Systematic Review and Meta-Analysis

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High/positive expression of ERCC1 predicts poor treatment response and survival prognosis in nasopharyngeal carcinoma

A systematic meta-analysis from 21 studies

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Abstract

Background: Excision repair cross-complementation group 1 (ERCC1) protein is a member of the nucleotide excision repair (NER) system, which plays an important role in DNA damage repair. Recently, its predictive and prognostic value in nasopharyngeal carcinoma (NPC) has been investigated by several studies. However, their results remain controversial.

Objectives: In an attempt to address this issue, we conducted the present comprehensive meta-analysis.

Data sources: Studies published until November 2017 were searched. Finally, total 21 literatures involving 22 cohorts and 2921 NPC patients fulfilled the inclusion criteria.

Results: The pooled results showed that high/positive expression of ERCC1 predicted poor objective response rate (ORR) [odds ratio (OR) = 2.83; 95% confidence interval (CI) = 2.11–3.80; $P < .001$], overall survival (OS) [hazard ratio (HR) = 1.77; 95% CI = 1.48–2.12; $P < .001$], and disease-free survival (DFS) (HR = 1.60; 95% CI = 1.43–1.79; $P < .001$) in NPC. Low heterogeneity was detected among these studies (ORR: $I^2 = 0.0\%$, $P = .776$; DFS: $I^2 = 38.7\%$, $P = .148$; OS: $I^2 = 0.0\%$; $P = .530$). The results of sensitivity analyses and publication bias verified the reliability of our findings.

Conclusions: This study suggested ERCC1 as a potential predictive and prognostic biomarker for the treatment response and survival prognosis of NPC patients.

Abbreviations: CI = confidence interval, DFS = disease-free survival, ERCC1 = excision repair cross-complementation group 1, HR = hazard ratio, NER = nucleotide excision repair, NOS = Newcastle–Ottawa Scale, NPC = nasopharyngeal carcinoma, OR = odds ratio, ORR = objective response rate, OS = overall survival.

Keywords: ERCC1, meta-analysis, nasopharyngeal carcinoma, prognosis

1. Introduction

Nasopharyngeal carcinoma (NPC) is an endemic disease, with high incidence of 15 to 50 cases/100,000 population per year in Southeast Asia and southern China. Whereas, in the USA and Western Europe, NPC is sporadic, with the incidence of 0.5 to 2 cases/100,000 population per year.[1–3] Radiotherapy alone for early-stage tumor or platinum-based concurrent chemoradiotherapy (CCRT) for locoregionally advanced tumor is the current standard treatment.[4,5] The 5-year overall survival (OS) for locoregionally advanced NPC is about 70%.[6] Treatment failure is due to local recurrence and distant metastasis. Therefore, it is crucial to identify patients with high risk and tail their treatment. Various clinicopathological parameters have been reported, including TNM classification, epidermal growth factor receptor (EGFR),[7] Human Papillomavirus (HPV),[8] and Epstein-Barr virus (EBV) infection.[9] However, these are still insufficient to guide clinical treatment modification. And new prognostic biomarkers are explored extensively.

Excision repair cross-complementation group 1 (ERCC1) protein, which plays an essential role in the pathway of DNA nucleotide excision repair (NER),[10] has been reported to be associated with a decreased tumor sensitivity to platinum-based chemotherapy[11,12] and radiotherapy.[13,14] A number of studies have established ERCC1 as a significant biomarker in predicting both treatment response and prognosis in several human cancers, including lung cancer,[12] gastric cancer,[15] colorectal cancer,[16] esophageal cancer.[17] In NPC, the reported conclusions are controversial.[18–21] Consequently, the role of ERCC1 to predict treatment response and survival prognosis in NPC patients remains unclear.

To date, 3 meta-analyses exploring the association between ERCC1 and treatment response or survival prognosis in head and neck squamous cell carcinoma (HNSCC) have been published.[22–24] Limited NPC patients were included (322 patients

Editor: Jianxun Ding.

This work was supported by the Natural Science Foundation of Hubei Province (2015CFB541).

The authors declare no conflicts of interest.

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Medicine (2019) 98:21(e15641)

Received: 27 April 2018 / Received in final form: 29 March 2019 / Accepted: 19 April 2019

http://dx.doi.org/10.1097/MD.0000000000015641

in Bisof et al,[22] 118 patients in Gao et al,[23] and 467 patients in Ma et al[24]). And only 2 studies reported the results of NPC subgroup.[22,23] As is well known, NPC has distinct genotype, clinical phenotype, and prognosis from HNSCC, which is more sensitive to regular chemotherapy and radiotherapy.[25] Furthermore, they only included English literatures. Since south China is one of the regions with highest incidence of NPC globally,[26] it is important to include literatures published in Chinese. Therefore, we conducted the present comprehensive meta-analysis to evaluate the predictive value of ERCC1 in both treatment response and survival prognosis in NPC, including literatures published in both English and Chinese languages.

2. Methods

2.1. Literature search strategy

Literature search was based on the database of Pubmed, Embase, Web of Science, Cochrane library, Chinese National Knowledge Infrastructure (CNKI) and Wanfang up to November 30th, 2017. The following terms were randomly combined as searching strategy: NPC ("nasopharyngeal carcinoma" or "nasopharyngeal neoplasm" or "NPC" or "cancer of nasopharynx" or "nasopharyngeal tumor" or "nasopharyngeal cancer") and ERCC1 ("ERCC1" or "excision repair cross-complementation group 1"). The retrieved publications and their bibliographies were manually examined for potential relevant articles.

Ethical approval was not necessary for our meta-analysis, because only the published data were collected and analyzed and no patients' individual information was involved or present in this study.

2.2. Eligibility criteria

Eligible studies included in this meta-analysis should meet the following criteria:

(1) histologically proven diagnosis of NPC;
(2) evaluated the relationship between ERCC1 expression and treatment response or survival prognosis;
(3) IHC or RT-PCR was used to assess ERCC1 expression level in primary tumor tissue;
(4) the odds ratio (OR) or HR and their 95% CI could be extracted directly or calculated from the original literature.

With regard to duplicated publications or overlapped data, only the most recent or more comprehensive article was included. The eligibility of articles was assessed independently by 2 reviewers. And any discrepancy between the 2 reviewers was discussed and resolved by consensus.

2.3. Data extraction

For the included studies, we extracted the following information: first author, publication year, country of origin, sample size, clinical stage, treatment, ERCC1 expression assay (methods and rate), statistical model, and outcome. If univariate and multivariate HRs or ORs were both reported, multivariate data were used.

2.4. Extraction of hazard ratio

ORs or HRs and their 95% CIs were extracted to conduct this meta-analysis. If they were reported in literatures, we extracted them directly. If they were not given originally, we obtained them from raw data or survival curves by methods of Parmar[27]and Tierney.[28]

2.5. Quality assessment

The quality of included literatures was evaluated independently by 2 reviewers according to the Newcastle–Ottawa Scale (NOS).[29] Studies with NOS score ≥6 were defined as high quality. Disagreements were resolved by discussion.

2.6. Statistical analysis

When 95% CI did not overlap 1 ($P < .05$), a pooled OR or HR >1 implied a worse treatment response or survival prognosis for the ERCC1 high/positive expression group. The Cochran Q-test and I^2 test were used to evaluate the heterogeneity among the included studies. $P \leq .10$ in Cochran Q test or I^2 value ≥50% in I^2 test suggested statistically significant heterogeneity and random-effects models were used. Otherwise, fixed-effects models were conducted. Stratified analyses were performed to explore the factors influencing the predictive value of ERCC1 expression level on objective response rate (ORR) and OS prognosis in NPC. In sensitivity analysis, each study was removed sequentially from pooled analysis to evaluate the stability and robustness of the meta-analysis results. To assess the publication bias, Begg test and Egger test was used and no publication bias was considered with $P > .05$. STATA Statistical Software, version 12.0 (Stata Corporation, College Station, TX) was used to perform all statistical analyses.

3. Results

3.1. Characteristics of eligible studies

The detailed study selection procedure was showed in Figure 1 by a flowchart. 23 potentially relevant literatures in English and 22 literatures in Chinese were initially identified by keywords searching. Then, through title and abstract screening, 21 articles were excluded, and through full articles screening, another 3 articles were further excluded by 2 independent reviewers. At last, 21 publications including 22 cohorts fulfilled the including criteria and were eligible for the present meta-analysis.

The characteristics of the eligible 21 articles (22 cohorts) were summarized in Table 1. All of the 21 studies involving 2921 patients were published from 2005 to November 2017. Among them, 2 studies (243 cases) were performed in non-Asians,[19,21] 2 studies (118 cases) in Korean,[30,31] and17 studies (2560 cases) in Chinese. Only 2 studies were extension of randomized study,[21,32] and the other 19 studies were retrospective and obstructive.

In ERCC1 detection assay, immunohistochemistry (IHC) was applied to detect the expression level of ERCC1 in 19 studies, fluorescence IHC was used in 1 study,[19] and reverse transcription-polymerase chain reaction (RT-PCR) was used in 1 study.[33] ERCC1-8F1 antibody was used in 10 studies, ERCC1-FL297 antibody was used in 1 study.[19] Other studies did not report the antibodies they used. The level of ERCC1 expression was evaluated by different assessment systems, including only positive cell proportion,[34–37] or the product of positive cell proportional score and staining intensity score,[18,20,30,31,38,39] or the sum of positive cell proportional score and staining intensity score,[40–42]

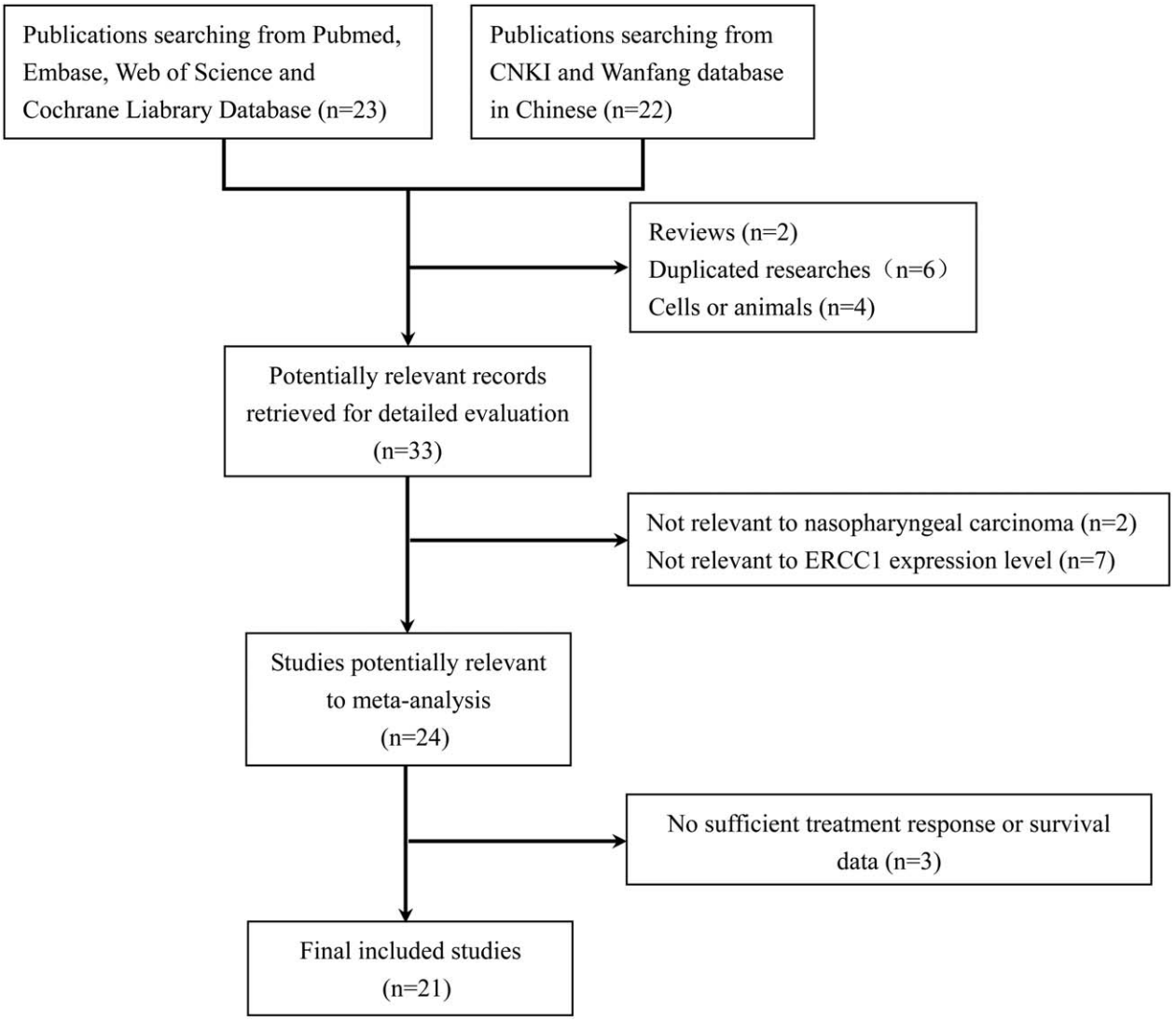

Figure 1. Flow chart of studies selection procedure.

or the automated quantitative analysis (AQUA).[19] And the cutoff values of high/positive ERCC1 were defined as from 10% to 50%, or score 3 - 4.

Among the 21 studies, 12 studies (13 cohorts) reported the results of ORR, 14 studies (15 cohorts) reported OS, 6 studies reported disease-free survival (DFS), 2 studies reported failure-free survival (FFS), 1 study reported progression-free survival (PFS), and 1 study reported recurrence-free survival (RFS). Consequently, only ORR, OS, and DFS were extracted as the endpoints of this meta-analysis. The NOS scores of the eligible studies varied from 6 to 9, suggesting high quality.

3.2. Meta-analysis

The results of meta-analyses for ERCC1 on ORR, OS, and DFS were shown in Figures 2–4. The heterogeneity test showed low heterogeneity among these studies (ORR: $I^2=0.0\%$, $P=.776$; OS: $I^2=0.0\%$; $P=.530$; DFS: $I^2=38.7\%$, $P=.148$), which suggested that the results from the included studies could be pooled together by fixed-effects models. And the results revealed that the high/positive expression of ERCC1 was significantly associated with poor ORR [odd ratio (OR)=2.83; 95% confidence interval (CI)=2.11–3.80; $P<.001$] (Fig. 2), OS [hazard ratio (HR)=1.77; 95% CI=1.48–2.12; $P<.001$] (Fig. 3) and DFS (HR=1.60; 95% CI=1.43–1.79; $P<.001$) (Fig. 4) in patients with NPC.

3.3. Stratified analysis

Since some factors would affect the predictive and prognostic role of ERCC1 on ORR and OS, subgroup analyses were stratified according to ethnicity, sample size, percentage of ERCC1 high/positive expression, treatment, tumor TNM stage, and statistical model.

For the impact of ERCC1 on ORR, as all studies included patients from Asia, the stratified analysis based on ethnicity could not be carried out. The results of the stratified analysis were listed in Table 2, which showed that the high/positive expression of

Table 1

Characteristics of studies included in this meta-analysis.

Author	Year	Country	Sample size	TNM stage	Treatment	Method	High/Positive (%)	Model	Outcome	NOS
Tan XH[58]	2005	China	103	I-IVa	RT	IHC	45.63%	UA	ORR	7
Lee HW[30]	2010	Korea	41	I-IV	C-CCRT	IHC (8F1)	61%	M	ORR, OS	8
Chan SH (RT)[18]	2011	China	118	III-IVb	RT	IHC (8F1)	29.5%	M	OS, FFS,	8
ChanSH (CRT)	2011	China	140	III-IVb	CCRT	IHC (8F1)	29.5%	M	OS, FFS,	8
Sun JM[31]	2011	Korea	77	I-IV	C-CCRT	IHC (8F1)	51%	M	ORR, OS, DFS	8
Li G[34]	2012	China	50	II-IVa	RT	IHC (SPM243)	46%	U	ORR, OS	7
Huang FX[35]	2012	China	58	III-IVb	CCRT	IHC (8F1)	69%	M	OS	7
Jagdis A[19]	2012	Canada	138	I-IV	RT, CCRT	F-IHC (FL297)	50%	U	OS, DFS	8
Huang PY[20]	2012	China	101	III-IVb	C	IHC (8F1)	49.5%	M	ORR, OS, FFS	8
Hu DF[59]	2013	China	84	III-IVb	C-CCRT	IHC	47.6%	UA	ORR	6
Krikelis D*,[21]	2013	Greece	105	II-IVb	C-CCRT	IHC (8F1)	74.3%	M	OS, PFS	7
Qin L[60]	2012	China	76	III-IVa	C-CCRT	IHC	42.1%	UA	ORR	6
Zhou J[38]	2013	China	205	III-IV	CCRT	IHC	53.7%	M	OS, DFS	6
Zhang ZX[40]	2014	China	66	III-IV	C-CCRT	IHC (8F1)	51.2%	M	OS	6
Li WH[39]	2015	China	107	II-IV	C-CCRT	IHC	48.6%	UA	ORR	6
Liang R[61]	2015	China	77	III-IVa	CCRT	IHC	42.1%	U	ORR, OS	7
Hui EP*,[32]	2015	China	105	IIb-IVb	RT, CCRT	IHC	NA	M	OS, RFS	8
Shen C[37]	2016	China	85	III-IV	C-CCRT	IHC	48.2%	U	ORR, DFS	7
Chen SJ[33]	2016	China	78	II	CCRT	RT-PCR	50%	UA	ORR	6
Cao YL[36]	2016	China	102	III-IV	CCRT	IHC	63%	UA	ORR	6
Lu Y[42]	2017	China	334	I-IV	CCRT, RT, C	IHC	35.3%	U	OS, DFS, DMFS, LRFS	8
Xu S[41]	2017	China	201	III-IV	C-CCRT	IHC	67.7%	M	ORR, OS	8

C = chemotherapy, DMFS = distant metastasis-free survival, F-IHC = Fluorescence IHC, LRFS = Local recurrence-free survival, M = multivariate, NA = not available, RT = radiotherapy, U = univariate.
* Extension of randomized study, NOS = Newcastle–Ottawa Scale.

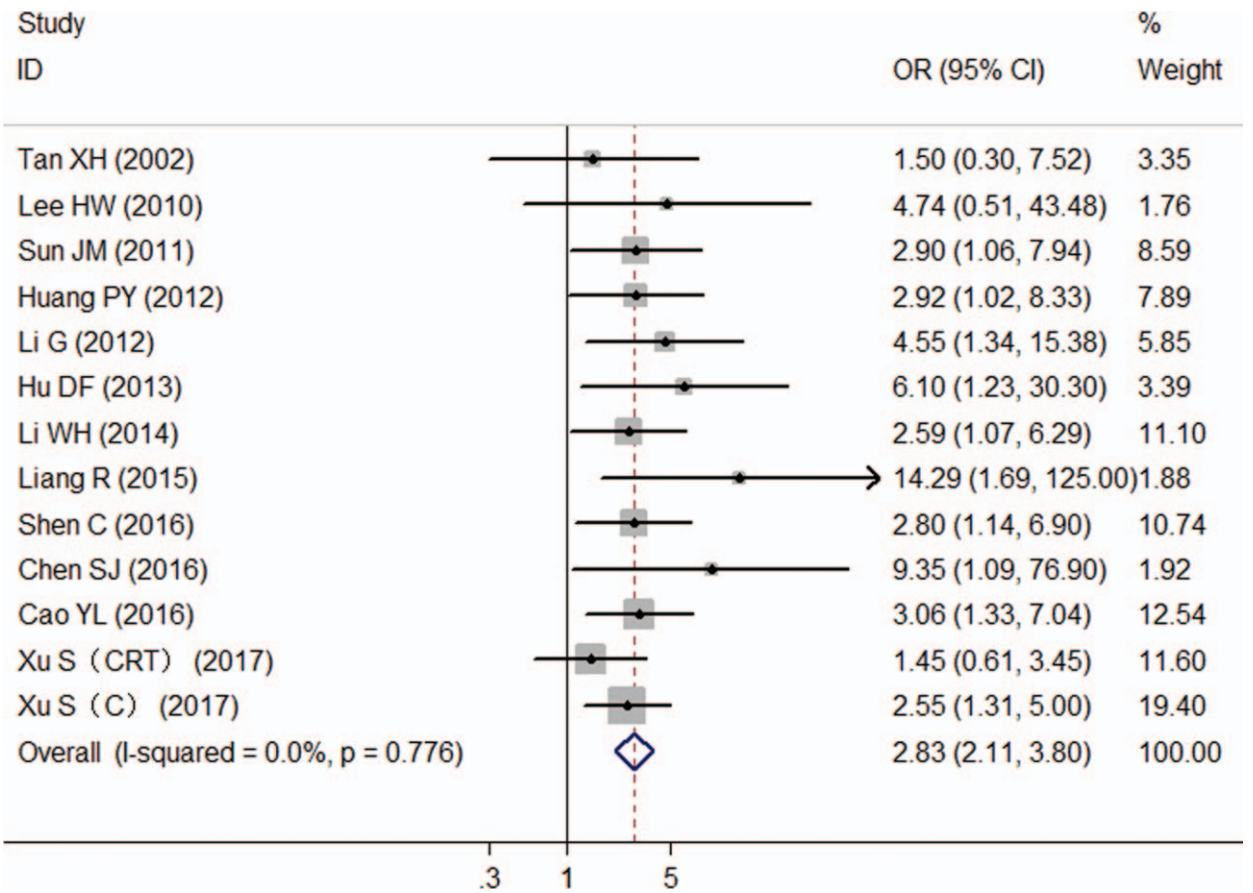

Figure 2. Forest plot for the association of ERCC1 expression level and ORR. ERCC1 = excision repair cross-complementation group 1, ORR = objective response rate.

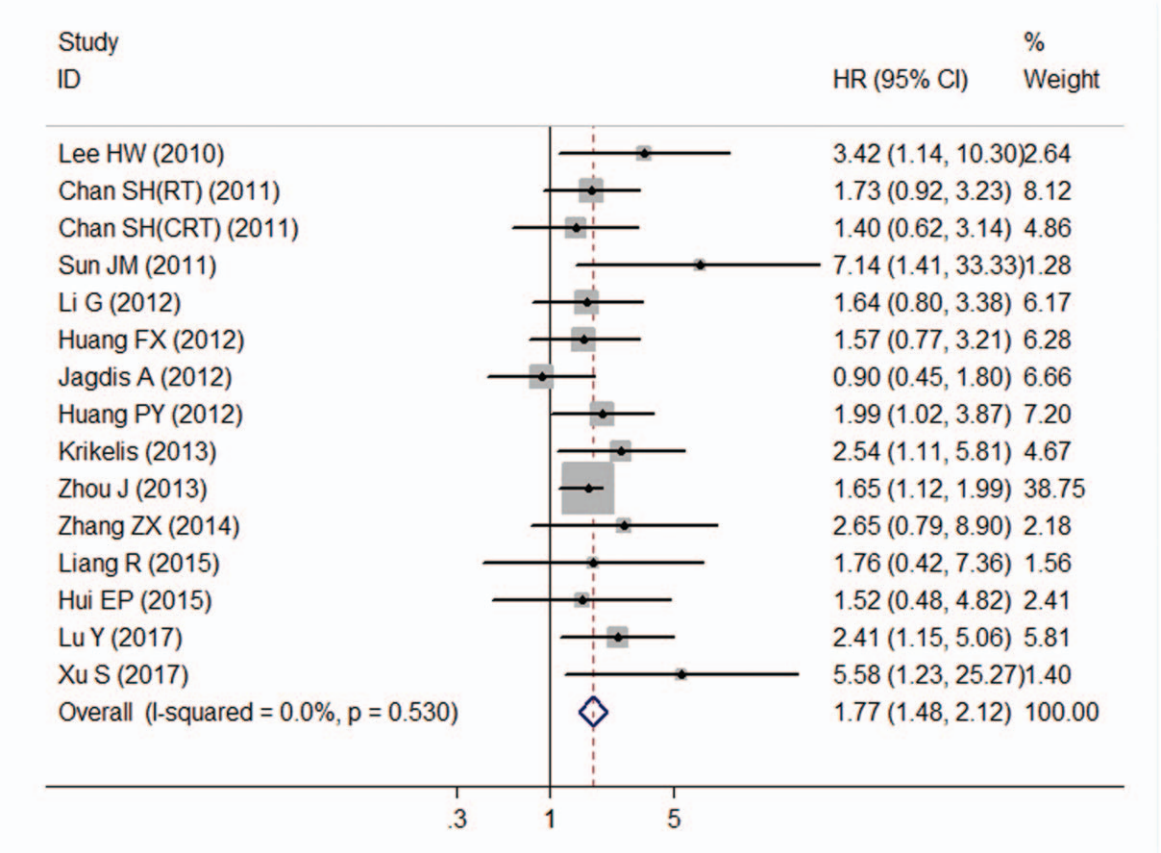

Figure 3. Forest plot for the association of ERCC1 expression level and OS. ERCC1 = excision repair cross-complementation group 1, OS = overall survival.

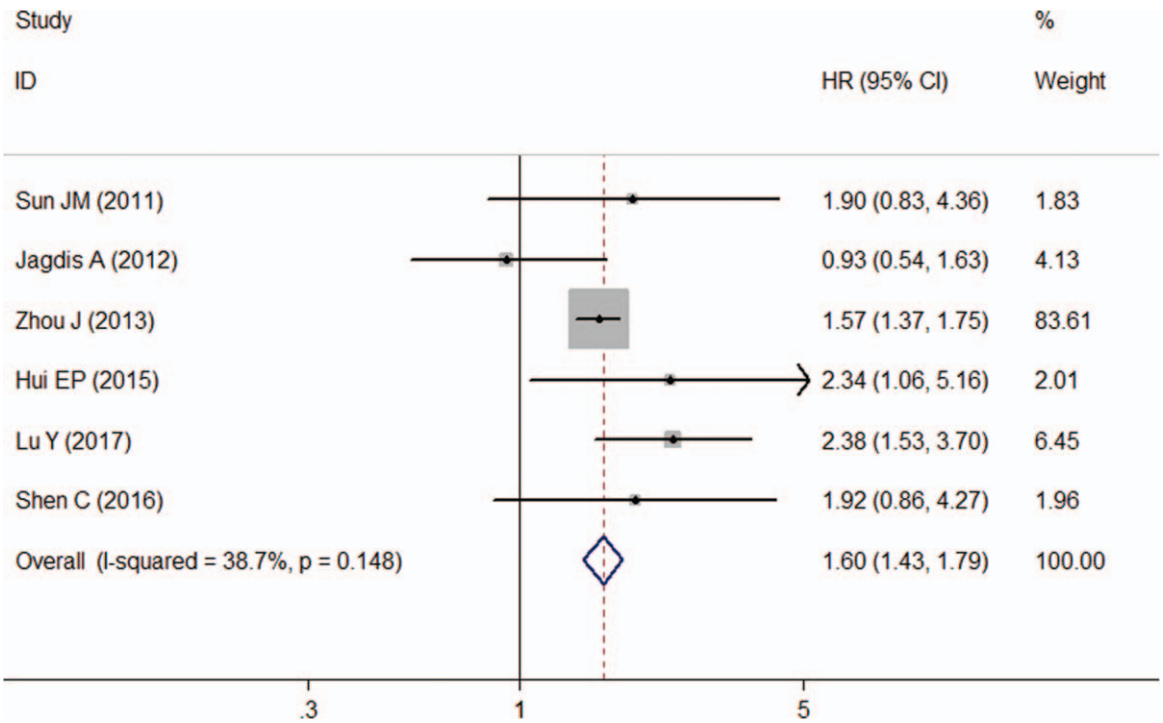

Figure 4. Forest plot for the association of ERCC1 expression level and DFS. DFS = disease-free survival, ERCC1 = excision repair cross-complementation group 1.

Table 2

Main results of the subgroup analyses for the impact of ERCC1 on ORR.

Subgroup analysis	No. of cohorts	No. of patients	OR (95%CI)	*P*	Heterogeneity test	
					I^2	*P*
ORR						
Overall	13	1477	2.83 (2.11, 3.80)	<.001	0.0%	.776
Sample size						
>200	3	736	2.23 (1.41, 3.53)	.001	0.0%	.510
≤200	10	741	3.36 (2.28, 4.94)	<.001	0.0%	.836
High/positive						
≤50%	8	855	3.35 (2.17–5.17)	<.001	0.0%	.670
>50%	5	622	2.45 (1.64–3.67)	<.001	0.0%	.710
Treatment						
Chemotherapy	2	302	2.65 (1.51,4.66)	.001	0.0%	.831
Radiotherapy	2	75	2.97 (1.03, 8.56)	.043	13.7%	.282
Chemoradiotherapy	9	1100	2.88 (1.99, 4.18)	<.001	0.0%	.555
TNM classification						
III-IV	7	1099	2.71 (1.89, 3.88)	<.001	0.0%	.491
II-IV	3	235	3.52 (1.78, 6.93)	<.001	0.0%	.487
Mix (I-IV)	3	143	2.63 (1.18, 5.83)	.017	0.0%	.680
Uni/Multivariate						
Univariate	3	460	3.85 (1.94–7.66)	<.001	0.0%	.372
Multivariate	5	621	2.39 (1.57–3.63)	<.001	0.0%	.743

CI = confidence Interval, ERCC1 = excision repair cross-complementation group 1, OR = odds Ratio, ORR = objective response rate.

ERCC1 predicted poor ORR in all subgroups, irrespective of sample size, percentage of ERCC1 high/positive expression, treatment, tumor TNM stage, and statistical model. The results suggested the reliability of the meta-analysis results.

For the impact of ERCC1 on OS, the stratified analysis revealed that high/positive expression of ERCC1 was associated with poor OS in all subgroups, except for non-Asians (HR = 1.47; 95% CI = 0.53–4.07; *P* = .454) and univariate subgroups (HR = 1.52; 95% CI = 0.97–2.40; *P* = .070) (Table 3).

Due to limited studies reporting the impact of ERCC1 on DFS, the stratified analysis could not be conducted.

3.4. Sensitivity analysis and publication bias

The results of sensitivity analysis were shown in Tables 4–6. The results of pooled ORs or HRs did not statistically change after the omission of single study, which verified the stability and reliability of our meta-analysis results.

Table 3

Main results of the subgroup analyses for the impact of ERCC1 on OS.

Subgroup analysis	No. of cohorts	No. of patients	HR (95%CI)	*P*	Heterogeneity test	
					I^2	*P*
OS						
Overall	15	1787	1.77 (1.48, 2.12)	<.001	0.0%	.530
Ethnicity						
Asian	13	1544	1.83 (1.51, 2.21)	<.001	0.0%	.749
Non-Asian	2	243	1.47 (0.53, 4.07)	.454	71.8%	.060
Sample size						
>200	3	740	1.26 (1.02, 1.56)	.004	35.5%	.212
≤200	12	1047	1.75 (1.38, 2.24)	<.001	0.0%	.545
High/positive						
≤50%	7	957	1.62 (1.22–2.14)	.001	0.0%	.622
>50%	7	753	2.08 (1.44–2.99)	<.001	23.9%	.255
Treatment						
Radiotherapy	3	269	1.79 (1.21, 2.63)	.030	0.0%	.921
Chemoradiotherapy	9	969	1.89 (1.48, 2.40)	<.001	2.7%	.412
TNM classification						
III-IV	8	965	1.73 (1.40–2.15)	<.001	0.0%	.846
II-IV	3	232	1.89 (1.15–3.09)	.011	0.0%	.678
Mix (I-IV)	4	590	2.29 (1.02–5.13)	.045	65.3%	.035
Uni/Multivariate						
Univariate	4	598	1.52 (0.97–2.40)	.070	20.2%	.289
Multivariate	11	1189	1.85 (1.51–2.26)	<.001	0.0%	.588

ERCC1 = excision repair cross-complementation group 1, HR = hazard ratio, OS = overall survival.

Table 4

Sensitivity analysis of hazard ratio for ERCC1 expression level and ORR.

Study Omitted	OR (95% CI)	P	I^2	P_H:
Tan XH (2005)	2.89 (2.14, 3.91)	<.001	0.0%	.758
Lee HW (2010)	2.81 (2.08, 3.78)	<.001	0.0%	.722
Sun JM (2011)	2.83 (2.08, 3.85)	<.001	0.0%	.703
Huang PY (2012)	2.82 (2.08, 3.84)	<.001	0.0%	.703
Li G (2012)	2.75 (2.03, 3.73)	<.001	0.0%	.757
Hu DF (2013)	2.76 (2.04, 3.72)	<.001	0.0%	.782
Li WH (2014)	2.86 (2.09, 3.92)	<.001	0.0%	.707
Liang R (2015)	2.75 (2.04, 3.70)	<.001	0.0%	.880
Shen C (2016)	2.84 (2.08, 3.87)	<.001	0.0%	.703
Chen SJ (2016)	2.77 (2.05, 3.73)	<.001	0.0%	.809
Cao YL (2016)	2.80 (2.04, 3.84)	<.001	0.0%	.706
Xu S (CRT) (2017)	3.09 (2.26, 4.23)	<.001	0.0%	.903
Xu S (C) (2017)	2.90 (2.09, 4.03)	<.001	0.0%	.713

P_H: the P value of Cochran Q-test for heterogeneity. CI = confidence Interval, ERCC1 = excision repair cross-complementation group 1, OR = odds Ratio, ORR = objective response rate.

Table 5

Sensitivity analysis of hazard ratio for ERCC1 expression level and OS.

Study Omitted	HR (95% CI)	P	I^2	P_H:
Lee HW (2010)	1.74 (1.45, 2.09)	<.001	0.0%	.565
Sun JM (2011)	1.74 (1.45, 2.09)	<.001	0.0%	.699
Chan SH (CRT) (2011)	1.79 (1.49, 2.16)	<.001	0.0%	.478
Chan SH (RT) (2011)	1.78 (1.47, 2.14)	<.001	0.0%	.452
Huang FX (2012)	1.79 (1.49, 2.15)	<.001	0.0%	.460
Huang PY (2012)	1.76 (1.46, 2.12)	<.001	0.0%	.461
Jagdis A (2012)	1.86 (1.55, 2.24)	<.001	0.0%	.772
Li G (2012)	1.78 (1.48, 2.14)	<.001	0.0%	.455
Krikelis (2013)	1.74 (1.45, 2.09)	<.001	0.0%	.512
Zhou J (2013)	1.86 (1.48, 2.33)	<.001	0.0%	.482
Zhang ZX (2014)	1.76 (1.47, 2.11)	<.001	0.0%	.485
Hui EP (2015)	1.78 (1.49, 2.13)	<.001	0.0%	.457
Liang R (2015)	1.77 (1.48, 2.12)	<.001	0.0%	.451
Xu S (2017)	1.74 (1.46, 2.09)	<.001	0.0%	.635
Lu Y (2017)	1.74 (1.45, 2.09)	<.001	0.0%	.506

P_H: the P value of Cochran *Q-test* for heterogeneity. CI = confidence Interval, ERCC1 = excision repair cross-complementation group 1, HR = hazard ratio

To evaluate the publication bias, Begg funnel plot and Egger test were conducted. Both Begg test (ORR: $P = .246$; DFS: $P = .707$; OS: $P = .743$) and Egger test (ORR: $P = .064$; DFS: $P = .842$; OS: $P = .230$) detected acceptable publication bias. In accordance with these results, the shape of the Begg funnel plot seemed basically symmetrical, indicating no obvious publication bias (Fig. 5).

Table 6

Sensitivity analysis of hazard ratio for ERCC1 expression level and DFS.

Study Omitted	HR (95% CI)	P	I^2	P_H:
Sun JM (2011)	1.67 (1.25, 2.24)	.001	50.0%	.092
Jagdis A (2010)	1.64 (1.46, 1.84)	<.001	6.4%	.370
Zhou J (2013)	1.78 (1.35, 2.35)	<.001	46.6%	.112
Hui EP (2015)	1.59 (1.42, 1.78)	<.001	44.9%	.123
Shen C (2016)	1.67 (1.25, 2.23)	.001	49.7%	.093
Lu Y (2017)	1.56 (1.39, 2.09)	<.001	17.7%	.302

P_H: the P value of Cochran Q-test for heterogeneity. CI = confidence Interval, ERCC1 = excision repair cross-complementation group 1, HR = hazard ratio.

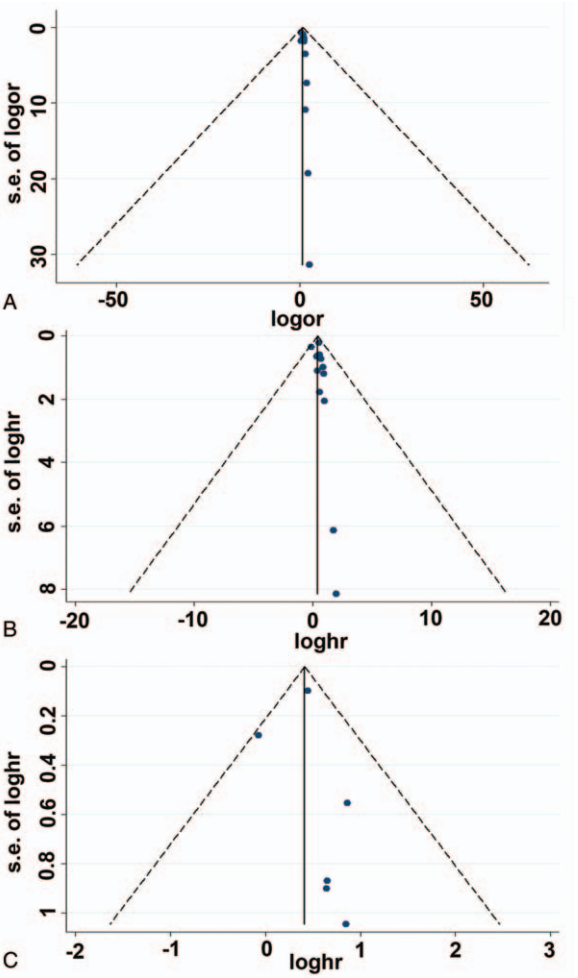

Figure 5. Funnel plot for included studies in the meta-analysis. (A) Risk ratio for ORR. (B) Hazard ratio for OS. (C) Hazard ratio for DFS. DFS = disease-free survival, ORR = objective response rate, OS = overall survival.

4. Discussion

To the best of our knowledge, this is the most comprehensive meta-analysis investigating the predictive and prognostic value of ERCC1 expression in NPC patients. Our study revealed that high/positive expression of ERCC1 predicted poor ORR (OR = 2.83; 95% CI = 2.11–3.80; $P < .001$), OS (HR = 1.77; 95% CI = 1.48–2.12; $P < .001$), and DFS (HR = 1.60; 95% CI = 1.43–1.79; $P < .001$). Results from heterogeneity testing, sensitivity analysis, and publication bias verified the reliability of our findings. In subgroup analyses, the correlation between high/positive expression of ERCC1 and poor ORR and OS existed regardless of sample size, percentage of ERCC1 high/positive expression, treatment, and tumor TNM stage. However, the association between the high/positive expression of ERCC1 and poor OS was not significant in non-Asians (HR = 1.47; 95% CI = 0.53–4.07; $P = .454$) and univariate (HR = 1.52; 95% CI = 0.97–2.40; $P = .070$) subgroup. Given limited patients in the 2 subgroups (non-Asian: 2 studies with 243 patients; univariate: 4 studies with 598 patients), the conclusion needs to be verified in future.

In 2015, 3 meta-analyses, exploring the predictive and prognostic role of ERCC1 expression level in HNSCC, were published.[22–24] Two of them reported the results of NPC

subgroup analysis, with the result that high/positive ERCC1 expression was connected with poor OS.[22,23] Such conclusion was consistent with our finding. However, our study, including larger sample size of NPC patients (2921 patients from 21 studies) and Chinese literatures, is more persuasive. In addition, we also demonstrated the predictive value of ERCC1 expression on ORR and DFS in NPC patients.

The ERCC1 gene is located on chromosome 19q13.2-q13.3, coding for 4 isoforms by alternative splicing. ERCC1 formed heterodimer with xeroderma pigmentosum group F (XPF) protein (ERCC1-XPF), which is a structure-specific endonuclease in recognizing and incising DNA damage lesions. In the heterodimer, ERCC1 functions in specific protein-protein and protein-DNA interactions, while XPF provides the endonuclease activity. ERCC1-XPF complex is essential for the repair of DNA damage by participating in several key cellular processes, including NER, DNA interstrand crosslink (ICL) repair, and DNA double-strand break (DSB) repair,[43,44] functioning in DNA repair of both radiation damage and chemo-drugs damage. In NER, ERCC1 was reported to be the limiting factor.[45] What is more, the ERCC1-XPF is also involved in telomere maintenance[46] and mitotic progression.[47] And recent work has investigated that ERCC1/XPF plays a facilitating role in transcription initiation during development.[48] High expression of ERCC1 has been linked to platinum-resistance in a number of cancers,[49,50] as well as radioresistance.[51] However, the results published in retrospective and prospective studies are not always consistent.[50,52]

Remarkably, our stratified analysis based on ethnicity suggested that ERCC1 expression level had a significant predictive value on the OS prognosis in NPC patients from Asia, but not in non-Asians. Studies have revealed that NPC patients in endemic area, like Southeast Asia and southern China, have different characteristics compared to those in the non-endemic regions, with regard to racial composition, histological subtype, and possible differences in etiology.[53] In endemic area, the non-keratinizing undifferentiated subtype (WHO type III of 2005 classification) is common, and Epstein-Barr virus (EBV) infection can be detected in the vast majority of the patients with a much favorable prognosis. On the contrary, the keratinizing and the nonkeratinizing differentiated subtypes (WHO I and II, respectively) account together for 50% to 75% of NPC in the United States.[54,55] Therefore, in Asian, the endemic region of NPC, the characteristics of patients are quite different from that in non-Asian, which might affect the predictive and prognostic value of ERCC1 expression, and lead to the results in our ethnicity subgroup analysis.

On the other hand, ERCC1 was reported to be associated with platinum-resistance at first.[49,50] Later, it was described as instrumental in lung cancer radioresistance.[51] In HNSCC, the predictive and prognostic role of ERCC1 has been studied with different treatment regimens, such as platinum-based therapy[22]and cisplatin-based concurrent chemoradiotherapy.[23] In the present meta-analysis, we included the studies irrespective of treatment scheme. To explore whether the treatment scheme will affect the predictive and prognostic role of ERCC1 in NPC, we conducted subgroup analyses stratified by treatment. And the results suggested that high/positive expression of ERCC1 predicted poor ORR and OS in NPC regardless of treatment modalities, including chemotherapy, radiotherapy, and chemo-radiotherapy.

4.1. Limitations

Notably, some limitations of our study should be emphasized. First, 19 studies were retrospective and observational, and only 2 studied were extension of randomized studies. Potential selection bias may exist. Thus, more prospective randomized controlled studies are warranted to confirm our findings. Second, only 2 studies, involving 243 patients, were from non-Asian population, leading to the conclusion in non-Asians less persuasive. And original studies in non-Asian NPC patients are requisite in future. Third, in several studies, HRs could not be extracted directly from the literature, and survival curves were used to calculate the HRs, which might cause small errors. However, the stable results of our sensitivity analyses suggested that the effects of such errors were limited. At last, IHC is the most common method to detect the expression level of ERCC1 in the included studies. As well known, IHC is a semi-quantitative method and has wide diversity, which may contribute to the heterogeneity of this meta-analysis. What is more, the most widely used 8F1 monoclonal ERCC1 antibody is still intensely debated, because literatures suggest that some ERCC1 isoforms may be inactive.[53,54] However, our heterogeneity analysis results showed the heterogeneity of the present meta-analysis was acceptable. More effective antibody and standardized methodology of ERCC1 expression detection should be established to facilitate its implementation in clinical practice.

5. Conclusion

In summary, irrespective of the above limitations, by far, this is the most comprehensive meta-analysis to evaluate the predictive and prognostic role of ERCC1 expression in NPC patients. Our results indicate that high/positive expression of ERCC1 is significantly associated with poor ORR, OS, and DFS for NPC patients, which may be utilized to identify patients with high risk and customize their personalized treatment. Multicenter prospective and randomized clinical trials are warranted to confirm our findings in the future. Furthermore, functional analysis of the whole DNA damage repair pathways could afford more information for clinical judgment on prognosis and therapy modification than single biomarker.

Acknowledgments

We thank Dr Rongxian Zhao for her contributions to the statistics.

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