.
[b]Bendardaf study was excluded, which was also excluded in subgroup analysis.

heterogeneity for DFS. The results showed that all the variables were not related with the heterogeneity (Table 4). The tested content was nearly significant ($P = .077$). In addition, Bendardaf study included 73 patients, and thymidylate synthase (TS) and MMR expressions were assessed for each patient.[27] Its HR was calculated by comparing 18 patients with both high TS and MMR expression with 27 patients with both low TS and MMR, while other patients with low MMR and high TS or high MMR and low TS were excluded. This may result in significant heterogeneity between Bendardaf study and other studies ($P = .001$). Thus, Bendardaf study was excluded in subgroup analysis.

The combined HRs for studies without Bendardaf study were 0.57 (95% CI: 0.50-0.73; $I^2 = 48.0\%$, $P = .052$). The HRs of deficient MMR on DFS in Asian studies or western studies were 0.62 (95% CI: 0.50-0.78; Figure 5) and 0.55 (95% CI: 0.38-0.81; Figure 5). The HR was 0.61 (95% CI: 0.47-0.79) for MMR as a marker in 5 studies, 0.32 (95% CI: 0.17-0.58) for hMLH1 as a marker in 2 studies, and 0.72 (95% CI: 0.52-1.00) for hMSH2 as a marker in 3 studies (Table 3; Figure 5). When the subgroups were analyzed based on the test method, the combined HRs for IHC and PCR were 0.62 (95% CI: 0.51-0.76) and 0.06 (95% CI: 0.01-0.30), respectively (Figure 5).

The publication bias was not significant (OS, $P = .113$; DFS, $P = .210$). However, one study was out of the reference line in the DFS group indicated that there might be publication bias for DFS (Figure 6).

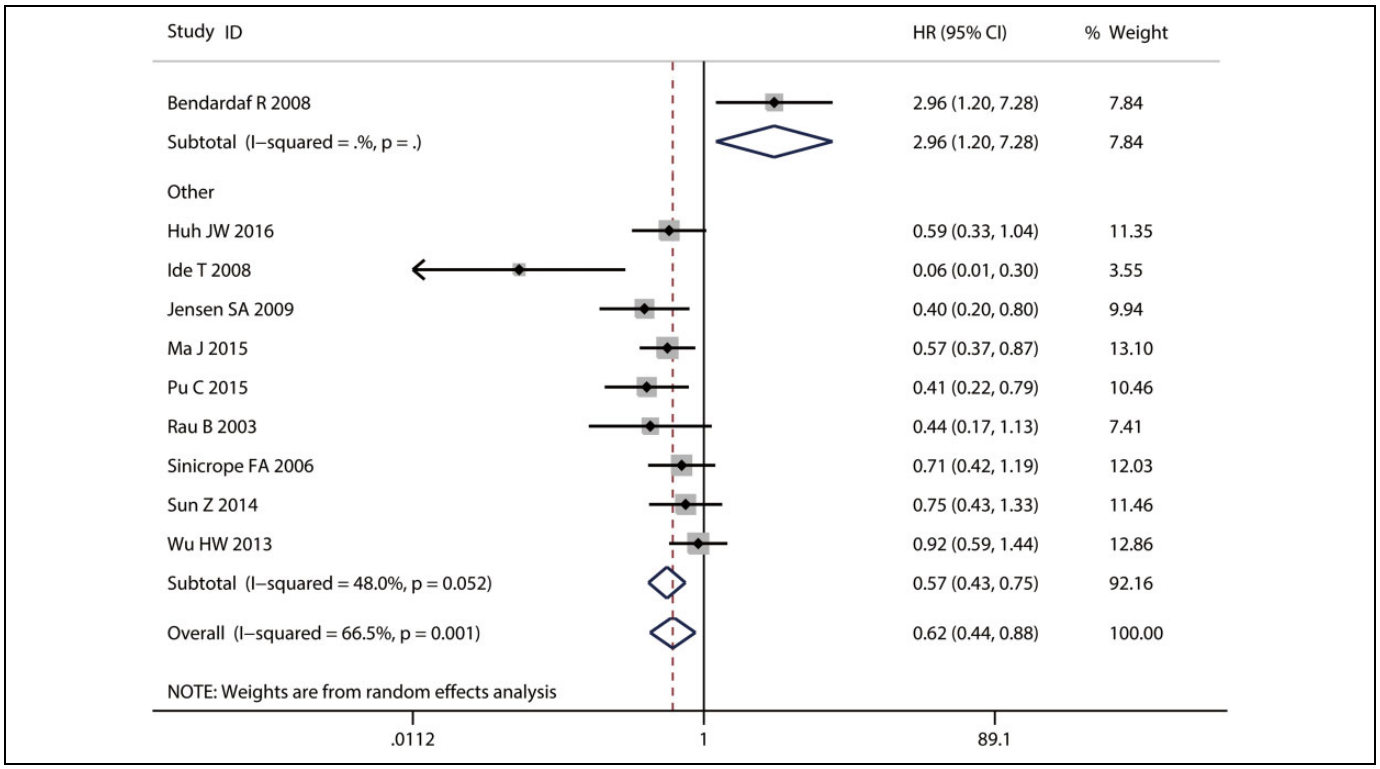

Figure 4. Forest plot for the association between MMR expression and DFS in CRC. CRC indicates colorectal cancer; DFS, disease-free survival; MMR; mismatch repair.

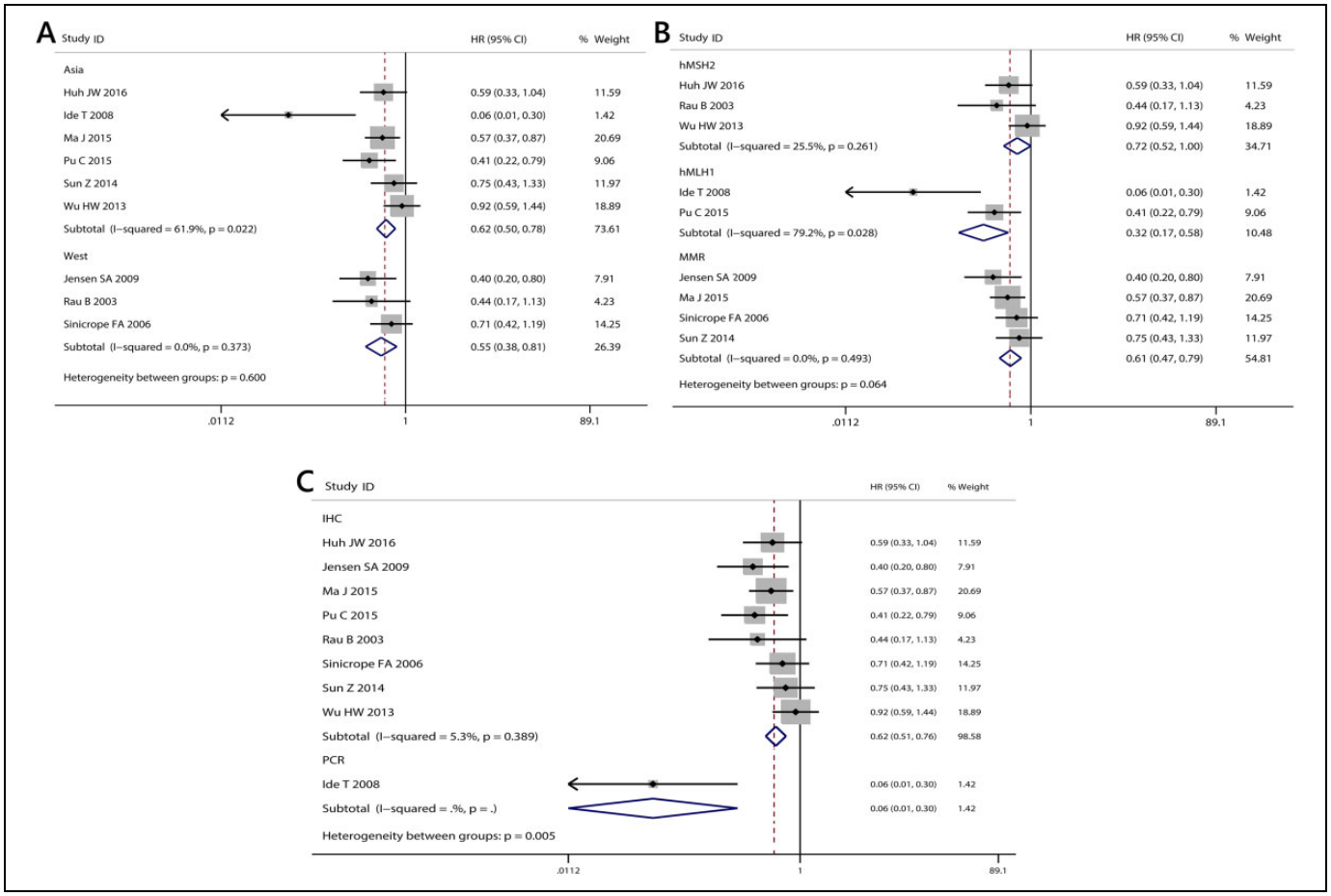

Figure 5. Subgroup analysis for the association between MMR expression and DFS in CRC. A, different geographical regions (Asia, west); (B) different subtypes of gene (MMR, hMSH2, hMLH1); (C) different methods for detection of MMR (immunohistochemistry [IHC], polymerase chain reaction [PCR]). CRC indicates colorectal cancer; DFS, disease-free survival; MMR; mismatch repair.

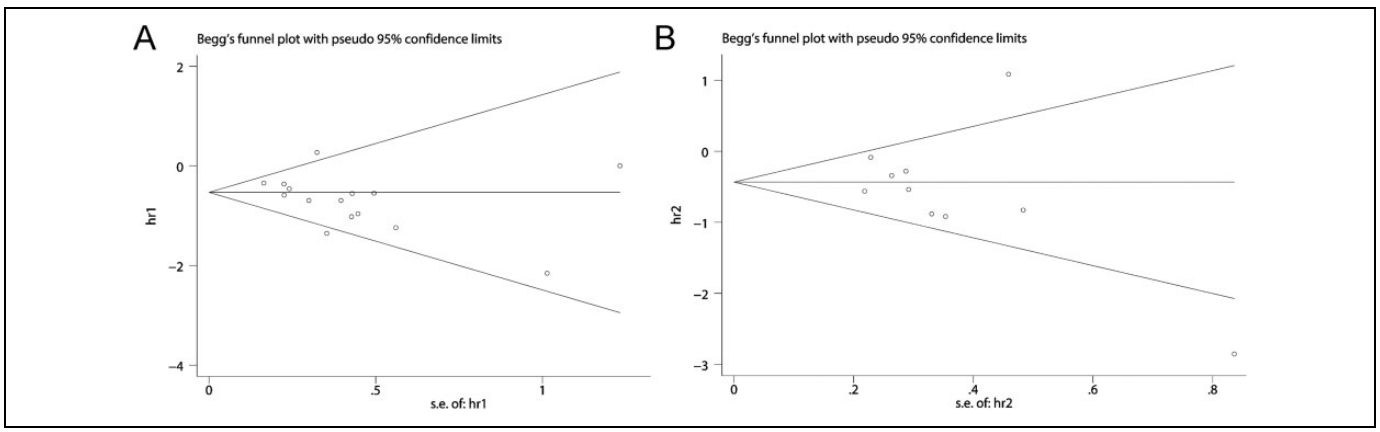

Figure 6. Begg funnel plot (A: OS, $P = .113$; B: DFS, $P = .210$). DFS indicates disease-free survival; OS, overall survival.

Discussion

Our pooled results from all the eligible studies showed that the HR was 0.59 for OS and 0.62 for DFS, with all showing statistically significant associations between MMR and CRC. The results indicated that deficient MMR was associated with better OS and DFS in the patients with CRC. Meanwhile, subgroup analysis of the different regions (Western and Asia) MMR showed consistent results. In addition, no obvious publication bias was determined by Begg test. These analyses enhanced the reliability of this meta-analysis.

Table 4. The results of meta-regression for DFS.

	Coefficient	95% CI	*P*
Patients	−0.149	(−1.196 to 0.898)	.681
Country	−0.124	(−1.812 to 1.563)	.830
Sample size	−0.723	(−2.387 to 0.940)	.260
Subtypes of gene	−0.220	(−1.140 to 0.699)	.501
Test content	3.157	(−0.626 to 6.940)	.077
Analysis method	−0.501	(−2.196 to 1.195)	.417

Abbreviation: CI, confidence interval.

Mismatch repairs are a group of enzymes that can recognize and repair mismatched base pairs during DNA replication, including hMLH1, hMSH2, hMSH3, hMSH6, hPMSH1, and hPMSH2, which are considered critical proteins for the formation of MSI.[9-18,21-31] Mismatch repairs, along with MSI, are proposed to be useful markers in CRC. Approximately 90% hereditary nonpolyposis CRC and 10% to 20% of sporadic CRC demonstrate MSI.[32] The vast majority of CRC with MSI is caused by aberrant hMLH1 expression (70% to 95%), while others primarily result from the inactivation of hMSH2 and hMSH6. Additionally, in sporadic CRC, approximately 95% deficient hMLH1 expression is due to hypermethylation of the hMLH1 promoter.[33,34]

In this meta-analysis, some studies defined negative hMLH1 or hMSH2 expression as MMR deficiency, and they demonstrated a significantly longer OS for patients with deficient MMR.[7,14,16,17,23,28,35] Some studies defined deficient hMLH1 (or hMSH2) expression as deficient MMR and demonstrated the same result for OS. [11-13,24,26] Four studies showed longer DFS in the patients with CRC with deficient hMLH1 or hMSH2.[14-16,28] However, Bendardaf *et al* suggested that deficient MMR demonstrated a shorter DFS. This inconsistency could be explained by combining with other genes (TS) and distinctive clinic features indicating that CRC with deficient MMR is apt to display marked peritumoral and intratumoral lymphocytic infiltration.[36-39] To summarize, these results suggest that detection of both hMLH1 and hMSH2 could be used to identify most MMR and could be useful methods to evaluate OS for patients with CRC. However, further studies are required to confirm the relationship between MMR and DFS because of significant heterogeneity.

The prognosis of CRC is strongly associated with tumor stage, tumor site, and treatment. MMR-deficient CRC exhibit distinct clinical and pathological features, including proximal location and early tumor stage.[38,40] Further, Scarpa *et al* reported that CRC with MMR deficiency exhibited a higher CD80 expression and CD8+ and Th1 T-cell infiltration.[41] *In vitro* silencing of hMSH2, hMLH1, and hMSH6 significantly increased the CD80+ cell rate. These results suggest an enhanced immune surveillance mechanism in the presence of MMR deficiency,[41] which may explain the improved OS and DFS for patients with CRC with MMR deficiency. These reports might explain our observations that deficient MMR was associated with better prognosis of patients with CRC. However, MMR-deficient CRC shows poor differentiation and mucinous histology, and strong preclinical and clinical evidence suggests a possible resistance to 5-FU in these tumors. Thus, further studies are required to explore the underlying mechanism of MMR deficiency and better CRC prognosis.

There are 2 broadly accepted methods for aberrant MMR detection including MSI testing by PCR and MMR protein expression analysis by IHC. It has been shown that the results of MMR protein expression by IHC are concordant with DNA-based MSI testing, with a favorable sensitivity and a dramatic specificity.[42] Immunohistochemistry is commonly used as an alternative test when a molecular laboratory is not available.[43] In addition, IHC for MMR is cost-effective and simple, which can determine the specific protein of MMR.[43] In this meta-analysis, most studies adopted the methods of IHC for the detection of aberrant MMR. The subgroup of IHC demonstrated that deficient MMR was a protective factor for the prognosis of CRC, which could predict a longer OS and DFS. As a result, the detection of aberrant MMR by IHC could be a promising method to assess the prognosis of CRC.

There were several limitations in our study. First, the detection of MMR is different among the studies; however, most studies adopted IHC to determine the expression of MMR, and the results were consistent. Second, the definition of aberrant MMR is inconsistent; some studies considered aberrant MMR as negative MMR expression, some selected negative hMLH1 expression alone or negative hMSH2 expression alone, and 2 studies selected negative expression of hMLH1, hMSH2, hMSH6, and hPMS2. This may result in significant heterogeneity among these studies. Third, there is significant heterogeneity among the DFS studies. Although we investigated the influence of each individual study on the overall estimate and conducted a meta-regression and subgroup analysis according to geographical regions and different detection methods, the heterogeneity remained significant in some subgroup analysis and could not be clearly classified. Fourth, some studies did not mention certain vital data, especially the follow-up information, such as studies by Langner E, Jansson A, and Smyth EF, which may influence the reliability of the statistical analysis.

Conclusion

In summary, our pooled results indicated that deficient MMR was associated with a better OS and DFS for the CRC patients. However, large well-designed studies with a uniform method of MMR detection are required to confirm these results.

Authors' Note

Jiang-tao Hou and Li-na Zhao equally contributed to the work. The study was approved by the ethics committees of Guangzhou University of Chinese Medicine.

Declaration of Conflicting Interests

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