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: P = .0%, P = .776; DFS: P = .987%, P = .148; OS: P = .00%, 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 tailor 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...
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 I² test were used to evaluate the heterogeneity among the included studies. P < .10 in Cochran Q test or I² value ≥ 50% in I² 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] and 17 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]
or the automated quantitative analysis (AQUA). 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-V       | C-CCRT    | IHC (8F1)  | 61%               | M     | ORR, OS     | 8   |
| Chan SH (RT)[18] | 2011 | China   | 118         | Ill-Mb    | RT        | IHC (8F1)  | 29.5%             | M     | OS, FFS     | 8   |
| Chan SH (CRT) | 2011 | China   | 140         | III-Mb    | CCRT      | IHC (8F1)  | 29.5%             | M     | OS, FFS     | 8   |
| Sun JN[31]   | 2011 | Korea   | 77          | I-V       | C-CCRT    | IHC (8F1)  | 51%               | M     | ORR, OS, DFS | 8   |
| Li G[34]     | 2012 | China   | 50          | II-Ma     | RT        | IHC (52/49) | 46%              | U     | ORR, OS     | 7   |
| Huang FX [59] | 2012 | China   | 58          | III-Mb    | CCRT      | IHC (8F1)  | 69%               | M     | OS          | 7   |
| Jagdis A[19] | 2012 | Canada  | 138         | I-V       | RT, CCRT  | F-IHC (FL297) | 50%             | U     | OS, DFS     | 8   |
| Huang PY[20] | 2012 | China   | 101         | III-Mb    | C         | IHC (8F1)  | 49.5%             | M     | ORR, OS, FFS | 8   |
| Hu DF[58]    | 2013 | China   | 84          | III-Mb    | C-CCRT    | IHC        | 47.6%             | U     | ORR         | 7   |
| Krikeli D[21] | 2013 | Greece  | 105         | II-Mb     | C-CCRT    | IHC (8F1)  | 74.3%             | M     | OS, PFS     | 7   |
| Qin L[60]    | 2012 | China   | 76          | III-Ma    | C-CCRT    | IHC        | 42.1%             | UA    | ORR         | 6   |
| Zhou J[34]   | 2013 | China   | 205         | III-Vi    | CCRT      | IHC        | 53.7%             | M     | OS, DFS     | 6   |
| Zhang ZX[40] | 2014 | China   | 66          | III-Vi    | C-CCRT    | IHC (8F1)  | 51.2%             | M     | OS          | 6   |
| Li Wh[28]    | 2015 | China   | 107         | II-N      | C-CCRT    | IHC        | 48.6%             | U     | ORR         | 6   |
| Liang F[41]  | 2015 | China   | 77          | III-Ma    | CCRT      | IHC        | 42.1%             | U     | ORR, OS     | 7   |
| Hu EP[30]    | 2015 | China   | 105         | Iib-Mb    | RT, CCRT  | IHC        | NA                | M     | OS, RFS     | 8   |
| Shen G[37]   | 2016 | China   | 85          | III-Vi    | C-CCRT    | IHC        | 48.2%             | U     | ORR, DFS    | 7   |
| Chen S[35]   | 2016 | China   | 78          | III-Vi    | CCRT, RT-PCR | 50%           | UA    | ORR         | 6   |
| Cao YL[36]   | 2016 | China   | 102         | III-Vi    | CCRT      | IHC        | 63%               | U     | ORR         | 6   |
| Lu X[50]     | 2017 | China   | 334         | I-V       | CCRT, RT, C | IHC        | 35.3%             | U     | OS, DFS, DMF, LRFS | 8   |
| Xu S[41]     | 2017 | China   | 201         | III-Vi    | 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.
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 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 |
|-------------------|----------------|-----------------|------------|---|-------------------|
| 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.

### 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 |
|-------------------|----------------|-----------------|------------|---|-------------------|
| 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             | 1.80 (1.46, 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             | 1.80 (1.15–3.09) | .011 | 0.0% | .678 |
| Mix (I-IV)        | 4              | 500             | 2.39 (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            | 1.86 (1.51–2.26) | <.001 | 0.0% | .588 |

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

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 = 2.38; 95% CI = 2.11–2.60; $P < .001$), OS (HR = 1.79; 95% CI = 1.49–2.14; $P < .001$), and DFS (HR = 1.79; 95% CI = 1.49–2.14; $P < .001$). 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 = 1.40–2.00; $P = .43$) and univariate (HR = 1.52; 95% CI = 0.97–2.40; $P = .47$) 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.\cite{22,23,24} Two of them reported the results of NPC.
subgroup analysis, with the result that high/positive ERCC1 expression was connected with poor OS. 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, functioning in DNA repair of both radiation damage and chemotherapeutic agents. In NER, ERCC1 was reported to be the limiting factor. What is more, the ERCC1- XPF is also involved in telomere maintenance and mitotic progression. And recent work has investigated that ERCC1/ XPF plays a facilitating role in transcription initiation during development. High expression of ERCC1 has been linked to platinum-resistance in a number of cancers, as well as radioresistance. However, the results published in retrospective and prospective studies are not always consistent.

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. 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. 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. Later, it was described as instrumental in lung cancer radioresistance. In HNSCC, the predictive and prognostic role of ERCC1 has been studied with different treatment regimens, such as platinum-based therapy and cisplatin-based concurrent chemoradiotherapy. 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 chemoradiotherapy.

4.1. Limitations
Notably, some limitations of our study should be emphasized. First, 19 studies were retrospective and observational, and only 2 studies 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. 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.

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References

[1] Alum M, Fandi A, Dupus O, et al. Undifferentiated nasopharyngeal cancer (UCNT): current diagnostic and therapeutic aspects. Int J Radiat Oncol Biol Phys 1995;32:859–77.

[2] Chen AT, Teo PM, Johnson PJ. Nasopharyngeal carcinoma. Ann Oncol 2002;13:1007–15.

[3] Lee AW, Foo W, Mang O, et al. Changing epidemiology of nasopharyngeal carcinoma in Hong Kong over a 20-year period (1980–99): an encouraging reduction in both incidence and mortality. Int J Cancer 2003;103:680–5.

[4] Lin JC, Jan JS, Huo CY, et al. Phase III study of concurrent chemoradiotherapy versus radiotherapy alone for advanced nasopharyngeal carcinoma: positive effect on overall and progression-free survival. J Clin Oncol 2003;21:631–7.

[5] Lee AW, Tung SY, Chuah DT, et al. Randomized trial of radiotherapy plus concurrent-adjuvant chemotherapy vs radiotherapy alone for regionally advanced nasopharyngeal carcinoma. J Natl Cancer Inst 2010;102:1188–98.

[6] Wu F, Wang R, Lu H, et al. Concurrent chemoradiotherapy in locoregionally advanced nasopharyngeal carcinoma: treatment outcomes of a prospective, multicentric clinical study. Radiother Oncol 2014;112:106–11.

[7] Sun W, Long G, Wang J, et al. Prognostic role of epidermal growth factor receptor in nasopharyngeal carcinoma: a meta-analysis. Head Neck 2014;36:1508–16.

[8] Stenmark MH, McHugh JB, Schipper M, et al. Nonendemic HPV-positive nasopharyngeal carcinoma: association with poor prognosis. Int J Radiat Oncol Biol Phys 2014;88:580–8.

[9] Lin JC, Wang WY, Chen KY, et al. Quantification of plasma Epstein-Barr virus DNA in patients with advanced nasopharyngeal carcinoma. N Engl J Med 2004;350:2461–70.

[10] Naegeli H, Sugawara K. The xeroderma pigmentosum pathway: decision tree analysis of DNA quality. DNA Repair (Amst) 2011;10:673–83.

[11] Reed E. ERCC1 and clinical resistance to platinum-based therapy. Clin Cancer Res 2005;11:6100–2.

[12] Olausen KA, Dunant A, Fourer P, et al. DNA repair by ERCC1 in non-small-cell lung cancer and cisplatin-based adjuvant chemotherapy. N Engl J Med 2006;355:983–91.

[13] Murray D, Macann A, Hanson J, et al. ERCC1/ERCC4 5'-endonuclease activity as a determinant of hypoxic cell radiosensitivity. Int J Radiat Biol 1996;69:319–27.

[14] Murray D, Valle-Lucía L, Rosenberg E, et al. Sensitivity of nucleotide excision repair-deficient human cells to ionizing radiation and cyclophosphamide. Anticancer Res 2002;22:21–6.

[15] Kwon HC, Roh MS, Oh SY, et al. Prognostic value of expression of ERCC1, thymidylate synthase, and glutathione S-transferase P1 for 5-fluorouracil/oxaliplatin chemotherapy in advanced gastric cancer. Ann Oncol 2002;13:1007–15.

[16] Kim MK, Cho KJ, Kwon GY, et al. ERCC1 predicting chemoradiation response in advanced nasopharyngeal carcinoma: a pooled analysis of two randomised controlled trials. Eur J Cancer 2016;67:119–29.

[17] Lang J, Gao L, Guo Y, et al. Comprehensive treatment of squamous cell cancer of head and neck: Chinese expert consensus 2013. Future Oncol 2014;10:1635–48.

[18] Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 1998;17:2815–34.

[19] Tierney JF, Stewart LA, Ghersi D, et al. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007;8:16.

[20] Wells G, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Ottawa Hospital Research Institute Web site. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

[21] Lee HW, Hwang YH, Han JH, et al. High expression of excision repair cross-complementation group I protein predicts poor outcome in patients with nasopharyngeal cancer. Oral Oncol 2010;46:209–13.

[22] Sun JM, Ahn MJ, Park MJ, et al. Expression of excision repair cross-complementation group 1 as predictive marker for nasopharyngeal cancer treated with concurrent chemoradiotherapy. J Int Radiat Oncol Biol Phys 2011;80:655–60.

[23] Hsu EP, Ma BB, Chan KC, et al. Clinical utility of plasma Epstein-Barr virus DNA and ERCC1 single nucleotide polymorphism in nasopharyngeal carcinoma. Cancer 2015;121:2720–9.

[24] Chen SJ, Wu MX, Wei XM, et al. Relationship between expression of ERCC1 mRNA and effect of cisplatin concurrent radiotherapy for stage II nasopharyngeal carcinoma. J Basic Clin Oncol 2016;29:4.

[25] Li G, Xue GX, Ouyang Y, et al. The effects of ERCC1 and hMLH1 expression on intensity modulated radiation therapy for local advanced nasopharyngeal carcinoma. Guangdong Med J 2012;33:3549–52.

[26] Huang FX, Li J, Zou GR, et al. The expression of TS and ERCC1 in nasopharyngeal carcinoma and its relationship with prognosis. Hebei Med 2012;18:633–4.

[27] Cao YL, Qiu XF, Deng L, et al. ERCC1 expression in local regionally advanced nasopharyngeal carcinoma and its clinical significance. Chin J of Oncol Prev and Treat 2016;6:84.

[28] Shen C, Chen L, Fu J, et al. Expression of excision repair cross-complementation group 1 in locoregionally advanced nasopharyngeal carcinoma treated with cisplatin-based induction chemotherapy. J Cancer Res Ther 2016;12:725–5.

[29] Zhou JZ, Wang JH, Xie W, WM, et al. Predictive value of ERCC1 expression in local advanced nasopharyngeal cancer receiving cisplatin-based concurrent chemoradiotherapy. Chin Clin Oncol 2015;18:996–1000.

[30] Li WH, Sun Q, Lu MY. Correlation between expression of ERCC1 and the treatment of cisplatin-based chemotherapy in local advanced nasopharyngeal carcinoma. J Clin Oncol 2007;5:44–54.

[31] Kim MK, Cho KJ, Kwon NY, et al. ERCC1 predicting chemoradiation resistance and poor outcome in oesophageal cancer. Eur J Cancer 2008;44:54–60.

[32] Chen SH, Chen JS, Cao RF, et al. The analysis of ERCC1 expression contribute to individualized therapy in nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 2011;79:1414–20.

[33] Jagds A, Phan T, Klimiowicz JC, et al. Assessment of ERCC1 and XPF protein expression using quantitative immunohistochemistry in nasopharyngeal carcinoma patients undergoing curative intent treatment. Int J Radiat Oncol Biol Phys 2013;85:140–5.

[34] Huang PY, Li Y, Mai HQ, et al. Expression of ERCC1 predicts clinical outcome in locoregionally advanced nasopharyngeal carcinoma treated with cisplatin-based induction chemotherapy. Oral Oncol 2012;48:964–8.

[35] Krikels D, Bobos M, Karayanopoulos G, et al. Expression profiling of 21 biomolecules in locally advanced nasopharyngeal carcinomas of Caucasian patients. BMC Clin Pathol 2013;13:1.

[36] Bisof V, Zajc Petranovic M, Ravacic Z, et al. The prognostic and predictive value of excision repair cross-complementation group 1 (ERCC1) protein in 1288 patients with head and neck squamous cell carcinoma treated with platinum-based therapy: a meta-analysis. Eur Arch Otorhinolaryngol 2015.
[45] Scharer OD. Nucleotide excision repair in eukaryotes. Cold Spring Harb Perspect Biol 2013;5:a012609.
[46] Zhu XD, Niedernhofer L, Kuster B, et al. ERCC1/XPF removes the 3’ overhang from uncapped telomeres and represses formation of telomeric DNA-containing double minute chromosomes. Mol Cell 2003;12:1489–98.
[47] Nunez F, Chipchase MD, Clarke AR, et al. Nucleotide excision repair gene (ERCC1) deficiency causes G (2) arrest in hepatocytes and a reduction in liver binucleation: the role of p33 and p21. Faseb J 2000;14:1073–82.
[48] Kamileri I, Karakasilioti I, Sideri A, et al. Defective transcription initiation causes postnatal growth failure in a mouse model of nucleotide excision repair (NER) progeria. Proc Natl Acad Sci USA 2012;109:2995–3000.
[49] Zhen W, Link CJ Jr, O’Connor PM, et al. Increased gene-specific repair of cisplatin interstrand cross-links in cisplatin-resistant human ovarian cancer cells. Mol Cell Biol 1992;12:3689–98.
[50] Bramson J, Panasci LC. Effect of ERCC-1 overexpression on sensitivity of Chinese hamster ovary cells to DNA damaging agents. Cancer Res 1993;53:3237–40.
[51] Guo WF, Lin RX, Huang J, et al. Identification of differentially expressed genes contributing to radioresistance in lung cancer cells using microarray analysis. Radiat Res 2005;164:27–35.
[52] Lord RV, Brabender J, Gambara D, et al. Low ERCC1 expression correlates with prolonged survival after cisplatin plus gemcitabine chemotherapy in non-small cell lung cancer. Clin Cancer Res 2002;8:2286–91.
[53] Tan EH, Chua ET, Wee J, et al. Concurrent chemoradiotherapy followed by adjuvant chemotherapy in Asian patients with nasopharyngeal carcinoma: toxicities and preliminary results. Int J Radiat Oncol Biol Phys 1999;45:597–601.
[54] Curado MP, Shin EB, Storm H, et al. Cancer incidence in five continents. Lyon, France: IARC Scientific Publications; 2007.
[55] Lee AW, Ma BB, Ng WT, et al. Management of nasopharyngeal carcinoma: current practice and future perspective. J Clin Oncol 2015;33:3356–64.
[56] Sijbers AM, van der Spek PJ, Odijk H, et al. Mutational analysis of the human nucleotide excision repair gene ERCC1. Nucleic Acids Res 1996;24:3370–80.
[57] Sun Y, Li T, Ma K, et al. The impacts of ERCC1 gene exon VIII alternative splicing on cisplatin-resistance in ovarian cancer cells. Cancer Invest 2009;27:891–7.
[58] Tan XH. The expression and significance of ERCC1 and hMLH1 in nasopharyngeal carcinoma. 2005. Chinese.
[59] Hu DF. Expression of ERCC1 and BRCA1 in nasopharyngeal carcinoma tissue and its relationship with chemosensitivity to cisplatin-based chemotherapy. 2013. Chinese.
[60] Qin LH, Huang HX, Chen FF, et al. Relationship between expression of ERCC1 and concurrent chemo-radiotherapy in patients with nasopharyngeal cancer. Cancer Research and Clinic 2012;24:4.
[61] Liang R, Liu Y, Liu ZH, et al. Correlation between ERCC1 expression and concurrent chemotherapy and radiotherapy in patients with locally advanced nasopharyngeal cancer. Genet Mol Res 2015;14:5804–11.