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XRCC1 Arg399Gln and clinical outcome of platinum-based treatment for advanced non-small cell lung cancer: a meta-analysis in 17 studies*

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Abstract: Objective: *XRCC1* polymorphism is a research hotpot in individual treatment for non-small cell lung cancer (NSCLC). To obtain the association between *XRCC1* polymorphism and clinical outcome of platinum-based treatment for NSCLC, a meta-analysis was conducted. Methods: Databases including PubMed, Embase, Cochrane, and Chinese National Knowledge Infrastructure (CNKI) were searched for publications that met the inclusion criteria. A fixed effect model was used to estimate pooled odds ratio (OR) and hazard ratio (HR) with 95% confidence interval (CI) for the association between *XRCC1* Arg399Gln and response or survival of platinum-based treatment for advanced NSCLC. A chi-squared-based Q-test was used to test the heterogeneity hypothesis. Egger's test was used to check publication bias. Results: Seventeen published case-control studies that focus on the association between *XRCC1* Arg399Gln and response or survival of platinum-based treatment for advanced NSCLC in 2 256 subjects were included in this meta-analysis, of whom 522 were AA genotypes (23.2% frequency), 916 AG genotypes (40.6% frequency), and 818 GG genotypes (36.2% frequency). The overall response rate (ORR) was 45.2% (110/243) for AA genotype patients, 29.9% for AG genotype (73/244), and 30.7% for GG genotype (124/403). The heterogeneity test did not show any heterogeneity and the Egger's test did not reveal an obvious publication bias among the included studies. The meta-analysis indicated that AA genotype patients presented higher response rates toward platinum drug treatment compared with G model (GG+GA) patients (GG vs. AA model: OR=0.489, 95% CI 0.266–0.900, *P*=0.021; AG vs. AA model: OR=0.608, 95% CI 0.392–0.941, *P*=0.026; GA+AA vs. GG model: OR=1.259, 95% CI 0.931–1.701, *P*=0.135; GG+GA vs. AA model: OR=0.455, 95% CI 0.313–0.663, *P*=0.0001). However, no evidence validates *XRCC1* associates with the survival following platinum drug therapy. Conclusions: Our meta-analysis suggested that *XRCC1* Arg399Gln is related with the sensitivity of NSCLC patients to platinum-based treatment. AA genotype patients present more desirable curative effectiveness compared with other patients.

Key words: Meta-analysis, *XRCC1*, Arg399Gln, Non-small cell lung cancer (NSCLC), Response, Survival
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1 Introduction

Platinum-based treatment regimes are now the standard first-line therapies for advanced non-small cell lung cancer (NSCLC). Tyrosine kinase inhibitors (TKIs) are also frequently used, but platinum-based therapy remains the best option for the treatment of advanced NSCLC when the mutation status of the epidermal growth factor receptor (EGFR) is unknown (Bidoli *et al*., 2007; Jemal *et al*., 2009; Vilmar and Sørensen, 2009; National Comprehensive Cancer Network, 2011). However, the development of platinum-based therapies has slowed and many

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NSCLC patients derived little therapeutic benefit from any of those currently available (Shellard *et al*., 1993; Pfister *et al*., 2004; Wang *et al*., 2011). Seeking an optimal prognostic biomarker for clinical efficacy of platinum-based treatment remains a hotspot in this field.

The X-ray repair cross-complementing group 1 gene (*XRCC1*), a limiting factor in the base excision repair (BER) pathway, acts as a vital component of the DNA single-strand break repair system (Thompson *et al*., 1990). The XRCC1 protein is critical for repairing DNA damage induced by the platinum-based anticancer drugs cisplatin (DDP) and carboplatin (CBP) (Mohrenweiser *et al*., 2002), suggesting that XRCC1-mediated DNA repair capacity may markedly impact the efficacy of platinum-based therapy against NSCLC. Several recent studies have examined the relationship between *XRCC1* polymorphisms and the efficacy of platinum-containing drugs. For example, Gurubhagavatula *et al*. (2004) suggested that *XRCC1* polymorphisms can act as prognostic factors for predicting the clinical efficacy of platinum-based and other treatments against the progression of NSCLC. Yuan *et al*. (2006) found that the *XRCC1* Arg194Trp allelic variant in particular was associated with the response to platinum-based therapy. However, Kang *et al*. (2010) did not find a significant association between *XRCC1* gene status and overall survival after surgical resection in NSCLC patients receiving platinum-based treatment. Thus, the predictive value of *XRCC1* polymorphisms remains in dispute. The limited number of subjects enrolled in these studies and the disparate study methods adopted may contribute to these discrepancies. We speculate that a meta-analysis may yield more reliable conclusions.

There are eight known *XRCC1* single-nucleotide polymorphisms (SNPs), three of which are relatively common: amino acid substitutions at codon 194 (exon 6, base C to T, amino acid Arg to Trp), codon 280 (exon 9, base G to A, amino acid Arg to His), and codon 399 (exon 10, base G to A, amino acid Arg to Gln) (Lamerdin *et al*., 1995; Shen *et al*., 1998). Through computer searches, we found that all patient cohorts in studies examining the Arg194Trp genotype were Asian, likely because this polymorphism is rare in Caucasians (<6%) (Lunn *et al*., 1999). Similarly, few studies have been conducted on the efficacy of platinum-based treatments in patients with the Arg280His genotype because codon 280 is located outside the known functional domains of *XRCC1* (Shen *et al*., 1998). In contrast, codon 399 is located within the functional domain and could have a major influence on *XRCC1* function. Thus, we chose Arg399Gln, a common polymorphism in both Asian and Caucasian individuals, as the focal genotype in the current meta-analysis, probing the relationship between *XRCC1* and platinum-based sensitivity and survival time.

2 Materials and methods

2.1 Publication search

Comprehensive computerized searches of the PubMed, Embase, Cochrane, and Chinese National Knowledge Infrastructure (CNKI) databases were conducted from inception through to January, 2012. The following search terms were used: "*XRCC1* or X-ray repair cross complementing 1 or polymorphisms" and "cisplatin or carboplatin or nedaplatin or platinum" and "lung cancer or NSCLC or carcinoma of the lungs or non-small-cell lung cancer". All eligible studies were retrieved and their bibliographies were hand-searched for further relevant publications. All studies were carefully evaluated to identify duplicate patient populations.

2.2 Inclusion criteria

The studies included for this meta-analysis have to meet the following criteria: (1) utilizing platinum-based treatment for pathologically proven advanced NSCLC, (2) evaluating the *XRCC1* mutation Arg399Gln status, and (3) sufficient data on response (including the total number of patients and the recurrence of complete response or partial response (CR+PR)) or progress-free survival (PFS) and overall survival (OS), and studies not directly reporting hazard ratios (HRs) were allowed if data were available for statistical estimation as described below.

2.3 Quality assessment

Quality of the studies was assessed using the Newcastle-Ottawa quality assessment scale for cohort studies (Wells *et al*., 2003). This scale is composed of eight items that assess patient selection, study

comparability, and outcome. The scale was recommended by the Cochrane Non-randomized Studies Methods Working Group. Two investigators performed quality assessment independently and disagreement was resolved by consensus.

2.4 Data extraction

Two investigators independently extracted data from each included studies. Disagreements were resolved by discussion between the two, or the third reviewer's decision if these two reviewers could not reach a consensus. The following data were collected: the first author, year of publication, study design, total number of patients included in the study, ethnicities (categorized as Asians, Caucasians, Africans, and not determined), *XRCC1* genotype, objective response, PFS, OS, and HR corresponding to 95% confidence interval (CI). Other variables included number of patients lost and reasons for patients lost during follow-up.

Commonly HRs with 95% CI values were reported for individual studies, with an HR of greater than 1.0 being considered as an adverse outcome. However, for some publications, HR and 95% CI needed to be calculated again according to the method recommended in literature (Parmar *et al*., 1998; Spruance *et al*., 2004). In order to estimate the HR value, included studies had to report the number of patients according to different *XRCC1* genotype, along with the number of observed deaths/cancer recurrences.

2.5 Statistical methods

Included publications were divided into two groups for analysis: those with data regarding overall response rate (ORR) and those with OS. For the former group, the relationship between *XRCC1* genotype and objective response was measured by pooled odds ratio (OR) with 95% CI, while pooled HR with 95% CI was calculated for the latter group to evaluate the relationship between *XRCC1* mutation and survival. An OR more than 1 corresponds to a direct correlation between higher ORR and the genotype foregoing in expression, e.g., AG vs. AA, and a tendency of worse responsiveness for the genotype foregoing in expression, e.g., AG vs. AA, is indicated by an OR less than 1. Heterogeneity was initially evaluated by the chi-square-based Q-test. A *P* value greater than 0.10 for the Q-test indicates a lack of heterogeneity among studies, so the fixed-effects model (Mantel-Haenszel model) was used for meta-analysis. Otherwise, the random-effects model (DerSimonian and Laird model) was used. A *P*-value of less than 0.05 was chosen for significance.

Sensitivity analyses (disease stage and population size less than 60) were conducted to detect additional clinical heterogeneity. An estimate of potential publication bias was carried out through the Egger's test by examining the relationship between the treatment effects and the standard error of the estimate (SE logOR). All statistics were performed by the software Stata 12.0.

3 Results

3.1 Selection of studies

Our systemic search strategy identified 114 potentially relevant studies from designated databases, of which 85 did not fulfill inclusion criteria after careful examination of the titles and abstracts. The remaining 29 articles were read in full and evaluated carefully by investigators. Twelve papers were excluded due to insufficient data. Finally, a total of 17 studies (Gurubhagavatula *et al*., 2004; Wang *et al*., 2004; de las Penas *et al*., 2006; Gao *et al*., 2006; Giachino *et al*., 2007; Fan *et al*., 2008; Liu *et al*., 2008; Kalikaki *et al*., 2009; Sun *et al*., 2009; Yao *et al*., 2009; 2010; Ding *et al*., 2010; Qian *et al*., 2010; Zhou *et al*., 2011; Dong *et al*., 2012; Joerger *et al*., 2012; Li *et al*., 2012) were included in the final meta-analysis. Ten of these were written in English (Gurubhagavatula *et al*., 2004; de las Penas *et al*., 2006; Giachino *et al*., 2007; Kalikaki *et al*., 2009; Sun *et al*., 2009; Yao *et al*., 2009; Zhou *et al*., 2011; Dong *et al*., 2012; Joerger *et al*., 2012; Li *et al*., 2012) and the other seven in Chinese (Wang *et al*., 2004; Gao *et al*., 2006; Fan *et al*., 2008; Liu *et al*., 2008; Ding *et al*., 2010; Qian *et al*., 2010; Yao *et al*., 2010).

All papers included were subjected to quality assessment based on the Newcastle-Ottawa quality assessment scale. Studies fulfilling five or more of the eight criteria (≥5 stars) were deemed higher-quality studies. All 17 articles included in the current meta-analysis scored highly.

3.2 Study characteristics

A total of 2256 patients with advanced NSCLC from 17 studies were included in this meta-analysis. In all reports, classical polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was utilized for detection of *XRCC1* polymorphisms in peripheral blood cells. The total cohort included 522 AA genotype patients (23.2%), 916 AG patients (40.6%), and 818 GG patients (36.2%).

Twelve papers (Wang *et al*., 2004; Gao *et al*., 2006; Fan *et al*., 2008; Kalikaki *et al*., 2009; Sun *et al*., 2009; Yao *et al*., 2009; 2010; Ding *et al*., 2010; Qian *et al*., 2010; Zhou *et al*., 2011; Joerger *et al*., 2012; Li *et al*., 2012) reported the objective remission rate. Eight papers included survival, seven of which directly reported OS and HR (Gurubhagavatula *et al*., 2004; de las Penas *et al*., 2006; Giachino *et al*., 2007; Kalikaki *et al*., 2009; Yao *et al*., 2009; Dong *et al*., 2012; Joerger *et al*., 2012), while the remaining article (Liu *et al*., 2008) calculated HR and 95% CI according to the statistical method mentioned above. We divided all studies into two groups based on the reported data; investigations reporting the ORR usually originated from Asian populations (10/12), whereas studies conducted in regions with Caucasian majorities selected survival time as the main outcome indicator. The relevant characteristics of the 17 eligible studies are listed in Table 1.

3.3 Arg399Gln and response

Among the 12 papers analyzed, 7 reported complete raw ORRs (Wang *et al*., 2004; Gao *et al*., 2006; Sun *et al*., 2009; Ding *et al*., 2010; Qian *et al*., 2010; Yao *et al*., 2010; Joerger *et al*., 2012) including the total number of subjects and the number of patients achieving CR+PR for each genotype. Another 5 articles (Fan *et al*., 2008; Kalikaki *et al*., 2009; Yao *et al*., 2009; Zhou *et al*., 2011; Li *et al*., 2012) only reported the number of individuals with dominant gene models and wild type GG. The ORR was 45.2% (110/243) for AA, 29.9% (73/244) for AG, and 30.7% (124/403) for GG genotype. The GG vs. AA, AG vs. AA, GA+AA vs. GG, and GG+GA vs. AA groups were then compared. A heterogeneity test indicated no differences among the studies regarding heterogeneity (Fig. 1). Thus, we performed a meta-analysis using fixed-effect models and calculated the OR for each comparison: GG vs. AA (OR=0.489, 95% CI: 0.266–0.900, P=0.021), AG vs. AA (OR=0.608, 95% CI: 0.392–0.941, P=0.026), GA+AA vs. GG (OR=1.259, 95% CI: 0.931–1.701, P=0.135), and GG+GA vs. AA (OR=0.455, 95% CI: 0.313–0.663, P=0.0001) (Table 2 and Fig. 1). The pooled results revealed that patients carrying the AA genotype tended to be more susceptible to platinum-based therapies compared with those carrying GG+GA.

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

Study	Total number	Median age (year)	Disease stage	Ethnicity	Criterion	Genotype distribution			ORR	HR
						AA	AG	GG		
Li *et al*., 2012	87	59.08	III–IV	Asian	RECIST	53	30	4	Yes	NR
Dong *et al*., 2012	564	NR	III–IV	Asian	RECIST	33	227	304	NR	Yes
Joerger *et al*., 2012	131	59.7	III_B–IV	Caucasian	WHO	17	63	51	Yes	Yes
Zhou *et al*., 2011	111	NR	IV	Asian	WHO	6	34	71	Yes	NR
Yao *et al*., 2010	106	61	III_B–IV	Asian	RECIST	5	41	60	Yes	NR
Qian *et al*., 2010	107	NR	III_B–IV	Asian	WHO	59	40	8	Yes	NR
Ding *et al*., 2010	54	60	III_B–IV	Asian	WHO	13	10	31	Yes	NR
Sun *et al*., 2009	87	59	IV	Asian	WHO	4	30	53	Yes	NR
Yao *et al*., 2009	108	61	III_B–IV	Asian	WHO	5	43	60	Yes	Yes
Kalikaki *et al*., 2009	119	119	$III_{A/B}$–IV	Caucasian	RECIST	10	76	33	Yes	Yes
Fan *et al*., 2008	81	62.9	III_B–IV	Asian	WHO	4	32	45	Yes	NR
Liu *et al*., 2008	53	61	I–IV	Asian	RECIST	8	18	27	NR	Yes
Giachino *et al*., 2007	248	62	III_A–IV	Caucasian	RECIST	119	100	29	NR	Yes
Gao *et al*., 2006	57	59	II–IV	Asian	RECIST	31	23	3	Yes	NR
de las Penas *et al*., 2006	135	62	III_B–IV	Caucasian	RECIST	51	65	19	NR	Yes
Wang *et al*., 2004	105	56	III_B–IV	Asian	WHO	53	42	10	Yes	NR
Gurubhagavatula *et al*., 2004	103	58	III_A–IV	Caucasian	RECIST	51	42	10	NR	Yes

NR: no report; RECIST: response evaluation criteria in solid tumours; WHO: World Health Organization; ORR: overall response rate; HR: hazard ratio

Table 2 Results of the meta-analysis for the association between *XRCC1* Arg399Gln and response to platinum-based treatment in NSCLC

Genotype model	Number of studies	CR+PR/total		OR (95% CI)	*P*-value	
		Case	Control		Test of OR=1	Test of heterogeneity from the Q-test
GG vs. AA	7	47/195	90/199	0.489 (0.266–0.900)	0.021	0.585
AG vs. AA	7	73/244	90/199	0.608 (0.392–0.941)	0.026	0.657
GA+AA vs. GG	11	238/642	124/403	1.259 (0.931–1.701)	0.135	0.225
GG+GA vs. AA	8	126/484	110/243	0.455 (0.313–0.663)	0.0001	0.323

CR+PR: complete response+partial response

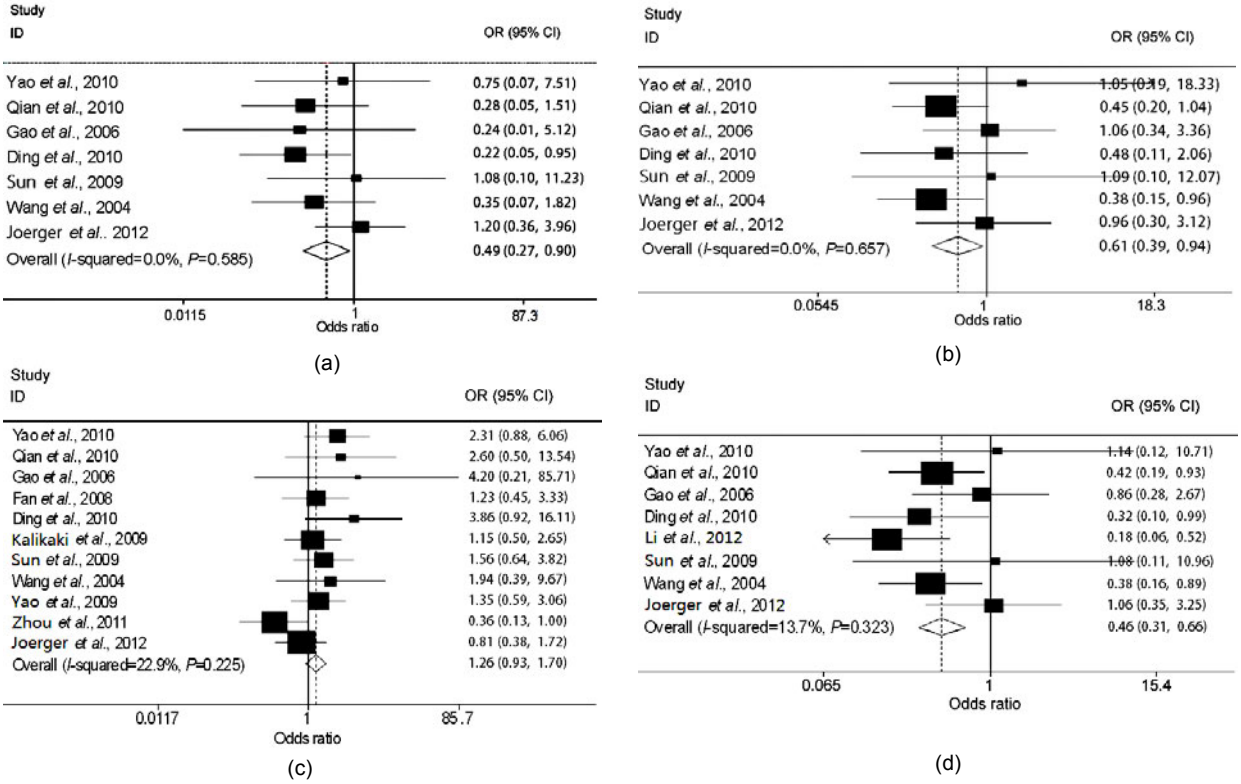

Fig. 1 Forest plots for the association of *XRCC1* Arg399Gln polymorphism and response to platinum-based treatment in NSCLC

Each study is represented by a point estimate of the OR and accompanying 95% CI. (a) GG vs. AA; (b) AG vs. AA; (c) GA+AA vs. GG; (d) GG+AG vs. AA

3.4 Arg399Gln allele and survival

Eight studies reported PFS and OS. However, different studies chose different genotypes as the reference value to calculate and report HR and 95% CI. Due to methodological difference and insufficient data reporting, the results could not be combined for a meta-analysis in most situations.

Two papers reported PFS (Liu *et al*., 2008; Joerger *et al*., 2012), but reported HR in different patterns, making it impossible to combine these studies. One paper suggested that the individuals carrying at least one G had a longer PFS, while another study found no relationship between Arg399Gln and PFS. No conclusion can be drawn due to insufficient data.

Eight papers reported OS, three of which (Gurubhagavatula *et al*., 2004; Giachino *et al*., 2007; Joerger *et al*., 2012) reported HR using AA as the reference value, three (Liu *et al*., 2008; Kalikaki *et al*., 2009; Dong *et al*., 2012) reported HR using GG as the reference value, and the other two papers (de las Penas *et al*., 2006; Yao *et al*., 2009) yielded limited data.

The median OS for AA, AG, and GG was 14.2, 15.4, and 16.1 months, respectively. We attempted to combine statistical data from those papers using the same reference value and found no correlation between genotype and OS (P>0.05). However, heterogeneity was observed among these studies (Table 3). Unfortunately, the data accrued to date do not allow for a firm conclusion on value of the Arg399Gln polymorphism as a prognostic factor in NSCLC.

3.5 Sensitivity analysis and publication bias

Sensitivity analyses were also conducted by excluding three studies (Gao *et al*., 2006; Liu *et al*., 2008; Ding *et al*., 2010) with small sample sizes. This did not change the final statistical outcomes but influenced statistical efficacy. Egger's test showed no evidence for significant publication bias (Table 4, P>0.05).

4 Discussion

The XRCC1 protein is essential for DNA repair and plays a key role in maintaining the stability of the genome. Numerous studies have assessed the relationship between *XRCC1* expression or SNP genotype and the efficacy of platinum-based therapies, but with disparate results. We performed a meta-analysis to determine if a specific *XRCC1* genotype, Arg399Gln, is predictive of improved or poorer clinical response of NSCLC patients to platinum-based anti-cancer drugs.

All the papers chosen for this meta-analysis study were case-control studies and were of high quality as determined by the Newcastle-Ottawa quality assessment. Nonetheless, the conclusions of these studies were often inconsistent. Regarding whether Arg399Gln acts as a suitable marker for predicting the

Table 3 Main results of studies for the association between *XRCC1* Arg399Gln and survival of NSCLC patients with platinum-based treatment

Study	AA			AG			GG		
	OS (month)	HR (95% CI)	Pooled value	OS (month)	HR (95% CI)	Pooled value	OS (month)	HR (95% CI)	Pooled value
Giachino *et al*., 2007	13.9	Reference		13.8	1.22 (0.86–1.74)	$^{*}P$=0.569	20.0	0.55 (0.30–1.00)	$^{*}P$=0.370
Joerger *et al*., 2012	6.0	Reference	Reference	10.4	0.62 (0.34–1.11)	I^2=51.2% $^{**}P$=0.129	10.8	0.56 (0.30–1.01)	I^2=87.0% $^{**}P$<0.001
Gurubhagavatula *et al*., 2004	17.3	Reference		11.4	1.22 (0.76–1.94)		7.7	3.17 (1.48–6.77)	
Liu *et al*., 2008	8.0	6.24 (1.86–20.91)	$^{*}P$=0.097	16.0	1.44 (0.66–3.12)	$^{*}P$=0.356	24.0	Reference	
Kalikaki *et al*., 2009	7.1	4.58 (1.92–10.92)	I^2=71.7% $^{**}P$=0.029	11.3	1.43 (0.86–2.40)	I^2=0.0% $^{**}P$=0.397	14.8	Reference	Reference
Dong *et al*., 2012	21.4	1.67 (1.08–2.60)		25.1	1.02 (0.81–1.29)		25.9	Reference	
Yao *et al*., 2009	29.0	NR		21.0	0.83 (0.49–1.41)		15.0	NR	
de las Penas *et al*., 2006	10.9	1.51 (1.03–2.40)		13.9	Reference		10.6	1.59 (0.81–3.10)	

OS: overall survival; HR: hazard ratio; NR: no report. * P-values for the test of HR=1; ** P-values for the test of heterogeneity from Q-test

Table 4 Main results from Egger's test for publication bias for all genotype models

Genotype model	Coefficient	t	P-value	95% CI	
				Lower	Upper
GG vs. AA	−0.65	−0.51	0.633	−3.95	2.64
AG vs. AA	1.53	1.99	0.103	−0.45	3.51
GA+AA vs. GG	1.71	1.65	0.133	−0.63	4.04
GG+GA vs. AA	1.47	1.23	0.266	−1.46	4.39

sensitivity of NSCLC patients to platinum-based chemotherapy, six papers (Wang *et al*., 2004; Kalikaki *et al*., 2009; Ding *et al*., 2010; Qian *et al*., 2010; Zhou *et al*., 2011; Li *et al*., 2012) suggested that Arg399Gln is able to predict the ORR, four articles (Gao *et al*., 2006; Sun *et al*., 2009; Yao *et al*., 2009; Joerger *et al*., 2012) found no relationship between Arg399Gln and ORR, and two papers (Fan *et al*., 2008; Yao *et al*., 2010) noted differences that did not reach statistical significance. Five papers (Gurubhagavatula *et al*., 2004; de las Penas *et al*., 2006; Liu *et al*., 2008; Kalikaki *et al*., 2009; Joerger *et al*., 2012) concluded that Arg399Gln is a prognostic factor while three (Giachino *et al*., 2007; Yao *et al*., 2009; Dong *et al*., 2012) found no significant correlation between *XRCC1* genotype and prognosis.

Of the 2256 cases included in this meta-analysis, 1520 were Asian and 736 Caucasian. Combined analysis of outcomes indicated that the patients carrying the G allele (GG+GA) were less sensitive to platinum-based therapies than patients with the AA genotype; so the Arg399Gln polymorphism is a predictive factor for the clinical response to platinum-based therapies. Nevertheless, we found no evidence that Arg399Gln was associated with survival time. Hence, Arg399Gln cannot yet be regarded as a prognostic factor. The knowledge gained from this study may be useful for selecting customized chemotherapy for advanced NSCLC.

Heterogeneity is a potential problem affecting the interpretation of meta-analyses. Studies included can differ significantly in terms of study design, inclusion criteria, treatment protocols, and evaluation standards for curative effectiveness. However, there was no statistically significant heterogeneity among the studies included that focused on clinical response, suggesting that *XRCC1* is a relatively independent predictive factor for clinical sensitivity. Nevertheless, we also noted heterogeneity in the combined analysis results for survival. In addition, it was impossible to perform further subgroup analysis due to the small number of studies included (n=3) in each available group (Table 3). We suggest that heterogeneity may stem from the variety of clinical treatments used during advanced NSCLC, including TKIs, chemotherapy, and radiotherapy, which may have distinct curative efficacies on different populations, eventually leading to inconsistent outcomes.

Our study has several limitations that had to be taken into consideration when interpreting the results. First, it was impossible to divide the data according to the specific platinum-based drug used (e.g., DDP, CBP, or oxaliplatin) because of limited number of studies published. Second, the number of studies included in meta-analysis for survival was relatively small due to the difficulty in HR data extraction. Thus, the survival prognosis of patients with different *XRCC1* allelic variants under platinum-based treatment requires further study. Furthermore, many other factors that could contribute to the objective response rate and survival of patients, such as sex, age, cancer type/stage, and smoking status, were not considered in this study, again due to limited sample sizes. This study also could not analyze the relationship between *XRCC1* alleles and the toxic effects of various platinum-based therapies or other chemotherapies. Furthermore, some data not explicitly reported were based on unadjusted estimates. Hence, more detailed individual data should be urgently supplemented.

Despite the limitations of this meta-analysis, it can be concluded that NSCLC patients with the AA genotype of the Arg399Gln *XRCC1* allele are more responsive to platinum-based therapies, but there is yet no convincing evidence that a specific Arg399Gln allele improves or diminishes actual survival under platinum-based chemotherapy. Therefore, *XRCC1* might act as a valuable marker of sensitivity to platinum-based chemotherapy. Considering the limitations mentioned above, it is imperative to conduct large scale prospective clinical studies of platinum-based drugs in NSCLC patients.

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