Excision Repair Cross-complementation Group 1 is a Prognostic Biomarker in Patients with Colorectal Cancer Receiving Chemotherapy

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Abstract

Background: Conflicting results about the association between expression level of excision repair cross-complementation group 1 (ERCC1) and clinical outcome in patients with colorectal cancer (CRC) receiving chemotherapy have been reported. Thus, we searched the available articles and performed the meta-analysis to elucidate the prognostic role of ERCC1 expression in patients with CRC.

Methods: A thorough literature search using PubMed (Medline), Embase, Cochrane Library, Web of Science databases, and Chinese Science Citation Database was conducted to obtain the relevant studies. Pooled hazard ratios (*HR*s) or odds ratios (*OR*s) with 95% confidence intervals (*CI*s) were calculated to estimate the results.

Results: A total of 11 studies were finally enrolled in this meta-analysis. Compared with patients with lower ERCC1 expression, patients with higher ERCC1 expression tended to have unfavorable overall survival (OS) (*HR* = 2.325, 95% *CI*: 1.720–3.143, *P* < 0.001), progression-free survival (PFS) (*HR* = 1.917, 95% *CI*: 1.366–2.691, *P* < 0.001) and poor response to chemotherapy (*OR* = 0.491, 95% *CI*: 0.243–0.990, *P* = 0.047). Subgroup analyses by treatment setting, ethnicity, *HR* extraction, detection methods, survival analysis, and study design demonstrated that our results were robust.

Conclusions: ERCC1 expression may be taken as an effective prognostic factor predicting the response to chemotherapy, OS, and PFS. Further studies with better study design and longer follow-up are warranted in order to gain a deeper understanding of ERCC1's prognostic value.

Key words: Colorectal Cancer; Excision Repair Cross-complementation Group 1; Prognosis

Introduction

Colorectal cancer (CRC) ranks as the third most common cancer and the third most killing cancer worldwide.[1] It is estimated that around 608,000 deaths from CRC worldwide, accounting for 8% of global cancer-related mortalities.[2] In the past decades, the dramatic development of surgical technology, chemotherapy, radiotherapy, and molecular targeted therapy, along with the widespread notion of multidisciplinary team, have momentously upgraded the clinical management and ameliorated the patients' prognosis. Surgical resection remains to be the potentially curative option for CRC, but postoperative tumor relapse and distal metastases greatly undermine the

long-term survival outcome. What is more, the majority of patients with CRC are not eligible for surgical operation at their initial diagnosis due to the asymptomatic nature of the disease. Currently, the treatment toward patients with CRC

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largely depends on the anatomical index-based tumor node metastasis (TNM) stage. Nevertheless, even at the same TNM stage, patients may exhibit observable variation in clinical outcome and response rate (RR) to treatment partially due to the marginal factors evading from the ongoing staging system.[3] Therefore, it is urgent to figure out the molecular markers those help us to stratify the patients according to the clinical prognosis as well as sensitivity to chemotherapy in order to adjust the management strategy toward them.

Excision repair cross-complementation group 1 (ERCC1) is widely recognized as a powerful component of nucleotide excision repair (NER) pathway, which not only involves the repair of interstrand cross-links in the DNA but also involves the recognition and remove of cytotoxic agents like platinum.[4] There are conflicting opinions toward the impaction of elevated ERCC1 expression on tumor progression. The tumor suppression effect of platinum agents as oxaliplatin mainly hinges on the platinum-DNA adducts secondary to their binding to cellular DNA, which can trigger cell destruction. Repair of DNA damage and removal of the DNA adducts by ERCC1 transmitted NER pathway are recognized as one of the mechanisms explaining cellular resistance to platinum agents;[5] meanwhile, some authors believed that the increased removal of bulky DNA adducts, which can also be produced by the other detrimental carcinogenic factors, are beneficial for the genome stability and cancer prevention.[6] The relationships between ERCC1 expression and clinical outcome have been explored in various kinds of malignant cancers including gastric cancer,[7] ovarian cancer,[8] and lung cancer.[9] For patients with CRC, the definite prognostic value of ERCC1 expression has not been established yet. Some authors suggested that increased expression of ERCC1 predicted inferior RRs to chemotherapy and survival outcome;[10] while some authors did not conclude any significant association between ERCC1 expression level and clinical prognosis.[11] In this setting, we felt it is essential to perform a systematic meta-analysis involving the relevant available articles to unveil the prognostic value of ERCC1 in patients with CRC.

METHODS

Literature research

A systematic literature search was performed using PubMed (Medline), Embase, Cochrane Library, Web of Science databases, and Chinese Science Citation Database for all years up to September 2015. Terms used in our search included: "ERCC1" (e.g., "ERCC-1," "excision repair cross complementing group 1", "excision repair cross complementing group-1"), "prognosis" (e.g., "outcome," "survival," "mortality," "recurrence"), and "CRC" (e.g., "colorectal cancer," "colon cancer," "rectal cancer"). The literature should be written in English or Chinese. In addition, the reference lists were carefully screened to identify as more related articles as possible.

Study inclusion/exclusion criteria

All candidate articles were scrutinized by two independent reviewers (Li MX and Bi XY) with the following criteria: (1) the diagnosis of CRC was made based on pathological examination; (2) ERCC1 expression was measured in the tumor samples; (3) correlation of ERCC1 expression level with survival outcomes as overall survival/progression free survival (OS/PFS) or response to chemotherapy was reported. The hazard ratios (*HR*s) or odds ratios (*OR*s) with the respective 95% confidence interval (*CI*) were either directly reported or could be reconstructed by the other available data[12] or figures in the essay;[13] (4) the study population received chemotherapy as the main treatment, which was defined as that over 70% of the studied patients received chemotherapy; (5) for studies with overlapping study population and data sets, only the most informative one was included. Any divergences were addressed by discussion.

Exclusion criteria were defined as: (1) abstracts, letters, editorials, expert opinions, reviews, case reports, case series <5 cases, meta-analyses; (2) articles without sufficient published data for determining an estimate of *HR* (*OR*) and a *CI*; (3) literature without the cut-off value defining "elevated ERCC1;" (4) Not human-based research.

Data extraction

The extracted data included: (1) first author's name, year of publication, country (region) of the population studied, patients' age, sample size, gender, treatment setting, follow-up period, and detection methods; (2) survival data including OS and PFS; (3) cut-off value defining "elevated ERCC1" and number of positive/high ERCC1 expression. OS was defined as the interval between the medical treatment and the death of patients or the last follow-up. PFS was calculated from the date of treatment until the detection of the recurrence tumor or death from any cause.

Quality assessment of primary studies

The quality of the retrieved studies was gauged by the Newcastle–Ottawa Quality Assessment Scale (NOS) [Supplementary Table 1]. NOS scores of ≥6 indicated high quality. Two reviewers (Li MX and Bi XY) independently carried out the assessment. The consensus was finally reached through discussion when discrepancy occurred.

Statistical analysis

The *HR*s and 95% *CI*s were directly retrieved from the essays or were synthesized indirectly from available statistics and/or figure plots in the articles by methods reported by Parmar *et al*.[12] and Tierney *et al*.[13] If several estimates were reported for the same value, the most persuading one was favored (multivariate analysis was superior to univariate analysis. And the latter one outweighed unadjusted Kaplan–Meier analysis).

A test of the heterogeneity of the included trials was undertaken using the Cochrane's Q statistic. $I^2 > 50\%$ referred to severe heterogeneity. The random-effects (DerSimonian–Laird method) models were adopted in the presence of sever interstudy

heterogeneity ($I^2 > 50\%$); otherwise, the fixed-effect model was applied. All statistical tests were two-sided, and the significance level was set at 5%. The subgroup analyses stratified by treatment setting (adjuvant chemotherapy [ACT] vs. palliative chemotherapy trial [PCT]), ethnicity (Asians vs. Caucasians), sample size (≥100 vs. <100), *HR* extraction (only in the analysis of OS and PFS, direct vs. indirect extraction), detection methods (immunohistochemistry [IHC] vs. polymerase chain reaction [PCR]), survival analysis (univariate analysis vs. multivariate analysis), and study design (prospective vs. retrospective) were performed. Egger's bias test was carried out to evaluate the publication bias. All analyses were performed using STATA statistical software package version 12.0 (STATA Corp., College Station, Texas, USA).

RESULTS

Description of the included studies

A total of 87 articles were identified in our initial literature search. After further evaluation of the primary identified articles, 11 articles[10,11,14-22] with sample sizes ranging from 50 to 895 patients were included in our final meta-analysis. The flowchart of literature selection is illustrated in Figure 1. For the study evaluating patients with gastrointestinal cancer by Uchida *et al.*,[14] 88 of the 91 (96.7%) enrolled patients were diagnosed as CRC, thus we finally admitted it into our further analysis. Nine of the included studies were English written articles, and 2 were published in Chinese. Tumor response to chemotherapy was evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) criteria[23] in 2 studies, by WHO criteria in 1 study, and by the specific criteria by the authors themselves in 3 studies. Expression of ERCC1 was assessed by IHC in 6 studies and by PCR in 5 studies. Coincidently, expression of ERCC1 in all of the studies from the Caucasian region was examined by PCR; while expression of ERCC1 in all of the trials performed in Asian region were assessed by IHC. Nine of the 11 included studies earned a NOS score ≥6. The basic information of the included studies was summarized in Table 1.
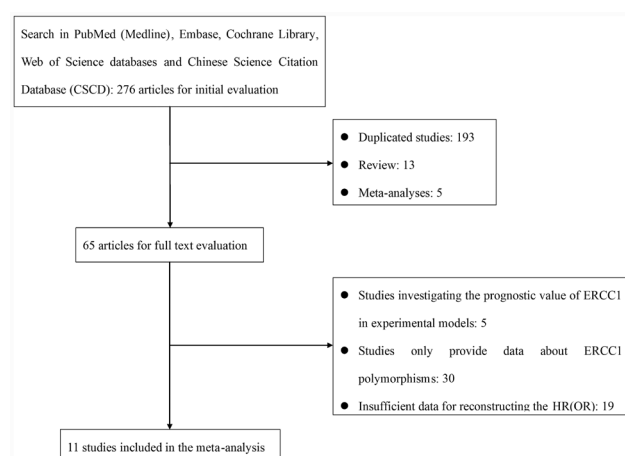

Figure 1: The flowchart describing the selection of the literature.

Excision repair cross-complementation group 1 and overall survival

A total of 8 essays presented the data about the relationship between ERCC1 expression and OS. Though with heterogeneity, the pooled analysis demonstrated that patients with increased ERCC1 expression predisposed to have shorter OS (*HR* = 2.325, 95% *CI*: 1.720–3.143, *P* < 0.001) [Figure 2a]. Except for the subgroup analysis of treatment setting as PCT, the majority of the subgroup analysis agreed with the overall results [Table 2].

Excision repair cross-complementation group 1 and progression free survival

The relationship between ERCC1 expression and PFS was explored in 6 studies. The combined *HR* of 1.917 revealed a significant association between elevated ERCC1 expression and inferior PFS (*HR* = 1.917, 95% *CI*: 1.366–2.691, *P* < 0.001) [Figure 2b]. Except for the subgroup analysis of studies with a sample size <100 and studies whose *HR* was indirectly retrieved, the majority of the subgroup analysis agreed with the overall results [Table 2].

Excision repair cross-complementation group 1 and response rate to chemotherapy

Information about the association between ERCC1 expression and RR to chemotherapy was described in 6 trials. Patients with elevated ERCC1 expression were inclined to response poorer to the chemotherapy compared with those with lower expression of ERCC1 (*OR* = 0.491, 95% *CI*: 0.243–0.990, *P* = 0.047) [Table 3 and Figure 3].

Subgroup analysis stratified by study region suggested that ERCC1 expression was associated with the RR to chemotherapy in Asian population (*OR* = 0.391, 95% *CI*: 0.172–0.888, *P* = 0.025); in the subgroup divided by the detection method, a significant relationship between elevated ERCC1 expression and resistance to chemotherapy was obtained in the IHC subgroup (*OR* = 0.391, 95% *CI*: 0.172–0.888, *P* = 0.025); when the studies were stratified by the sample size, we found that the significant relationship between ERCC1 overexpression in the subgroup with sample size larger than 100 (*OR* = 0.235, 95% *CI*: 0.094–0.588, *P* = 0.002); significant association between elevated ERCC1 expression and improved RR was also detected in the subgroup of prospective designed studies (*OR* = 0.399, 95% *CI*: 0.160–0.995, *P* = 0.049) [Table 3].

Sensitivity analysis

In the sensitivity analysis, the influence of each study on the pooled *HR/OR* was examined by repeating the meta-analysis while omitting one of the enrolled studies at a time. The respective *HRs/ORs* was not materially changed (data not shown). The results showed that our results were robust.

Publication bias

In the present meta-analysis, Egger's test was used to

Table 1: Main characteristics of all the studies included in the meta-analysis

Studies	Year	Study region	n (male/ female)	Age (years)	Study design	Follow-up (months)	TNM	Treatment
Shirota et al.	2001	USA	36/14	NR	Prospective	10.5 (1.8–21.2)*	IV	PCT
Uchida et al.	2008	USA	61/30	56 (26–74)*	Prospective	NR	Advanced	PCT
Gustavsson et al.	2009	Sweden	68/76	Responders: 66 (37–84)* Progressive: 65 (33–82)*	Retrospective	NR	IV	PCT
Kim et al.	2009	Korea	49/21	54 (24–78)*	Prospective	NR	IV	PCT
Xu et al.	2011	the mainland of China	41/31	46 (25–76)*	Retrospective	48	12/19/19/22	ACT
Grimminger et al.	2012	USA	90/32	63 (28–83)*	Prospective	NR	IV	PCT
Li et al.	2012	the mainland of China	144/111	Mayo clinic: 56.1 (27–78)* mFOLFOX6/XELOX: 53.9 (26–83)*	Retrospective	Combined subgroup: 68 Single drug subgroup: 86	III	ACT
Basso et al.	2013	Italy	62/38	Median: 64	Retrospective	NR	IV	ACT
Huang et al.	2013	Taiwan, China	112/68	<65 years: n = 93 ≥65 years: n = 87	Prospective	24.99 ± 1.04	III	ACT
Gu and Mao	2014	the mainland of China	54/43	57 (32–78)*	Retrospective	NR	NR	ACT
Zhang et al.	2015	the mainland of China	524/371	≤60: 481 >60: 414	Retrospective	37.5 (range 0–65)	III	ACT

Studies	Detection method	Cut-off (%)	Number of elevated (n (%))	Survival outcome	HR extraction	Response criteria	NOS score
Shirota et al.	PCR	4.9×10^{-3}	10 (20)	OS	R (U)	–	7
Uchida et al.	PCR	75th	46 (74.2)	PFS, RR	R (U)	NR	6
Gustavsson et al.	PCR	25th	132 (56.8)	PFS, RR	R (U)	WHO	6
Kim et al.	IHC	4	39 (55.7)	OS, RR	R (M)	Specific	6
Xu et al.	IHC	2	31 (43.06)	OS	E (U)	–	5
Grimminger et al.	PCR	1.73	6 (20.69)	OS	R (U)	–	6
Li et al.	IHC	2	140 (55.78)	OS, PFS	R (M)	–	6
Basso et al.	PCR	6.21×10^{-3}	30 (50)	PFS, RR	R (U)	RECIST	6
Huang et al.	IHC	2	20 (11.1)	OS, PFS, RR	E (U)	Specific	5
Gu and Mao	IHC	2	40 (41.24)	OS, RR	R (M)	RECIST	6
Zhang et al.	IHC	2	406 (45.4)	OS, PFS	R (M)	–	7

*Median (range). OS: Overall survival; PFS: Progression-free survival; RR: Response rate; HR: Hazard ratio; obtained by reporting in text (R) or estimating (E); M: The HR come from multivariate analysis; E: Extent; I: Intensity; NR: Not reported; NOS: Newcastle–Ottawa scale; TNM: Tumor node metastasis; ACT: Adjuvant chemotherapy; PCT: Palliative chemotherapy; PCR: Polymerase chain reaction; IHC: Immunohistochemistry; RECIST: Response Evaluation Criteria in Solid Tumors; WHO: World Health Organization.
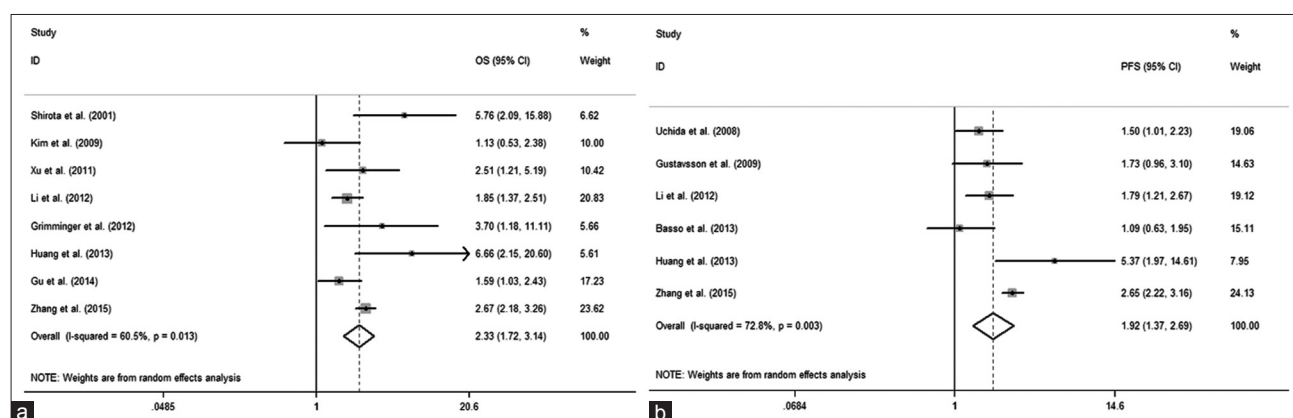

Figure 2: Forest plots of the hazard ratio for the association between excision repair cross-complementation group 1 expression and overall survival (a) and progression-free survival (b) in patients with colorectal cancer with random effects model. Horizontal lines correspond to the study-specific hazard ratio and 95% confidence interval, respectively. The size of the squares reflects the study-specific weight. The diamond represents the results for the pooled hazard ratio and 95% confidence interval.

assess the publication bias of literature. Egger's tests indicated no significant publication bias among studies with overall analysis of OS (P = 0.733), PFS (P = 0.365) and RR (P = 0.063).

Table 2: Meta-analysis results for OS and PFS

Analysis		OS					PFS			
	n	HR (95% CI)	P	I² (%)	Ph	n	HR (95% CI)	P	I² (%)	Ph
Total	8	2.325 (1.720–3.143)	<0.001	60.5	0.013	6	1.917 (1.366–2.691)	<0.001	72.8	0.003
Subgroup 1: ACT	5	2.261 (1.667–3.066)	<0.001	61.8	0.033	4	2.113 (1.329–3.358)	0.002	77.3	0.004
PCT	3	2.740 (0.957–7.846)	0.060	72.5	0.026	2	1.569 (1.129–2.181)	<0.001	0	0.693
Subgroup 2: Caucasian	2	4.724 (2.226–10.026)	<0.001	0	0.567	3	1.431 (1.077–1.902)	0.013	0	0.513
Asian	6	2.106 (1.545–2.870)	<0.001	63.8	0.017	3	2.503 (1.686–3.716)	<0.001	62.6	0.069
Subgroup 3: Sample size ≥100	4	2.585 (1.796–3.721)	<0.001	60.2	0.057	4	2.320 (1.663–3.237)	<0.001	56.2	0.077
Sample size <100	4	2.054 (1.178–3.580)	0.011	60.8	0.054	2	1.350 (0.975–1.869)	0.070	0	0.370
Subgroup 4: PCR	2	4.724 (2.226–10.026)	<0.001	0	0.567	3	1.431 (1.077–1.902)	0.013	0	0.513
IHC	6	2.106 (1.545–2.870)	<0.001	63.8	0.017	3	2.503 (1.686–3.716)	<0.001	62.6	0.069
Subgroup 5: direct	6	2.146 (1.549–2.973)	<0.001	64.9	0.014	4	1.831 (1.239–2.705)	0.002	74.0	0.009
Indirect	2	3.700 (1.451–9.436)	0.006	50.7	0.154	2	2.604 (0.755–8.984)	0.130	81.4	0.020
Subgroup 6: Univariate analysis	4	3.833 (2.385–6.159)	<0.001	0	0.416	4	1.722 (1.078–2.750)	0.023	60.2	0.057
Multivariate analysis	4	1.895 (1.361–2.640)	<0.001	70.3	0.018	2	2.269 (1.560–3.298)	<0.001	67.9	0.078
Subgroup 7: Prospective	4	2.630 (1.297–5.332)	0.007	72.8	0.012	3	2.008 (1.222–3.300)	0.006	62.8	0.068
Retrospective	4	2.458 (2.066–2.924)	<0.001	42.3	0.158	3	1.796 (1.026–3.143)	0.040	79.7	0.007

OS: Overall survival; PFS: Progression-free survival; ACT: Adjuvant chemotherapy; PCT: Palliative chemotherapy; Ph: P value of Q test for heterogeneity test; HR: Hazard ratio; CI: Confidence interval; PCR: Polymerase chain reaction; IHC: Immunohistochemistry; n: Number.

Table 3: Meta-analysis results for RR

Analysis		RR			
	n	OR (95% CI)	P	I² (%)	Ph
Total	6	0.491 (0.243–0.990)	0.047	68.0	0.008
Subgroup 1: ACT	3	0.470 (0.139–1.594)	0.226	84.9	0.001
PCT	3	0.535 (0.271–1.058)	0.072	0	0.382
Subgroup 2: Caucasian	3	0.616 (0.208–1.821)	0.381	67.0	0.048
Asian	3	0.391 (0.172–0.888)	0.025	52.9	0.120
Subgroup 3: Sample size ≥100	2	0.235 (0.094–0.588)	0.002	0.0	0.580
Sample size <100	4	0.640 (0.296–1.383)	0.256	68.9	0.022
Subgroup 4: PCR	3	0.616 (0.208–1.821)	0.381	67.0	0.048
IHC	3	0.391 (0.172–0.888)	0.025	52.9	0.120
Subgroup 5: Prospective	3	0.399 (0.160–0.995)	0.049	51.1	0.129
Retrospective	3	0.581 (0.194–1.741)	0.332	74.4	0.012

RR: Response rate; n: Number; OR: Odds ratio; CI: Confidence interval; Ph: P value of Q test for heterogeneity test; ACT: Adjuvant chemotherapy; PCT: Palliative chemotherapy; IHC: Immunohistochemistry.
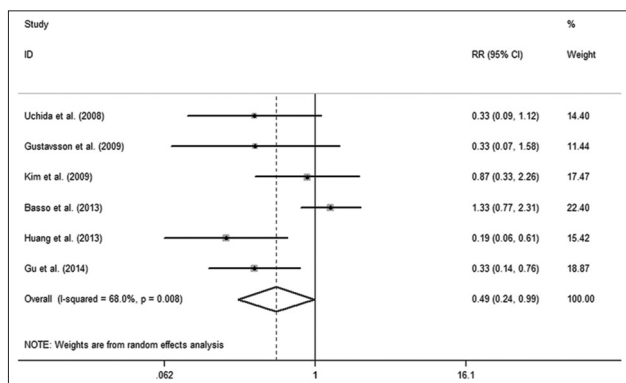

Figure 3: Forest plots of the hazard ratio for the association between excision repair cross-complementation group 1 expression and response rate to chemotherapy in patients with colorectal cancer with random effects model. Horizontal lines correspond to the study-specific hazard ratio and 95% confidence interval, respectively. The size of the squares reflects the study-specific weight. The diamond represents the results for the pooled hazard ratio and 95% confidence interval.

DISCUSSION

The pooled analysis involving 11 studies and 2076 patients revealed that increased expression of ERCC1 is significantly correlated with shorter OS and PFS. Moreover, an elevated level of ERCC1 expression significantly predicted patients' resistance to chemotherapy. In the subsequent subgroup analysis, the majority of the results went along with the overall results.

The neoadjuvant and adjuvant chemotherapy mainly involving oxaliplatin and (or) 5-fluorouracil (5-FU) have been proved to downstage the tumor and to reduce the tumor recurrence effectively.[24] In our subgroup analysis on the basis of treatment setting, elevated expression of ERCC1 was significantly related with poor survival outcome no matter in the ACT subgroup and in the PCT subgroup. Nevertheless, resistance to chemotherapy seriously hinders the further improvement of its therapeutic effects. It was estimated that at least half of the patients had poor responses to the FOLFOX regiments as the first-line

treatment.[25] Kirsten rat sarcoma viral oncogene (KRAS) and V-rafmurine sarcoma viral oncogene homolog B1 (BRAF) status, which stratify the patients according to their sensitivity to the anti-EGFR agent cetuximab, have been incorporated into the clinical guideline as a part of the indication for molecular targeted therapy.[26] But no molecular marker predicting the therapeutic efficacy of oxaliplatin and (or) 5-FU-based chemotherapy has been widely accepted yet.[27] ERCC1, the rate-limiting enzyme in the NER pathway, is an attractive target to modulate the cellular sensitivity to platinum-based chemotherapy. Several preclinical studies discovered that cancer cells with an elevated ERCC1 expression often possessed a high DNA-repair capability on exposure to platinum drugs. It was reported that the oxaliplatin resistance induced by ERCC1 was abrogated by siRNA-mediated gene silencing in human CRC cells.[28] The present meta-analysis, chiefly focused on patients underwent chemotherapy, revealed that patients with increased expression of ERCC1 predisposed to be resistant to chemotherapy and a short PFS, and OS was very likely the consequence. It was consistent with the theoretical inference and the analogous meta-analyses assessing the prognostic value of ERCC1 in gastric cancer,[29] small cell lung cancer,[30] and nonsmall cell lung cancer.[31] Thus, we inferred that ERCC1 might be employed as an indicator of therapy effects and the survival outcome.

Observable interstudy heterogeneity was marked in our meta-analysis. As meta-regression analysis is best suitable for meta-analysis involving more than 10 studies, we can only try to figure out the source of heterogeneity through the subgroup analysis. In the meta-analysis concerning OS, we found that survival analysis (univariate vs. multivariate analysis), study region, and detecting method might account for the heterogeneity to some extent. Coincidently, expression of ERCC in studies conducted in the Caucasian region was determined by PCR; while studies from the Asian region all took IHC as the assessing tool. Limited by the relevant information, the relationship between study region and detection method could not be conducted. Thus, we could not determine whether the discrepancy in I^2 value was the result of the underlying ethnicity background or the result of the detection methods of studies. Moreover, confounding factors such as the baseline differences among the study population, the laboratory protocol, and the chemotherapy regiment were not taken into our analysis due to the limited information or the limited number of studies sharing the same features. We could only infer that survival analysis, study region, and detecting method may explain the source of heterogeneity to some extent. Further studies were warranted to investigate the impaction of ethnicity background on ERCC1 expression and the clinical prognosis. In addition, for the pooled estimate focusing on PFS, we came to find that the treatment setting, study region, and detecting method might partially be responsible for the heterogeneity. The study region and detecting method may in part explain the source of interstudy heterogeneity in the meta-analysis evaluating the relationship between ERCC1 expression and response to chemotherapy.

Response to treatment is usually assessed by imaging manifestation and pathological examination. The pathological examination has long been regarded as the golden standard, but it is only available in limited cases. There are several imaging appraising criteria including WHO criteria, European Association for the Study of the Liver guidelines criteria,[32] and modified RECIST criteria.[23] Until now, none of the above guidelines has been acknowledged as the best standard for gauging the treatment response through imaging modalities. In the meta-analysis involving 6 cohorts gauging the predictive value of ERCC1 expression in RR to chemotherapy, 2 adopted the RECIST criteria and 1 was measured by the WHO criteria; meanwhile, the rest 3 articles took the specific criteria defined by them or even did not report the detailed criteria. In the present meta-analysis, we could not perform the subgroup analysis based on the criteria evaluating the response to treatment due to a limited number of studies sharing the same criteria.

In our study, ERCC1 expression was detected in 5 studies at the transcriptional level by PCR and at the protein level by IHC in another 5 trials. Differences in the Taq polymerase, the primer, and the concentration of dNTP are all recognized as sources of bias in the outcomes measured by PCR.[33] No standard procedure of IHC is erected now. Variation in the sample storage, fixation time, the source of antibody, and the dilution of the antibody may greatly influence the results.[34] Moreover, the scoring of the expression was subjectively gauged by the technicians in each study. In addition, the cut-off value defining the elevated expression of ERCC1 in the enrolled studies varied from institution to institution, which might be a source of heterogeneity. In some studies using IHC as the detection method, score as 1.73, 2, or 4 was taken as the cut-off value. And in studies using PCR as the detection method, cut-off value was set as 25%, 75%, 4.9×10^{-3}, or 4.9×10^{-3}. We could not perform the subgroup analyses accordingly, as few studies shared the same cut-off value. And also, the comparability of PCR and IHC in detecting the expression of ERCC1 is a concern in the meta-analysis. Recent studies discovered several isoforms of ERCC1 (201, 202, 203, and 204).[35] Of them, ERCC1-202 isoform was supposed as the only isoform implying the DNA-repair capability and might function as the predictor of response to platinum-based chemotherapy, which has been proved in patients with NSCLC.[35] However, the commonly used detection approaches of clinical samples, including IHC and PCR, cannot correctly discriminate the isoforms. It may lead to inaccurate interpretation of ERCC1 and NER pathway activity.

Despite our efforts to conduct a systematic analysis, admittedly, there were some other limitations in our meta-analysis. First, the study design may be a concern, as 5 of the enrolled studies were prospectively performed and 6 of them were retrospectively performed. Retrospective studies had intrinsic defects such as selection bias and recalling bias. The significant relationships between elevated ERCC1 expression and survival outcome were not altered by the respective subgroup analysis, which further strengthened

our results. Second, some *HRs* were indirectly produced by the relevant data[12] or retrieved from the Kaplan–Meier curves,[13] which were less reliable than the directly reported ones. It should be noted that the *P* values for the Kaplan–Meier curves in the study by Huang *et al*.[19] were presented as *P* < 0.001, we could only adopt the *P* value as 0.001, i.e., the upper limit of the actual *P* value, in our *HR* (95% *CI*) estimating process. We could infer that the positive results of our meta-analysis were robust as the pooled *HRs* (95% *CIs*) evaluating ERCC1 overexpression and survival outcome were somehow underestimated. What is more, *HRs* were synthesized by different survival analyses in the pooled articles. Subgroup analysis stratified by the survival analysis and *HR* extraction method all agreed with the overall results, which suggested that our results were steadfast. Third, the dosage and detailed regiment were not uniform among the included institutions. Moreover, chemotherapy was performed as the first-line treatment in some trails while in some other studies it was conducted as the second line treatment. They all might contribute to the heterogeneity in the meta-analysis. Fourth, publication bias remains to be the main concern for all meta-analysis. Articles with positive results were much more favored by the journal's editorial board than the negative ones.[36] Thus, the present results may be overvalued to some extent.[36] Moreover, due to limited information regarding the association between ERCC1 and toxicity were provided, we could not perform the respective meta-analysis. In addition, though we tried our best to identify as more relevant articles as possible, we only searched the above-listed databases and only referred to essays written in English and Chinese. The included number of studies may be somehow insufficient.

In conclusion, elevated ERCC1 expression is a useful prognostic biomarker which is significantly associated with unfavorable survival outcomes (OS and PFS) in patients with CRCs. And increased expression of ERCC1 can also function as a molecular marker predicting patients' resistance to chemotherapy. Future prospective studies with large sample sizes and better study designs are required to confirm our findings.

Supplementary information is linked to the online version of the paper on the Chinese Medical Journal website.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Quality assessment of eligible studies with Newcastle–Ottawa scale

Author	Year	Selection	Comparability	Outcome	NOS
Shirota *et al.*	2001	★★*	★★★*	★★*	7
Uchida *et al.*	2008	★★*	★★†	★★*	6
Gustavsson *et al.*	2009	★★*	★★*	★★*	6
Kim *et al.*	2009	★★★*	★*	★★*	6
Xu *et al.*	2011	★★*	★*	★★*	5
Grimminger *et al.*	2012	★★*	★★*	★★*	6
Li *et al.*	2012	★★*	★★*	★★*	6
Basso *et al.*	2013	★★†	★★*	★★*	6
Huang *et al.*	2013	★★*	★*	★★*	5
Gu *et al.*	2014	★★*	★★*	★★*	6
Zhang *et al.*	2015	★★★*	★★*	★★*	7

The table presented the final quality assessment score of the enrolled studies by the authors. *The score was consistent in the initially separate assessment by Li MX and Bi XY; †The score was produced by the joint discussion. NOS: Newcastle–Ottawa scale.