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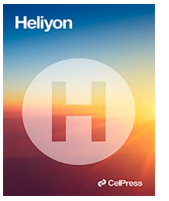

Association between *XRCC1 Arg399Gln* polymorphism with prognosis of head and neck squamous cell carcinomas: A meta-analysis

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ABSTRACT

Objective: The *X-ray repair cross complementing group 1* (*XRCC1*) gene is involved in DNA repair. Defects in DNA repair may lead to head and neck squamous cell carcinomas (HNSCCs). Several researches have focused on relationship between *XRCC1* Arg*399Gln* genetic polymorphism with HNSCC's prognosis with conflicting results. So, the aim of the present meta-analysis was evaluation of relationship between *XRCC1* Arg*399Gln* polymorphism with HNSCC's prognosis.
Methods: Published articles up to July 2022 were systematically searched through international databases like PubMed, Web of Science, Scopus, etc. I^2 test was applied to assess the heterogeneity. Data were analyzed using random effects model. Funnel plots and Egger test were applied for assessing publication biases. The hazard ratios (HRs) and 95 % confidence intervals (CIs) were calculated for evaluation of relationship between the polymorphism with HNSCC's prognosis.
Results: Fifteen articles were included for the systematic review. Six of those articles were considered for inclusion in meta-analysis. The different forms of *XRCC1* Arg*399Gln* polymorphism had not significant association with overall survival (OS) under varied genetic models (heterozygous: Ln (HR) = 0.02, 95 % CI= (−0.33,0.37), p-value = 0.90; homozygous: Ln (HR) = 0.33, 95 % CI= (−0.03,0.69), p-value = 0.07 and dominant: Ln (HR) = 0.06, 95 % CI = (−0.17,0.28), p-value = 0.62). Analysis showed that variants of the polymorphism had no significant relationship with OS in Asian and Caucasian ethnicity under dominant model (Ln (HR) = 0.14, 95 % CI= (−0.13,0.40), p-value = 0.31; Ln (HR) = -0.01, 95 % CI= (−0.41,0.38), p-value = 0.96).
Conclusion: Different forms of *XRCC1* Arg*399Gln* polymorphism had no significant relationship with HNSCC's prognosis under varied genetic models and based on different ethnicity.

1. Introduction

Head and neck squamous cell carcinomas (HNSCCs) are among the most frequent cancers worldwide which its etiopathogenesis involves genetic and environmental risk factors [1].

The prognosis of HNSCC's patients is still poor despite advances in treatment modalities (reported 5-year survival rate is about 25–60 %) [2,3]. Efforts to find factors affecting survival in head and neck cancers continue and many studies have been conducted in

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this field [3]. Even sometimes the prognosis of patients with similar clinical characteristics, clinical stage and treatment methods are different from each other. Variation of HNSCC patients' prognosis can be at least in part justified by polymorphisms in genes involving in the biological pathways of HNSCC's carcinogenesis. Radiotherapy and/or chemotherapy are among the main treatments of HNSCCs. Chemoradioresistance in HNSCCs is related to genetic factors and the genetic alteration finally affects the clinical outcome. Genetic variation including gene polymorphism may bring about differential radiosensitivity and/or chemosensitivity in the patients which may result in different prognosis of patients. Identifying radiosensitive/radioresistant or chemosensitive/chemoresistant patients through gene polymorphisms, on the one hand, helps to predict the survival and prognosis of HNSCC's patients, and on the other hand, it will help to carry out personalized treatments [4–6].

Radiotherapy and/or chemotherapy (as the main treatments of HNSCCs) exert a major part of their effects by inducing DNA damage which subsequently causes cell apoptosis. HNSCC's cells may acquire radio/chemo-resistance by enhancing DNA damage repair capacity. Analysis of the polymorphic variants of genes involved in the DNA repair pathway (including X-ray repair cross-complementing or *XRCC* genes) and carcinogen metabolism pathway are among the most studied genetic polymorphisms in relation to HNSCC's prognosis [2,3]. The *X-ray repair cross-complementing group 1* (*XRCC1*) gene plays an important role in the base excision repair (BER) pathway of DNA repair. The *XRCC1* was the first gene known to have impact on sensitivity to ionizing radiation (in radiotherapy) and chemotherapeutic drugs. The *XRCC1* protein can repair DNA damage induced by ionizing radiation or chemotherapeutic drugs. In HNSCC's patients, the *XRCC1* expression has been reported to be associated with poorer survival due to higher cell resistance to chemoradiation. Resistance to radiotherapy/chemotherapy may lead to treatment failure, and this failure affects patient's outcome and prognosis. Some polymorphisms of *XRCC1* gene may change the gene expression or protein function which influences cell function and cellular response. In fact, the *XRCC1* gene polymorphism may affect the DNA damage repair capacity, and in this way, it will affect the response to radiotherapy and chemotherapy treatments, which in turn can affect the prognosis of patients [7].

Several studies have focused on relationship between *XRCC1* Arg*399Gln* single nucleotide polymorphism (SNP) and HNSCC's

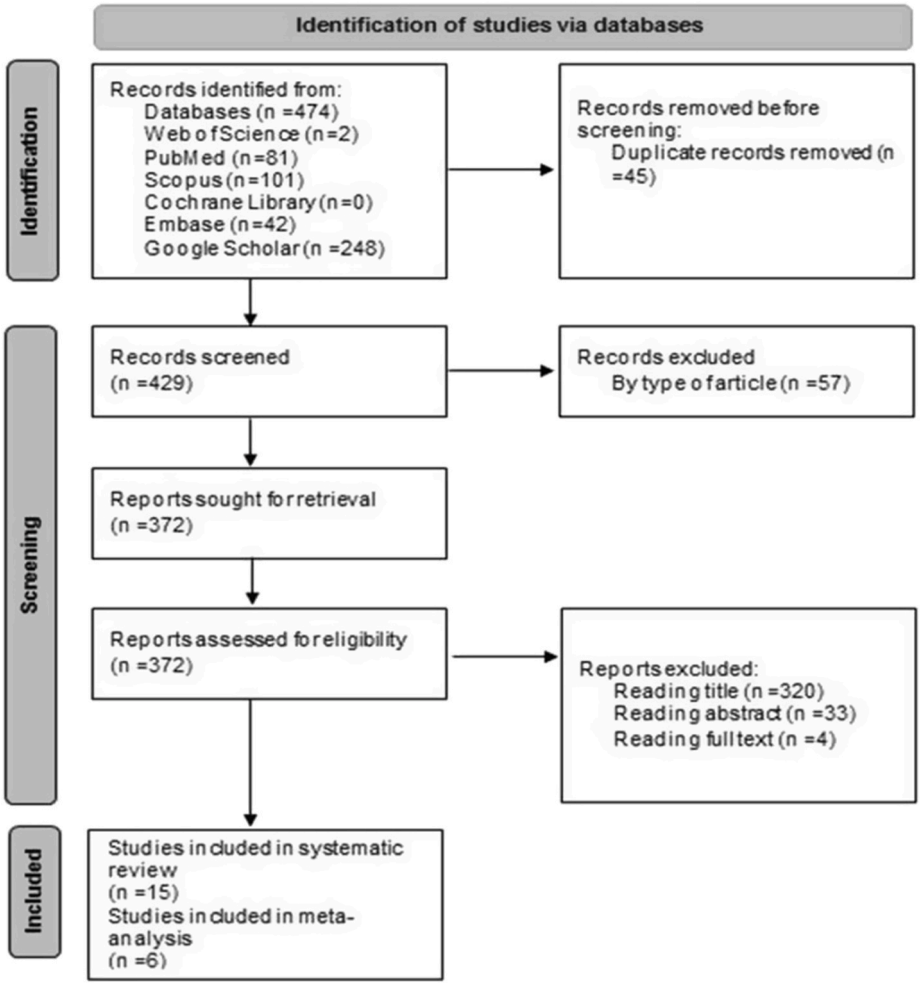

Fig. 1. PRISMA flow diagram showing studies identification and selection process.

prognosis with conflicting results [3]. So, the aim of the present meta-analysis was evaluation of relationship between *XRCC1* Arg*399Gln* polymorphism with prognosis of HNSCCs.

2. Materials and methods

The present meta-analysis was recorded in the PROSPERO (Identity Document Number: CRD42022335207).

3. Searching the articles

PRISMA diagram applied to identify and include studies (Fig. 1).

Articles searched for eligibility using MeSH terms:

Genetic polymorphism, genetic variation, single nucleotide polymorphism, X-ray repair cross complementing protein 1, DNA repair, Prognosis, Survival, head and neck neoplasms, squamous cell carcinoma of head and neck.

4. Databases

The searched was done using international databases including Google Scholar, Web of Science, Scopus, PubMed, Embase and Cochrane.

5. Eligibility criteria

The present meta-analysis consisted of published articles till July 2022 from any language.

Report of hazard ratios (HRs) with 95 % confidence intervals (CIs) was one of the selection criteria. Meta-analysis was performed if at least four studies with associated HR and 95 % CI were present.

A score of quality lower than expected (<60 % based on JBI checklist) would cause the article to be removed. According to PRISMA, irrelevant articles were excluded (rejected) from the study based on duplicated titles, type of article, and by reading the articles.

6. Data extraction

Articles were checked through the information of the following items, respectively: title, abstract and full text. Duplicate articles were also excluded.

Table 1
Characteristics of the studies included in this systematic review.

First Author, year	Ethnicity	Sample size	Tumor site	Clinical stage	Genotyping methods	Survival analysis	Measurement of survival
Gal, 2005 [8]	Caucasian	267	Oral cavity	NS	MALDI-TOF MS	OS, DSS	HR
Geisler, 2005 [9]	Caucasian	155	Oral cavity, pharynx, larynx	I, II, III, IV	PCR-RFLP	OS, DSS, DFS	HR
Quintela-Fandino, 2006 [10]	Caucasian	103	Oral cavity, pharynx, larynx	IV	PCR-RFLP	OS	SC
Carles, 2006 [11]	Caucasian	98	Oral cavity, pharynx, larynx	I, II	TaqMan	OS, PFS	SC
Csejtei, 2009 [12]	Caucasian	108	Oral cavity, pharynx, larynx	I, II, III, IV	PCR-RFLP	OS	SC
Azad, 2012 [13]	Caucasian	530	Oral cavity, pharynx, larynx	I, II	TaqMan	OS, DFS	HR
Liu, 2013 [14]	Asian	421	Pharynx	III, IV	LDR-PCR	OS, PFS	HR
Jin, 2014 [15]	Asian	75	pharynx	II, III, IV	Sanger sequencing	DFS	HR
Stur, 2015 [16]	Mixed	311	Oral cavity, pharynx, larynx	NS	PCR-RFLP	DFS, DSS	SC
Costa, 2016 [17]	Mixed	125	Pharynx	IV	PCR-RFLP	OS, PFS	HR
Hirakawa, 2020 [18]	Asian	225	Pharynx, larynx	I, II, III, IV	PCR-RFLP	OS	HR
Dutta, 2020 [19]	Asian	45	Oral cavity, pharynx, larynx	I, II, III, IV	PCR-RFLP	OS, PFS	Mean, SC
Senghore, 2020 [20]	Asian	319	Oral cavity	III, IV	Sequenom	OS, DFS	HR
Duran, 2021 [21]	Caucasian	110	Oral cavity, pharynx, larynx	III, IV	Sequenom	OS, DFS	HR
Novais, 2021 [22]	Mixed	91	Oral cavity, pharynx, larynx	I, II, III, IV	PCR-RFLP	OS, DFS	Mean

OS: overall survival; DSS: disease-specific survival; DFS: disease-free survival; PFS: progression-free survival; HR: hazard ratio; SC: survival curve; NS: not specified.

7. Quality Assessment

This is done using JBI appraisal tool.

8. Data analysis

The data were analyzed by STATA software (version 17.0). Stata is a statistical software created by Stata Corporation for manipulation of data, statistical visualization, and automated reporting [1]. The Ln (HRs) with 95 % CIs applied for evaluation of relationship between *XRCC1* Arg*399Gln* polymorphism with HNSCC's prognosis. The pooled Ln (HRs) obtained from Random effects model [2,3]. The pooled Ln (HRs) obtained under varied genetic models. The evaluation of heterogeneity was implemented using I^2 test. Forest plots helped to visualize overall effect. A forest diagram is a useful graphical show of the results of the meta-analyses that provides important information for interpreting the results [5]. Publication bias was assessed by Egger test and funnel plot. A funnel plot is applied to check for publication bias in the meta-analyses. This chart is a simple scatter plot arranged on the horizontal axis of the effect size and the vertical axis of the standard error of the effect size [4]. The Egger test uses linear regression to assess the association between effect size estimates and the standard errors (SEs) [6].

9. Results

Among 474 screened articles, 15 articles were selected for the study. Six articles included in meta-analysis. All the studies had acceptable quality.

Table 1 represents all the studies that were systematically selected.

Heterogeneity data are presented in Table 2. The results of Egger test showed no publication biases. Fig. 2 shows the funnel plot for evaluation of publication bias in analysis of relationship between *XRCC1* Arg*399Gln* gene polymorphism with overall survival (OS) under dominant model (Fig. 2).

Table 2 represents the relationship between studied polymorphism with HNSCC's prognosis.

Relationship between *studied* polymorphism with HNSCC's overall survival with respect to varied genetic models.

There was no significant relationship between studied polymorphism with HNSCC's OS based on homozygous, heterozygous and dominant genetic models; the *AA*, *GA* and *GA* + *AA* polymorphic variants had no significant relationship with worse OS in comparison to wild-type (*GG* genotype).

Figs. 3–5 show forest plots for the relationship of studied polymorphism with HNSCC's overall survival under homozygous, heterozygous and dominant genetic models (Figs. 3–5).

9.1. Relationship between studied polymorphism with HNSCC's overall survival with respect to ethnicities

There was no significant relationship between studied polymorphism with HNSCC's overall survival with respect to Asian and Caucasian ethnicities in dominant genetic model; the *GA* + *AA* variants had no significant relationship with worse overall survival

Table 2
Results of meta-analysis on relationship between *XRCC1* Arg*399Gln* polymorphism with HNSCC's overall survival in different subgroups.

survival Subgroup/genetic model		First author, Year	Overall survival HR (95% CI)	Statistic (I^2 [%])	Pooled ln (HR) (%95 CI)	P-value
Genetic model	**Heterozygous**	Gal, 2005 [8]	−0.42 (−0.79, −0.04)	70.88	0.02 (−0.33,0.37)	0.90
		Azad, 2012 [13]	0.39 (0.09,0.68)			
		Liu, 2013 [14]	0.12 (−0.28,0.53)			
		Senghore, 2020 [20]	−0.06 (−0.51,0.39)			
	Homozygous	Gal, 2005 [8]	−0.26 (−0.92,0.40)	26.04	0.33 (−0.03,0.69)	0.071
		Azad, 2012 [13]	0.40 (−0.05,0.85)			
		Liu, 2013 [14]	0.59 (−0.02,1.19)			
		Senghore, 2020 [20]	0.60 (-0.26,1.47)			
	Dominant	Gal, 2005 [8]	−0.39 (-0.75, −0.02)	49.70	0.06 (−0.17,0.28)	0.620
		Geisler, 2005 [9]	0.06 (−0.45,0.56)			
		Azad, 2012 [13]	0.25 (0.05,0.45)			
		Liu, 2013 [14]	0.22 (-0.15,0.59)			
		Hirakawa, 2020 [18]	0.15 (−0.75,1.04)			
		Senghore, 2020 [20]	0.03 (-0.40,0.46)			
Ethnicity	**Asian**	**Dominant** Liu, 2013 [14]	0.22 (−0.15,0.59)	0	0.14 (−0.13,0.40)	0.315
		Hirakawa, 2020 [18]	0.15 (-0.75,1.04)			
		Senghore, 2020 [20]	0.03 (-0.40,0.46)			
	Caucasian	**Dominant** Gal, 2005 [8]	−0.39 (−0.75, −0.02)	74.85	−0.01 (−0.41,0.38)	0.960
		Geisler, 2005 [9]	0.06 (−0.45,0.56)			
		Azad, 2012 [13]	0.25 (0.05,0.45)			

HR: hazard ratio; CI: confidence interval.

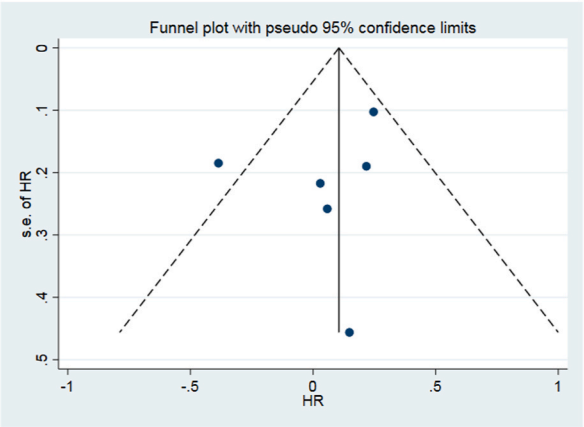

Fig. 2. Funnel plot drawn for evaluation of publication bias of studies included in the meta-analysis of relationship between *XRCC1* Arg*399Gln* polymorphism with overall survival under dominant model.

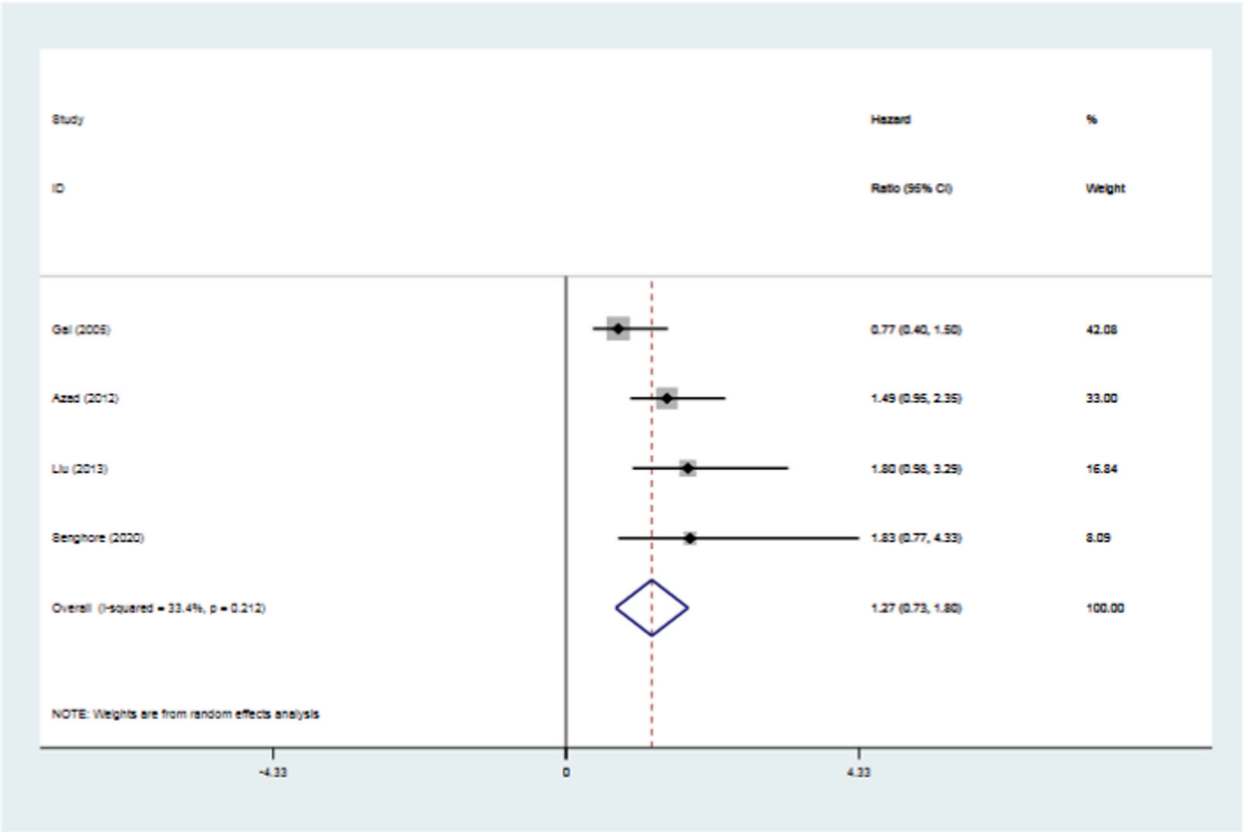

Fig. 3. Forest plot for analyzing relationship between *XRCC1* Arg*399Gln* polymorphism with HNSCC's overall survival under homozygous genetic model.

compared to *GG* genotype in Asian ethnicity; these polymorphic variants were not also significantly associated with worse overall survival compared to *GG* genotype in Caucasian ethnicity.

Fig. 6 represents forest plot in analyzing relationship between studied polymorphism with HNSCC's OS with respect to Asian ethnic group in dominant genetic model (Fig. 6).

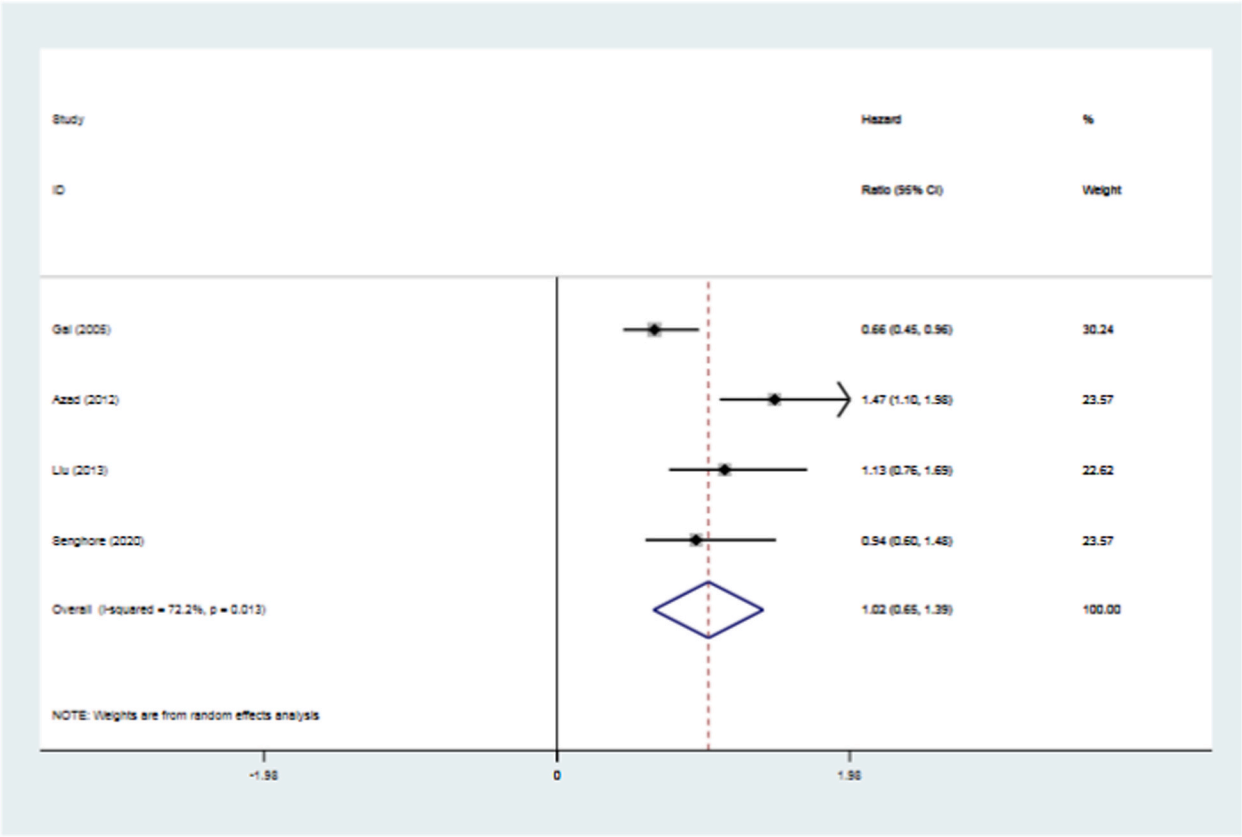

Fig. 4. Forest plot for analyzing relationship between *XRCC1* Arg*399Gln* polymorphism with HNSCC's overall survival under heterozygous genetic model.

10. Discussion

The meta-analysis displayed that different forms of studied polymorphism had no significant relationship with HNSCC's prognosis. Analysis showed that the polymorphic variants were not also significantly associated with OS in Asian and Caucasian ethnic groups. These results demonstrate that the studied gene polymorphism is not involved in prognosis of HNSCC's patients, and as a result, the studied polymorphism cannot be mentioned as a prognostic factor in HNSCCs. These results cannot help in predicting the prognosis of patients through the determination of different forms of *XRCC1* Arg*399Gln* polymorphism. Various factors such as clinical stage, tumor location, histopathologic grade, health status, gender, age, treatment modalities, race and etc. have been implicated in the prognosis of HNSCC's patients. Genetic factors and variations and interaction between different polymorphisms should be added to these factors; all of these factors in interaction with each other will ultimately define prognosis of patient, and each of them alone cannot define prognosis of patient. Therefore, due to the existence of different prognostic factors in different geographical regions and among different ethnicities, it is possible that gene polymorphisms have different prognostic significance among different ethnicities. The *XRCC1* Arg*399Gln* polymorphism was investigated in this study for this reason, although it was not associated with different results in Asian and Caucasian ethnicities. It implies that the polymorphism is not associated with increased or decreased survival in one population compared to another ethnic group [22].

Table 3 presents a list of four studied polymorphisms of *XRCC1* gene in different studies in relation to HNSCC's prognosis (Table 3). As you can see, most of the existing studies on relationship of HNSCC's prognosis with *XRCC1* polymorphisms have focused on the Arg399Gln (rs25487) polymorphism, and there are few studies on other polymorphisms. Focusing on the above-mentioned polymorphism indicates its importance in creating variant protein and subsequently altering DNA damage repair capacity, which can in turn affect the response to radiotherapy and chemotherapy treatments (mainly exert their effects through DNA damage), and ultimately to affect the patient prognosis. The reason for selecting the mentioned polymorphism in this study was existence of more studies about selected polymorphism in addition to the importance of it in relation to HNSCC's prognosis.

Some chemotherapeutic agents like cisplatin induce their cytotoxic effects via DNA damage and production of DNA-adducts which subsequently interfere with DNA transcription and replication of cancer cells. The *XRCC1* gene and its related protein play important role in repairing damage to DNA and DNA adducts. Genetic variations can cause differences in DNA repair ability and drug metabolism in different individuals. So, XRCC1 SNPs may have some association with chemotherapy response and prognosis of cancers [23,24].

The results of the present meta-analysis regarding the non-existence of a significant relationship between survival and *XRCC1*

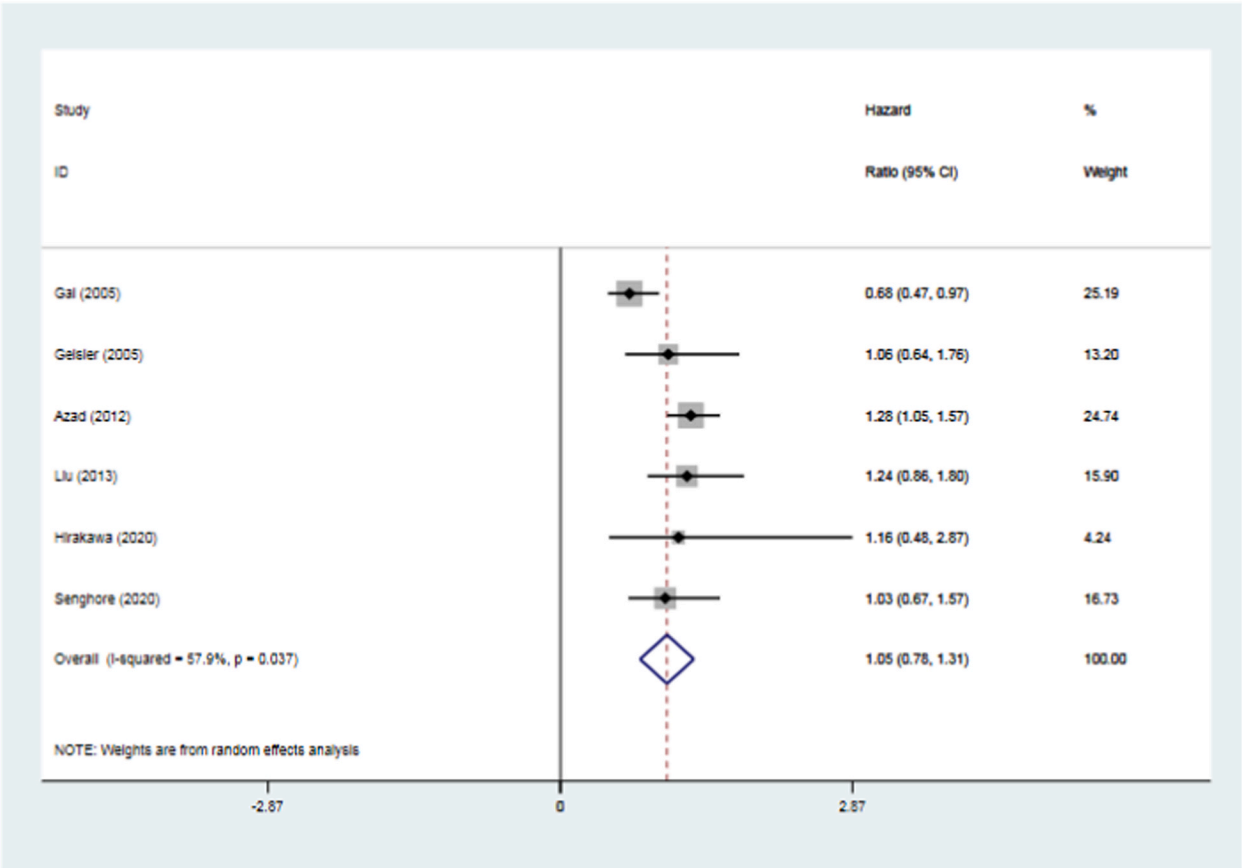

Fig. 5. Forest plot for analyzing relationship between *XRCC1* Arg*399Gln* polymorphism with HNSCC's overall survival under dominant genetic model.

Arg*399Gln* polymorphism are somewhat inconsistent with the results of the some meta-analyses conducted on cancers of other parts of the body [23,25,26,27]. This inconsistency can indicate the different impact of the polymorphism on the prognosis of cancers in different parts of the body, which can be due to different etiological factors and carcinogenesis processes of cancers of different parts of the body, or because of the use of different chemotherapy drugs with different mechanisms which consequently will determine the impact of such a polymorphism on the patient prognosis. For example, damage to DNA in the carcinogenesis process of cancers of other parts of the body may be more important compared to HNSCCs, and polymorphism in the *XRCC1* gene, which is a DNA repair gene, has more impact on the prognosis of corresponding patients; or, for example, chemotherapeutic agents such as cisplatin (which its mechanism is through damage to DNA and production of DNA-adducts in cancer cells) may be applied more frequently and playing a more prominent role in cancers of other areas compared to HNSCCs; so, the *XRCC1* gene polymorphism (which is related to repair of DNA and DNA-adducts) has consequently more impact on the prognosis of those cancers. In the meta-analysis by Cui on lung cancers, the *GA* and *AA* genotypes had significant relationship with worse OS [23]. In meta-analyses of Cao and Xu on gastric cancers, the *A* allele (*GA* + *AA* genotypes) had significant relationship with worse 2-year OS in comparison to *GG* genotype [25,26]; no significant relationship was found between the *A* allele and 5-year OS [25]. In a meta-analysis by Zhang on Asian group with non-small cell lung cancers (NSCLC), the *AA* genotype was related with better OS and progression-free survival (PFS) [27].

The results of the present meta-analysis are somewhat consistent with the results of some other meta-analyses conducted on cancers of other parts of the body (except head and neck) [24,28,29,30]. Similar to the lack of significant relationship between survival and studied polymorphism in the present meta-analysis, in meta-analyses of Ye [24], Chen [28], Zhang [29] and Zhao [30] no significant relationships between the polymorphism with survival were found in the studied cancers. In a meta-analysis of Ye on colorectal cancers, there were not significant relationship between *XRCC1* Arg*399Gln* polymorphism with progression-free survival (PFS) under homozygous and heterozygous genetic models [24]. In a study of Chen on non-small cell lung cancers, no significant relationship was present between the polymorphism with overall survival following platinum-based chemotherapy [28]. In the meta-analysis by Zhang [29] on ovarian cancers, although the polymorphism was not related with OS, there was significant relationship when the percentage of stage III or IV cases was >80 so that the AA genotype was related with worse OS; considering the last analysis, there was inconsistency between their result and our results. In the meta-analysis by Zhao, there was no significant relationship between the polymorphism with OS of hepatocellular carcinoma patients [30].

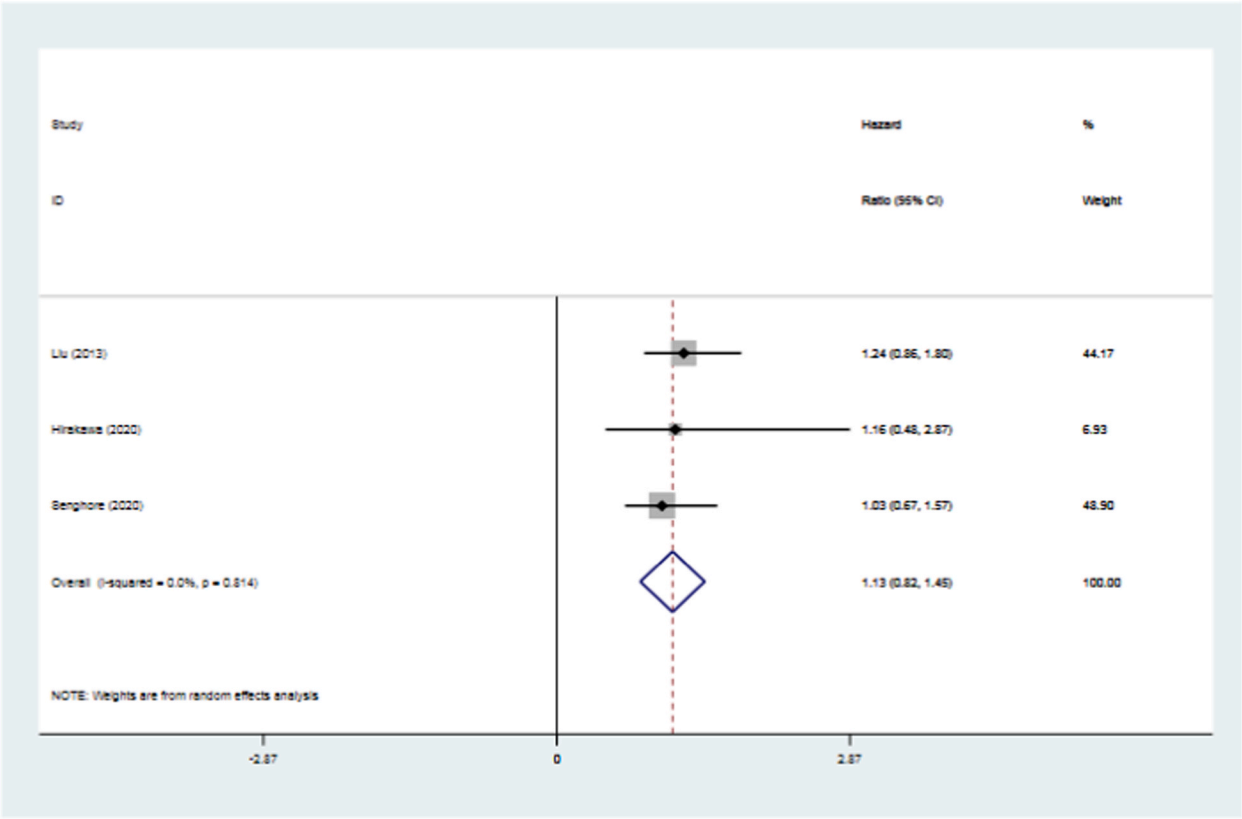

Fig. 6. Forest plot for analyzing relationship between *XRCC1* Arg*399Gln* polymorphism with HNSCC's overall survival based on Asian ethnicity under dominant genetic model.

Table 3
A list of studied *XRCC1* gene polymorphisms in different studies in relation to HNSCC prognosis.

Studied polymorphisms	First author, year
Arg399Gln (rs25487)	Gal, 2005 [8]; Geisler, 2005 [9]; Quintela-Fandino, 2006 [10]; Carles, 2006 [11], Csejtei, 2009 [12]; Azad, 2012 [13]; Liu, 2013 [14]; Jin, 2014 [15]; Stur, 2015 [16], Costa, 2016 [17]; Hirakawa, 2020 [18]; Dutta, 2020 [19]; Senghore, 2020 [20]; Duran, 2021 [21]; Novais, 2021 [22]
Arg194Trp (rs1799782)	Nanda, 2018 [6]; Geisler, 2005 [9]; Stur, 2015 [16]; Costa, 2016 [17]; Senghore, 2020 [20]
rs3213245	Costa, 2016 [17]
rs25489	Costa, 2016 [17], Senghore, 2020 [20]

At the end of the discussion, we add some points about relationship between studied polymorphism with HNSCC's risk. As published in our previous systematic review article, there are conflicting results about this association so that in one study, the frequency of the AA genotype was higher in HNSCC's group in comparison with control group; on the other hand, in four studies, the AA variant was related with a decreased risk for HNSCC and in other studies (5 studies), all variants were not related with increasing or decreasing risk of HNSCC [31].

The strength of present study is performing a meta-analysis on existing studies in order to obtain a general conclusion from the studies by the readers of the systematic review. Among other strengths, we can point out to investigation of relationship between gene polymorphism with the prognosis of patients according to different gene models, including homozygous, heterozygous and dominant, as well as examining this association in Asian and Caucasian ethnic subgroups.

The main limitation of the present study was the small number of studies with enough information for inclusion in the study. Other limitation of study was the lack of enough data from other ethnic groups except Asians and Caucasians to perform meta-analysis, and also according to the available information, it was only possible to perform meta-analysis based on the dominant model in ethnic subgroups.

11. Conclusion

No significant relationship was present between *XRCC1* Arg*399Gln* polymorphism with HNSCC's prognosis in varied genetic models so that the polymorphic variants were not associated with worse or better overall survival. Based on different ethnic groups, the polymorphic variants were not related with overall survival in Asian and Caucasian ethnic groups in dominant model.

Ethics approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Funding

None.

Data availability statement

The data associated with our study has not been deposited into a publicly available repository.
Data included in article/supplementary material.

CRediT authorship contribution statement

Khadijeh Najafi-Ghobadi: Conceptualization, Data curation, Formal analysis, Methodology, Software, Writing – original draft, Writing – review & editing. **Mahdieh Rajabi-Moghaddam:** Conceptualization, Data curation, Investigation, Supervision, Writing – original draft, Writing – review & editing. **Hamid Abbaszadeh:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e21111.

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