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Genetic polymorphisms of ERCC-1 and ERCC-2 are not prognostic markers in osteosarcoma patients with chemotherapy

A meta-analysis in Chinese population

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Abstract

Aim: To make an accurate estimation of the association of ERCC1 and ERCC2 polymorphisms with osteosarcoma (OS) prognosis in Chinese population.

Methods: Total 7 qualified studies with 1404 osteosarcoma patients were included. Odds ratios (OR) with 95% CIs were pooled for the survival rate in different osteosarcoma patients with ERCC1 and ERCC2 genetic polymorphisms. The heterogeneity was assessed by I^2 test. Potential publication bias was assessed by Begg funnel plot and Egger linear regression test.

Results: In rs11615, no significant association was found under dominant [TT+TC vs. CC: OR = 1.252, 95% CI:0.864–1.815, $P = .235$], recessive [TT vs. TC+CC: OR = 0.850, 95% CI: 0.695–1.030, $P = .095$] or allelic model [T vs. C Allele: OR = 1.219, 95% CI: 0.922–1.612, $P = .165$]. In rs13181, no significant association was found under dominant [AA+AC vs. CC: OR = 1.031, 95% CI: 0.800–1.329, $P = .801$], recessive [AA vs. AC+CC: OR = 1.005, 95% CI: 0.875, 1.154, $P = .944$] or allelic model [A vs. C Allele: OR = 1.009, 95% CI: 0.903–1.128, $P = .870$]. In rs1799793, no significant association was found under dominant [GG+GA vs. AA: OR = 1.134, 95% CI: 0.884–1.454, $P = .322$, recessive [GG vs. AG+AA: OR = 1.025, 95% CI: 0.881–1.192, $P = .750$], or allelic model [G vs. A Allele: OR = 1.046, 95% CI: 0.930–1.177, $P = .450$].

Conclusion: This study did not support rs11615, rs13181 or rs1799793 to be used as surrogate markers for clinical outcome of osteosarcoma with chemotherapy.

Abbreviations: ERCC1 = excision repair cross-complementation group 1, ERCC2 = excision repair cross-complementation group 2, ICLs = intrastrand and interstrand crosslinks, MeSH = medical subject headings, NER = nucleotide excision repair, ORs = odd ratios, OS = osteosarcoma.

Keywords: osteosarcoma, rs11615, rs13181, rs1799793

1. Introduction

Osteosarcoma (OS) is the most common primary bone malignancy which is approximately 19% of all bone tumors. Treatments usually combine aggressive standard-of-care surgical techniques and alkylating agent-based chemotherapy regimens, as improved survival was reported in combined chemotherapy compared to surgical only treatment.[1] However, sarcomas are usually diagnosed at an advanced stage, most primary therapeutic modalities including surgery, chemotherapy and biological therapies are not particularly effective. As one of the lowest survival rates among various cancers, although the 5-year survivorship of OS patients is 70% with localized disease, the survival rate drops to 30% for metastatic cases.[2–4] And significant differences were observed on the treatment effect even from patients received same therapeutic modalities.[5] Hence, it is of great clinical significance to explore the underlying mechanisms of disease development and progression.

Excision repair cross-complementation group 1 (ERCC1) and excision repair cross- complementation group 2 (ERCC2) are important enzymes in nucleotide excision repair (NER) pathway responsible for restoring cisplatin-induced DNA damages, such as intrastrand and interstrand crosslinks (ICLs). Germline polymorphisms in DNA damage repair genes, such as ERCC1 and ERCC2, could have an important impact on both survival rates and chemotherapy treatment-related toxicity.[6] Therefore, the identification of predictive markers could lead to improved drug selection and treatment outcomes.[7,8]

However, the published results from previous studies on the association of ERCC1 and ERCC2 polymorphism with prognosis in chemotherapy-treated osteosarcoma in China were inconsistent. For example, some studies showed that ERCC1 rs11615 is associated with OS survival treatment with cisplatin,[9] and the ERCC1 rs11615CC genotype had a longer overall survival compared with the TT genotype.[10] While there are also results suggested that the ERCC1 rs11615 TT genotype and ERCC2 rs1799793 AA genotype were associated with longer overall survival when compared with those with the wild-type

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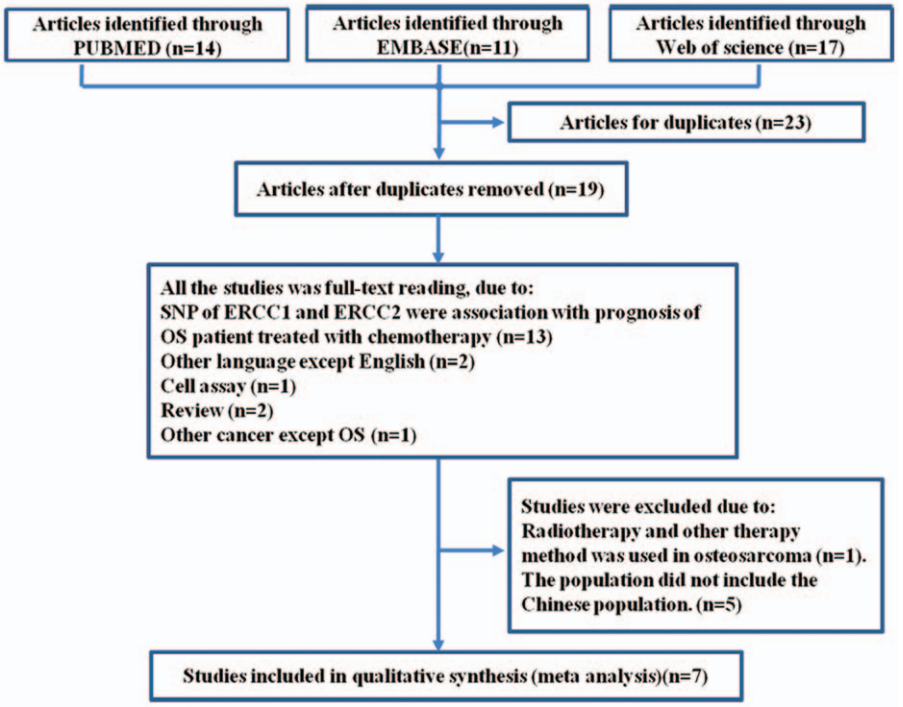

Figure 1. Data collection procedure. Seven studies were included in the final meta-analysis.

Table 1

Characteristics of studies in the meta-analysis.

Study	Population	No. of patient	Age	Male (%)	Based on therapy	Method of SNP assay	Survival
Yang, LM (2012)	Zhengzhou	187	17.7±9.6	56.68	neoadjuvant chemotherapy*	PCR-RFLP	OS
Hao, T (2012)	Inner Mongolia	267	13.6±5.2	65.5	cisplatin-based chemotherapy	MassARRAY	OS and EFS
Zhang, Q (2015)	Shangdong	260	18.4±8.5	43.84	cisplatin-based chemotherapy	PCR-RFLP	OS
Ji, WP (2015)	Shanghai	214	18.7±11.5	62.15	cisplatin-based chemotherapy	PCR-RFLP	OS
Sun, YJ (2015)	Guangzhou	175	17.8±9.7	66.28	chemotherapy	PCR-RFLP	OS
ZF Liu (2015)	Urumchi	115	-	56.52	cisplatin-based chemotherapy	MassARRAY	OS
Cao, ZH (2015)	Guangzhou	186	19.2±9.4	57.53	cisplatin-based chemotherapy	PCR-Probes	OS

* Neoadjuvant chemotherapy based on doxorubicin, methotrexate, cisplatin and ifosfamide before and after surgery.
EFS = event-free survival, OS = overall survival.

Table 2

Pooled data for the correlation between ERCC1 and ERCC2 SNP and the response rate of chemotherapy.

SNP	No. of study	Total patient	model	OR	LCI	UCI	p	I2	p	Begg test (p)	Egger test (p)
rs11615	6	1284	dominant model (TT+TC/CC)	1.252	0.864	1.815	.235	70.50%	.005	0.260	0.007
			recessive model (TT/TC+CC)	0.850	0.695	1.030	.095	61.10%	.025	0.452	0.049
			allelic model (T/C)	1.219	0.922	1.612	.165	81.30%	<.001	0.133	0.015
rs13181	7	1398	dominant model (AA+AC/CC)	1.031	0.800	1.329	.801	2.30%	.408	0.133	0.012
			recessive model (AA/AC+CC)	1.005	0.875	1.154	.944	<0.01%	.502	0.306	0.298
			allelic model (A/C)	1.009	0.903	1.128	.870	26.70%	.225	1.000	0.179
rs1799793	6	1215	dominant model (GG+GA/AA)	1.134	0.884	1.454	.322	27.80%	.227	0.060	0.150
			recessive model (GG/AG+AA)	1.025	0.881	1.192	.750	<0.01%	.502	0.707	0.206
			allelic model (G/A)	1.046	0.93	1.177	.45	39.80%	.14	0.707	0.218

LCI = lower 95% confidence interval, OR = odds ratio, UCI = upper 95% confidence interval.

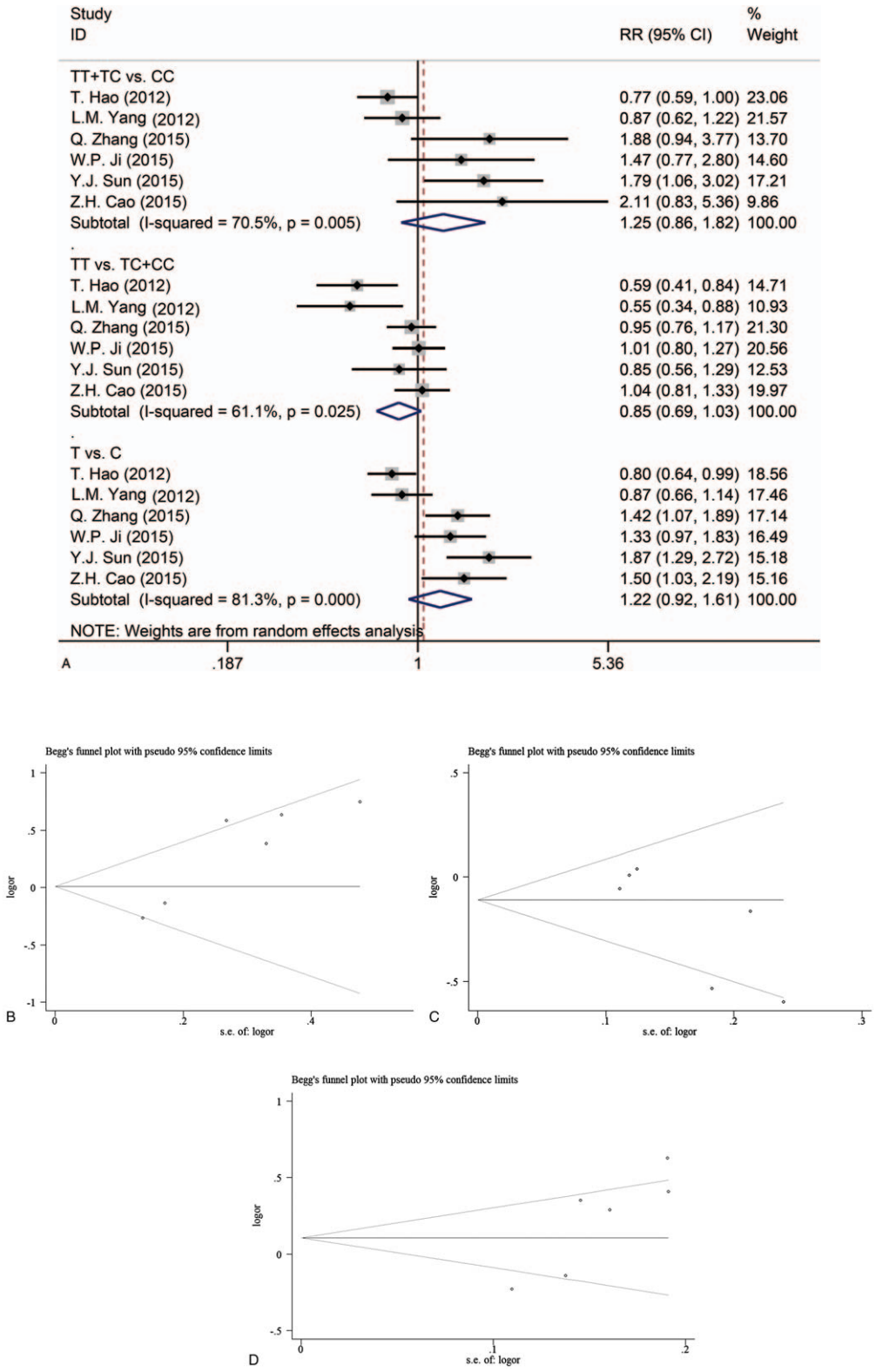

Figure 2. A: Forest plots for association between ERCC1 rs11615 polymorphism and survival rate in OS patient treated with chemotherapy [Dominant model (AA +AC vs. CC); Recessive model (AA vs. AC+CC); Allelic Model (A allele vs. C allele)]; Funnel plots for B: Dominant model (AA+AC vs. CC); C: Recessive model (AA vs. AC+CC); D: Allelic Model (A allele vs. C allele). OS= osteosarcoma.

genotype.[11] The conclusions on ERCC2 polymorphism were also inconsistent. Some studies suggested no association between ERCC2 rs13181 polymorphisms and overall survival in patients with osteosarcoma under cisplatin-based chemotherapy.[12–14] However, a recent meta-analysis found that the ERCC2 rs13181 polymorphisms might influence osteosarcoma prognosis.[15]

Thus, we performed a meta-analysis based on the most updated qualified studies trying to make an accurate estimation of such association in Chinese population.

2. Methods

This study was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements. All data were extracted from previous studies, and no direct patient contact or influence on patient care was involved in this research. Thus, ethical approval and informed patient consent were not required.

2.1. Search strategy and data collection

Literature search was carried out by 2 investigators (Dabiao Liu and Xuesong Liu) independently from the PubMed (1966–2015), Embase (1980–2015) and the Web of Science (1945–2015) using the search term based on a combination of Medical Subject Headings (MeSH) and text words relating to "ERCC1", "ERCC2", " osteosarcoma", and "chemotherapy". Dabiao Liu reviewed the literature and extract the data. Possible review author's bias, however, might exist due to limited literature resources.

The retrieved literature (up to November 11, 2015) was further screened based on the following criteria for inclusion in our analysis: ERCC1 and ERCC2 genetic polymorphisms and overall survival (OS), event-free survival (EFS), progression-free survival (PFS) and 5 years survival rate, the event at the end of follow-up time in osteosarcoma patients' treatment with chemotherapy in Chinese population. During this screening process, all included studies were also evaluated in terms of the selection bias in the clinical trials. All participants recruited in the related studies were randomly selected to allow random sequence generation. The

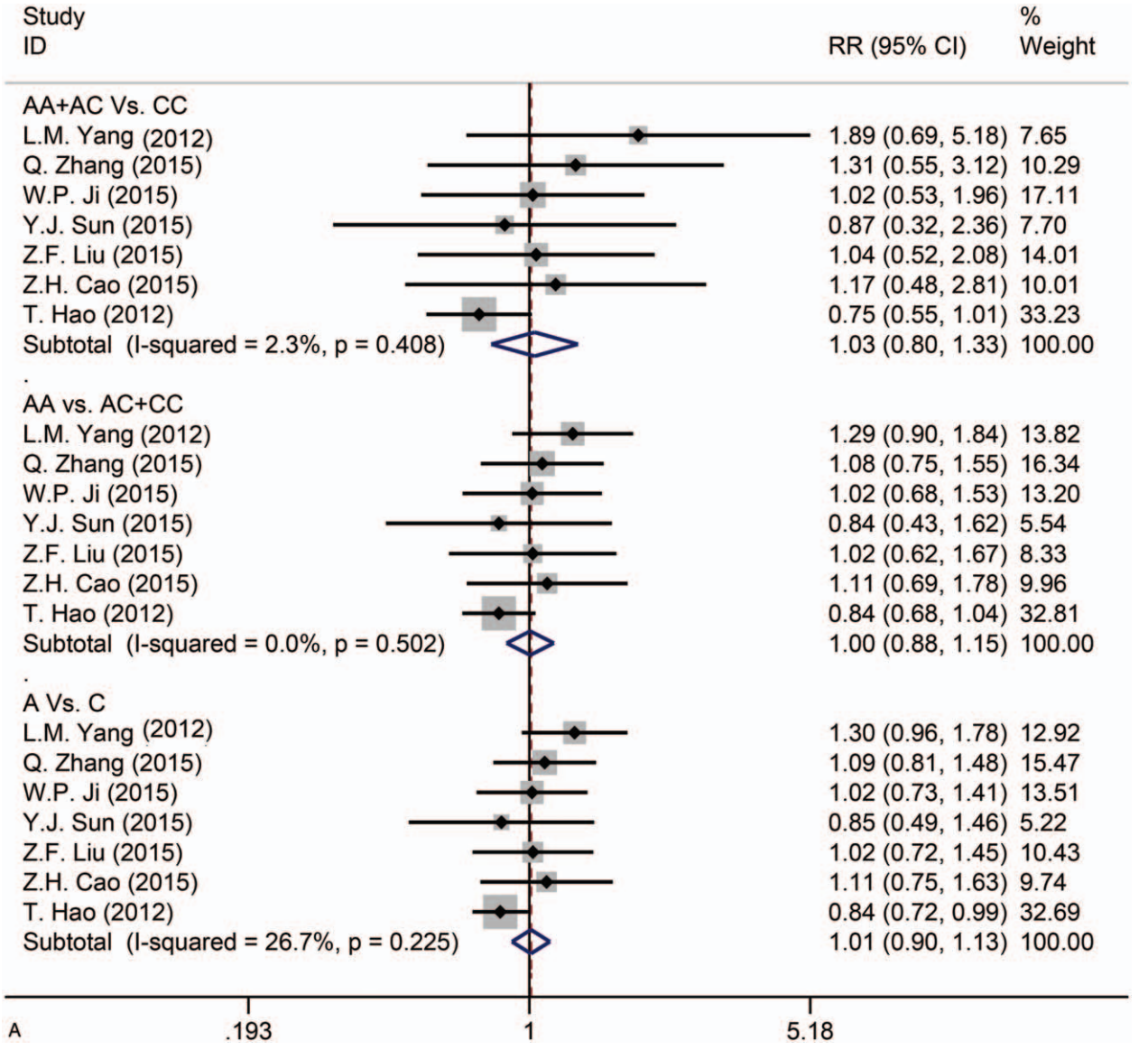

Figure 3. A: Forest plots for association between ERCC2 rs13181 polymorphism and survival rate in OS patient treated with chemotherapy [Dominant model (AA +AC vs. CC); Recessive model (AA vs. AC+CC); Allelic Model (A allele vs. C allele).]; Funnel plots for B: Dominant model (AA+AC vs. CC); C: Recessive model (AA vs. AC+CC); D: Allelic Model (A allele vs. C allele). OS= osteosarcoma.

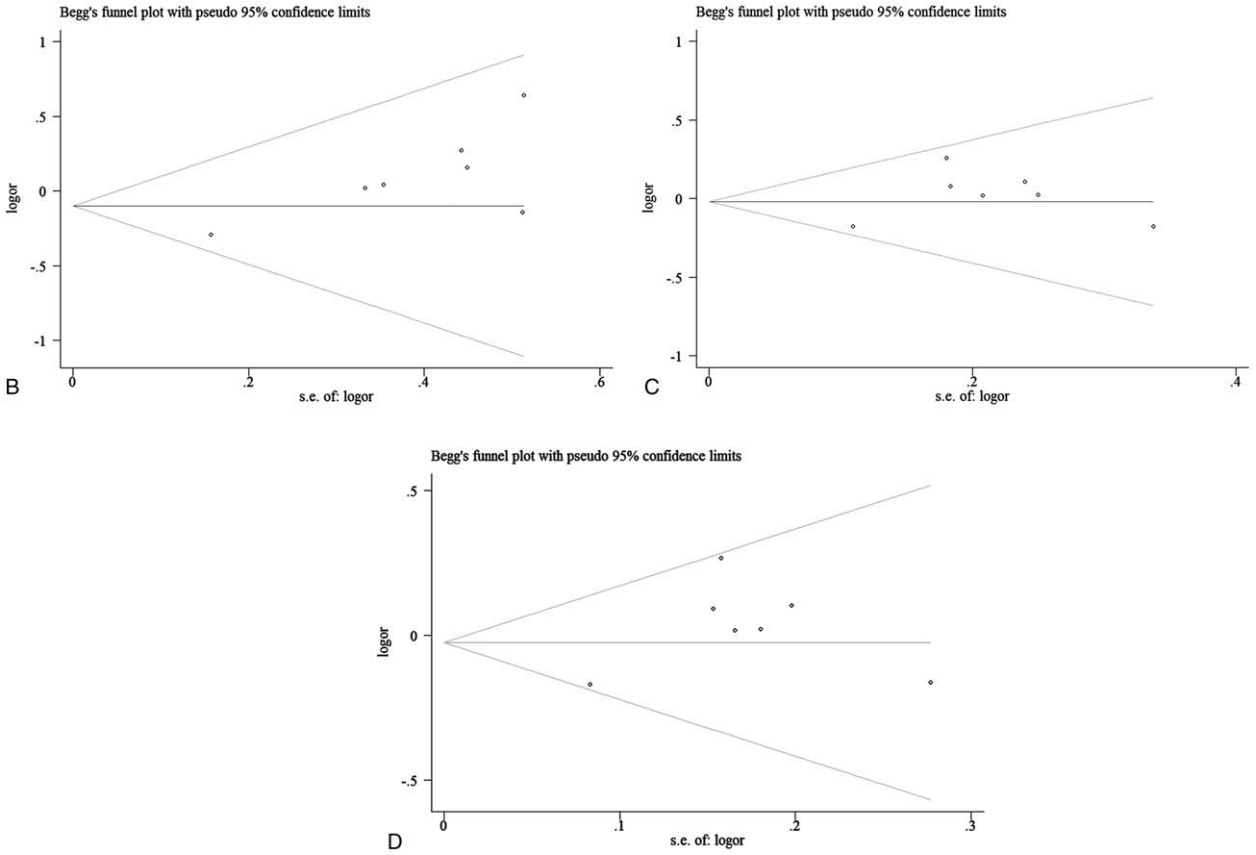

Figure 3. (Continued)

groups, if applicable, were all randomly assigned without foreknowledge of the forthcoming allocations. Performance and detection bias was also reduced in all included studies by performing effective blinding during the monitoring period in the clinical trials. Both groups described in the included studies received similar treatment and interventions. Possible reporting bias might exist in those studies which might slightly affect the results from individual studies. Exclusion criteria were the following:

(1) other treatment method such as surgery and radiotherapy;
(2) the study population is not Chinese;
(3) duplicates, review articles.

We collected the data of outcomes from all qualified studies for the construction of a 2×2 (dichotomous data) table, to assess the relationship between SNP of ERCC1 and ERCC2 and the prognosis in osteosarcoma patient from chemotherapy. All randomized controlled trials included in the manuscript were evaluated to meet the quality assurance of the meta-analysis based on the quality of reports of meta-analyses (QUORUM) guidelines.

2.2. Statistical methods

Forest plots were constructed using STATA 12 software (STATA Corp LP, College Station, Texas, United States). Where appropriate, odds ratios (ORs) with 95% CIs were pooled for the survival rate in different osteosarcoma patients with ERCC1 and ERCC2 genetic polymorphisms. The heterogeneity of results across the studies was assessed using the I^2 test. If statistical heterogeneity was small ($I^2 < 50\%$) a Mantel–Haenszel fixed-effects model was used. For studies with moderate statistical heterogeneity ($I^2 > 50\%$), the D-L random-effect model was applied. Potential publication bias of the datasets used in our analysis was assessed by Begg funnel plot and Egger linear regression test.

3. Result

3.1. Study description

Total 42 articles were retrieved from first round search, of which 35 studies were excluded after a careful review. Seven qualified studies with 1404 OS patients were included in this meta-analysis. The selection process and the reasons for exclusion were illustrated in Figure 1. The characteristics of included studies were summarized in Table 1. Possible bias might exist in the included studies, however, full evaluations were performed on each included studies.

3.2. ERCC1 rs11615 SNP and prognosis of chemotherapy in OS patient

Total of 1284 OS patients from 6 studies were pooled to investigate the relationship between rs11615 and prognosis of chemotherapy. The D-L random-effect model was applied due to the obvious between-study heterogeneity ($P < .10$ and $I^2 > 50\%$ under all models). We did not find significant association under either dominant [TT+TC vs. CC: OR = 1.252, 95% CI:0.864–1.815, $P = .235$], recessive [TT vs. TC+CC: OR = 0.850 95% CI: 0.695–1.030, $P = .095$] or allelic model [T vs. C Allele: OR = 1.219, 95% CI: 0.922–1.612, $P = .165$] (Table 2, Fig. 2A). Begg funnel plots and Egger test were used to assessing the potential publication bias in included studies under all model. Begg funnel

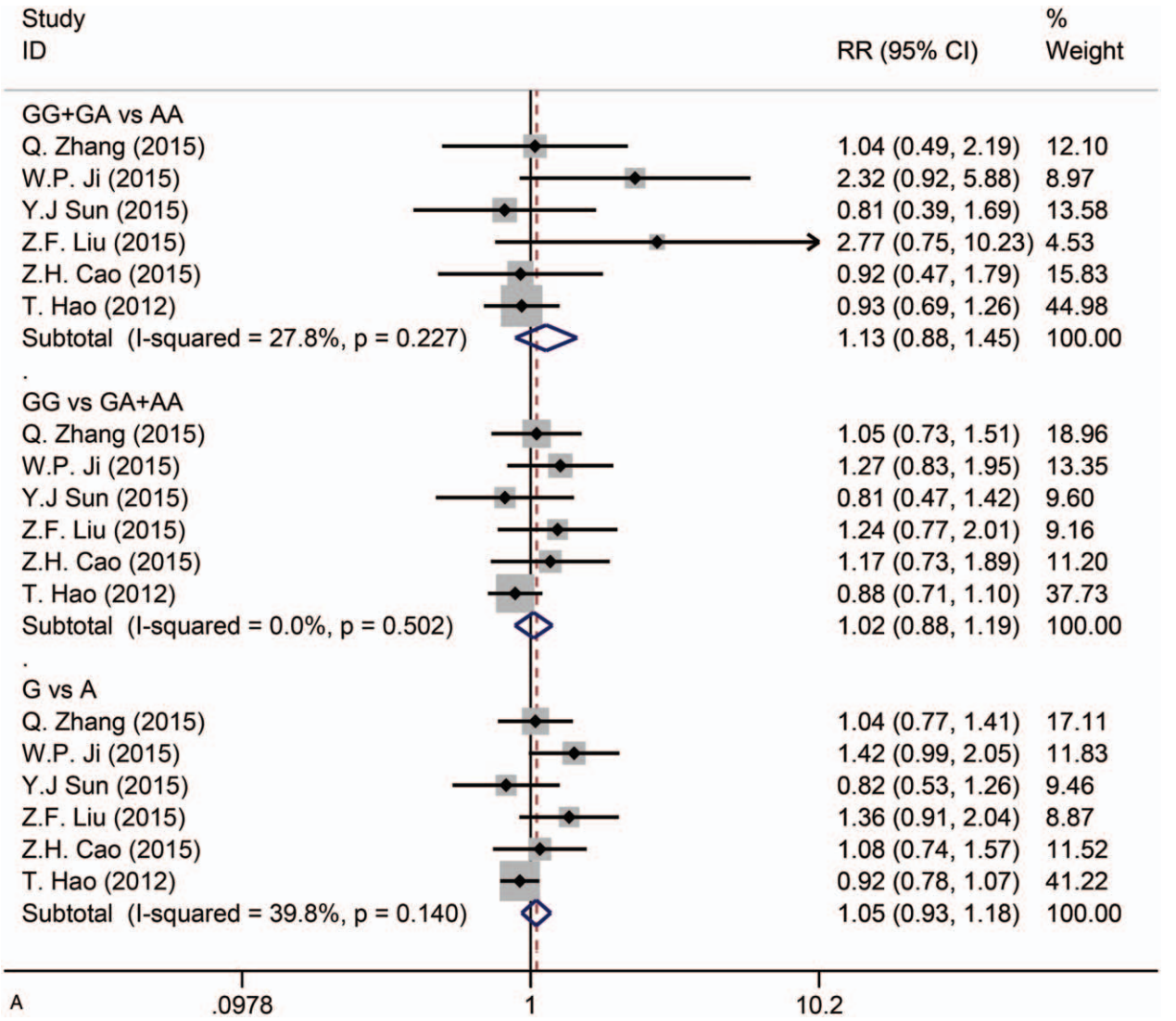

Figure 4. A: Forest plots for association between ERCC2 rs1799793 polymorphism and survival rate in OS patient treated with chemotherapy [Dominant model (GG+GA vs. AA); Recessive model (GG vs. AG+AA); Allelic Model (G allele vs. A allele).]; Funnel plots for B: Dominant model (GG+GA vs. AA); C: Recessive model (GG vs. AG+AA); D: Allelic Model (G allele vs. A allele). OS= osteosarcoma.

plot did not show asymmetry for all 3 models with $P > .05$ (Fig. 2B–D, Table 2). However, the P value of Egger linear regression test reveals evidence of obvious asymmetry (Table 2, $P < .05$).

3.3. Relation between response rate and ERCC2 SNP in OS patient

Seven studies were pooled to investigate the relationship between rs13181 and prognosis of chemotherapy with a total of 1398 OS patients. As no between-study heterogeneity was observed ($P > .10$ and $I^2 < 50\%$ under all genetic models), the fix-effect model was used for all genetic models. No significant association was detected under either dominant [AA+AC vs. CC: OR = 1.031, 95% CI: 0.800–1.329, $P = .801$], recessive [AA vs. AC +CC: OR = 1.005, 95% CI: 0.875–1.154, $P = .944$] or allelic model [A vs. C Allele: OR = 1.009, 95% CI: 0.903–1.128, $P = .870$] (Table 2, Fig. 3A). Begg funnel plots did not show asymmetry for all 3 models with $P > .05$ (Fig. 3B–D, Table 2). The P values of the Egger test were greater than .05 for the recessive and allelic model; while $P = .012$ in dominant model (Table 2).

The relationship between rs1799793 and prognosis of chemotherapy was analyzed with a total of 1215 OS patients from 6 studies. Due to the obvious between-study heterogeneity ($P > .10$ and $I^2 < 50\%$ under all genetic models), the fix-effect model was used for all genetic models. As shown in Figure 4A, no significant association was found under dominant [GG+GA vs. AA: OR = 1.134, 95% CI: 0.884–1.454, $P = .322$, recessive [GG vs. AG+AA: OR = 1.025, 95% CI: 0.881–1.192, $P = .750$], or allelic model [G vs. A Allele: OR = 1.046, 95% CI: 0.930–1.177, $P = .450$] (Table 2). All the Begg funnel plots under 3 models were symmetrical and P values of Egger test were all greater than .05 (Fig. 4B–D, Table 2).

4. Discussion

Currently, the multidisciplinary approach for osteosarcoma patients follows a neoadjuvant therapy, including 4 drugs:

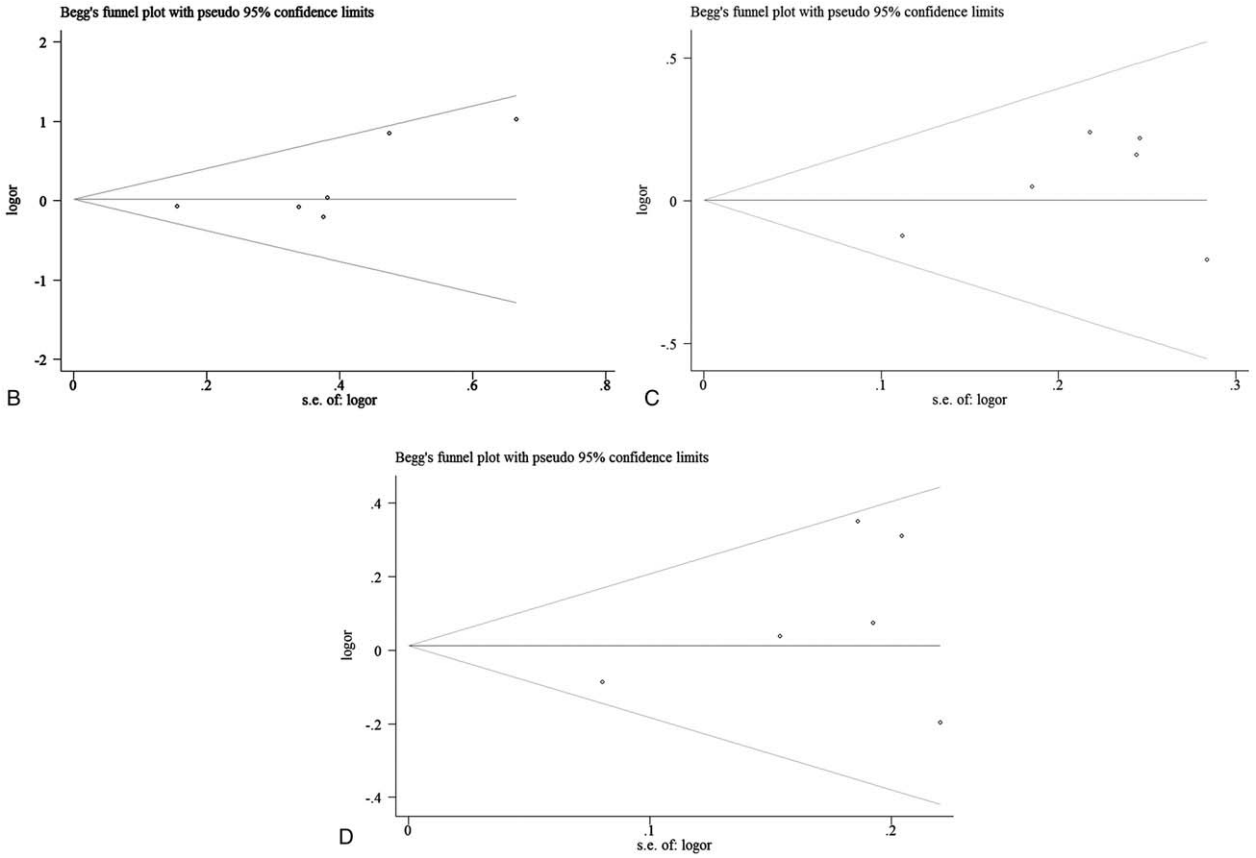

Figure 4. (Continued)

high-dose methotrexate, doxorubicin, cisplatin, and ifosfamide, followed by surgery.[16] Studies showed that the outcome of neoadjuvant chemotherapy varies for patients with tumors show >90% necrosis vs whose tumors do not respond to the chemotherapy.[17] The identification and validation of surrogate biomarkers are of great clinical significance for personalized therapy and patients' quality of life in osteosarcoma treatment regimen. For those patients unlikely to respond to the alkylating agent-based chemotherapy, alternative therapy should be offered.

In the present meta-analysis, with the most updated sample size from 7 qualified studies of 1404 OS patients in the Chinese population, we tried to validate some ERCC1 and ERCC2 prognostic biomarkers for osteosarcoma after chemotherapy. Under all models tested, contrary to previous publications, our results could not find prominent association between 3 ERCC1 and ERCC2 polymorphisms (rs11614, rs13181, and rs1799793) and prognosis of OS patient treated with chemotherapy in the Chinese population. The discrepancy of our results from previous studies may be caused by different study design, tumor types and most likely the sample size. Our result suggested that rs11615, rs13181, and rs1799793 could not be used as surrogate markers for clinical outcome of osteosarcoma treatment with chemotherapy.

Similar to all other meta-analysis, our study might have some limitations. First of all, different source data may generate heterogeneity in the current meta-analysis. For example, moderate-high heterogeneity was detected by the I^2 test in some data sets. Secondly, publication bias might be an issue. In this study, we used a funnel plot for the detection of potential publication bias or heterogeneity and further evaluated by Egger linear test. For some model, although no asymmetry was observed, but the *P* values of Egger are smaller than .05, suggesting publication bias might not be excluded. More studies should be included in the future to further confirm our result.

In conclusion, rs11615, rs13181, and rs1799793 are not prognostic markers for osteosarcoma patients. The developing of validated clinical prognostic biomarkers and treatments based on the individual molecular profile instead of general chemotherapy will open new avenues for osteosarcoma patient care.

Author contributions

Formal analysis: Dabiao Liu.
Methodology: Dabiao Liu.
Writing – original draft: Dabiao Liu.
Writing – review, and editing: Dabiao Liu and Xuesong Liu.

References

[1] Kuhelj D, Jereb B. Pediatric osteosarcoma: a 35-year experience in Slovenia. Pediatr Hematol Oncol 2005;22:335–43.
[2] Ritter J, Bielack SS. Osteosarcoma. Ann Oncol 2010;21:vii320–5.
[3] Mans DR, BudhuLall AE, Macnack VL, et al. Incidence, and gender, age and ethnic distribution of sarcomas in the republic of suriname from 1980 to 2008. West Indian Med J 2014;63:121–7.
[4] Denduluri SK, Wang Z, Yang Z, et al. Molecular pathogenesis and therapeutic strategies of human osteosarcoma. J Biomed Res 2016;30:5–18.

[5] Hattinger CM, Pasello M, Ferrari S, et al. Emerging drugs for high-grade osteosarcoma. Expert Opin Emerg Drugs 2010;15: 615–34.
[6] Marsh S, McLeod H, Dolan E, et al. Platinum pathway. Pharmacogenet Genom 2009;19:563–4.
[7] Yu H, Wu X, Zhang Y, et al. Genetic variability of DNA repair mechanisms influences chemotherapy outcome of gastric cancer. Int J Clin Exp Pathol 2015;8:4106–12.
[8] Goricar K, Kovac V, Jazbec J, et al. Genetic variability of DNA repair mechanisms and glutathione-S-transferase genes influences treatment outcome in osteosarcoma. Cancer Epidemiol 2015;39: 182–8.
[9] Ji WP, He NB. Investigation on the DNA repaired gene polymorphisms and response to chemotherapy and overall survival of osteosarcoma. Int J Clin Exp Pathol 2015;8:894–9.
[10] Zhang Q, Lv LY, Li BJ, et al. Investigation of ERCC1 and ERCC2 gene polymorphisms and response to chemotherapy and overall survival in osteosarcoma. Genet Mol Res 2015;14:11235–41.
[11] Wang MJ, Zhu Y, Guo XJ, et al. Genetic variability of genes involved in DNA repair influence treatment outcome in osteosarcoma. Genet Mol Res 2015;14:11652–7.
[12] Cao ZH, Yin HP, Jiang N, et al. Association between ERCC1 and ERCC2 gene polymorphisms and chemotherapy response and overall survival in osteosarcoma. Genet Mol Res 2015;14:10145–51.
[13] Sun Y, Wu Y, Li W, et al. Genetic polymorphisms in nucleotide excision repair pathway influences response to chemotherapy and overall survival in osteosarcoma. Int J Clin Exp Pathol 2015;8:7905–12.
[14] Liu ZF, Asila AL, Liu ZF, et al. Influence of ERCC2 gene polymorphisms on the treatment outcome of osteosarcoma. Genet Mol Res 2015;14:12967–72.
[15] Li J, Liu S, Wang W, et al. ERCC polymorphisms and prognosis of patients with osteosarcoma. Tumour Biol 2014;35:10129–36.
[16] Marulanda GA, Henderson ER, Johnson DA, et al. Orthopedic surgery options for the treatment of primary osteosarcoma. Cancer Control 2008;15:13–20.
[17] Ferguson WS, Goorin AM. Current treatment of osteosarcoma. Cancer Invest 2001;19:292–315.