Article

Not peer-reviewed version

Role of rs873601 polymorphisms in prognosis of lung cancer patients treated with platinum-based chemotherapy

Ting Zou , Jun Yan Liu , Qun Qin , Jie Guo , Wen Zhi Zhou , Xiang Ping Li , Honghao Zhou , Juan Chen * , Zhao Qian Liu *

Posted Date: 13 October 2023

doi: 10.20944/preprints202310.0897.v1

Keywords: Lung cancer; Platinum-based chemotherapy; ERCC5; Genetic polymorphism; Prognosis

Article

Role of rs873601 Polymorphisms in Prognosis of Lung Cancer Patients Treated with Platinum-Based Chemotherapy

Ting Zou [1,2,3,4], Jun-Yan Liu [5], Qun Qin [1,4], Jie Guo [1,4], Wen-Zhi Zhou [1,4], Xiang-Ping Li [1], Hong-Hao Zhou [2], Juan Chen [1,3]* and Zhao-Qian Liu [2,3]*

[1] Department of Pharmacy, and National Institution of Drug Clinical Trial, Xiangya Hospital, Central South University, Changsha, China, 410008;
[2] Department of Clinical Pharmacology, Hunan Key Laboratory of Pharmacogenetics, Xiangya Hospital, Central South University, Changsha, China, 410078;
[3] National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha, China, 410008;
[4] International Science and Technology Innovation Cooperation Base for Early Clinical Trials of Biological Agents in Hunan Province.
[5] Department of Orthopaedics, Department of orthopaedics, Xiangya Hospital, Central South University, Changsha, China, 410008
* Correspondence: Professor **Zhao-Qian Liu**, Department of Clinical Pharmacology, Hunan Key Laboratory of Pharmacogenetics, Xiangya Hospital, Central South University, Changsha 410008，P. R. China. Tel: +86 731 89753845, Fax: +86 731 82354476, E-mail: zqliu@csu.edu.cn. Or **Juan Chen**, Department of Pharmacy, Xiangya Hospital, Central South University, Changsha 410008; P. R. China. E-mail: cj1028@csu.edu.cn.

Abstract: Background: Lung cancer is still the most lethal malignancy in the world from the report of Cancer Statistics in 2021. Platinum-based chemotherapy combined immunotherapy is the first-line treatment in lung cancer patients. However, the 5-year survival rate always affected by the adverse reaction and drug resistance caused by platinum-based chemotherapy. DNA damage and repair system is one of the important mechanisms which can affect the response to chemotherapy and clinical outcome in lung cancer patients. Objective: The objective of this study is to find the relationship between the polymorphisms of DNA repair genes with the prognosis in platinum-based chemotherapy in lung cancer patients. Patients and Methods: We performed genotyping in 17 single nucleotide polymorphisms (SNPs) of Excision Repair Cross-Complementation group (*ERCC*) genes and X-ray Repair Cross-Complementing (*XRCC*) genes of 345 lung cancer patients by Sequenom MassARRAY. We used Cox proportional hazard models, state and plink to analyze the associations between SNPs and the prognosis of lung cancer patients. Results: We found that the *ERCC5* rs873601 was associated with the overall survival time in lung cancer patients treat by platinum-based chemotherapy (p=0.031*). We also discovered that the polymorphisms in rs873601 was significantly associated with the prognosis in age more than 55 years, Small Cell Lung Cancer (SCLC) and smoking patients, Long Intergenic Non-protein Coding RNA (*PNKY*) rs2444933 in age less than 55 years, SCLC, metastasis and stage III/IV/ED patients, Short Tau Inversion Recovery (*STIR1*) rs3740051 in SCLC and metastasis patients, *PNKY* rs1869641 in SCLC patients, *XRCC5* rs1051685 in non-metastasis patients, respectively. Conclusion: The *ERCC5* rs873601(G>A) maybe a valuable biomarker for predicting the prognosis in lung cancer patients treated with platinum-based chemotherapy.

Keywords: lung cancer; platinum-based chemotherapy; *ERCC5*; Genetic polymorphism; prognosis

Introduction

Lung cancer is one of the leading cancer types and the highest lethal malignancies in the world [1]. It consists of Small Cell Lung Cancer (SCLC) and Non-Small Cell Lung Cancer (NSCLC), NSCLC account for almost 80% for the lung cancer cases, including adenocarcinoma, squamous cell cancer and large cell lung cancer [2]. The treatment strategy of lung cancer consists of surgery, radiation oncology, chemotherapy, immunotherapy and targeted therapy [3]. Despite the progress of

 doi:10.20944/preprints202310.0897.v1

immunotherapy and targeted therapy in the past years, platinum-based chemotherapy combined immunotherapy is still the first-line treatment for lung cancer patients [4]. The 5-year survival is a crucial indicator for the treatment efficacy [5]. The occurrence of drug-resistance and treatment toxicity creates substantial barriers to disease control, such as gastrointestinal toxicity and hematological toxicity, which result in a poor 5-year survival 6. It's remarkable that the chemotherapy outcomes differ from individuals, which means the genetic polymorphisms may play an important role in the efficacy of chemotherapy treatment [7]. Until now, more and more genetic polymorphisms have been found to be associated with the outcomes of chemotherapy, such as Eukaryotic translation Initiation Factor 3 subunit A (*eIF3A*), Rac family small GTPase 1 (*RAC1*), WNT1 Inducible Signaling Pathway protein 1 (*WISP1*) and so on [8-10]. The specific mechanisms are still discovering on the way.

As we all know, DNA damage and repair pathway is of great importance in heath and disease [11]. DNA damage can be classified into two main categories based on its origin: endogenous and exogenous [12]. DNA damage and repair pathway can prevent DNA damage from causing mutations and cytotoxicity, but the unbalanced repair of DNA damage always leads to the development of tumors [13, 14]. It has been reported that the genetic polymorphisms of DNA repair pathways can significantly affect the response to cisplatin treatment in lung cancer patients [15, 16]. The DNA damage and repair pathway are consist of mismatch repair (MMR), base excision repair (BER), nucleotide excision repair (NER) and double-strand break (DSB) repair systems [17].

The Excision Repair Cross-Complementation 5 (*ERCC5*), also called as Xeroderma Pigmentosum Group (*XPG*), is a gene performing its function in nucleotide excision repair (NER), and it can also protect replication forks by promoting homologous recombination [18]. *ERCC5* contains 17 exons, spans 32 kb with a location of chromosome 13q33.1 [19]. It plays an essential role in the occurrences and clinical outcomes of lung cancer. The *ERCC5* rs4771436 and rs1047768 genotypes have been found to be associate with the risk of lung cancer [20]. The *ERCC5* His46His genomic polymorphisms can significantly affect the response to chemotherapy in advanced NSCLC patients [21].

The Xeroderma Pigmentosum group A (*XPA*) is another key member of NER, it can catch the damage site of the DNA substrate through binding the NER core repair factors [22]. It is also reported to be connected with the development and efficacy of lung cancer. *XPA* rs1800975 polymorphisms has been found to be associated with the susceptibility in lung cancer patients [23]. The genomic variabilities of *XPA* rs2808668 is also considered to jointly contribute to lung cancer risk [24]. The mutation of *XPA* rs3176658 is significantly associate with the progress free survival in NSCLC patients [25].

The other genes of NER are also reported to play vital roles in lung cancer occurrences and clinical outcomes. The single nucleotide polymorphisms of *XRCC3* rs861539 is related to the prognosis of NSCLC patients [26]. The variables of *XRCC5* (rs1051685, rs6941) were associated with hematologic toxicity in lung cancer patients treat with platinum-based chemotherapy, which means it can predict the platinum-based chemotherapy toxicity in lung cancer patients [27]. The expression of *ERCC1* may be a useful prognostic marker in lung adenocarcinoma, the lower expression had a longer overall survival [28]. And patients with the C/C genotype in rs3212986 of the *ERCC1* gene had longer median progress free survival in NSCLC patients [29].

In this study, we selected 17 SNPs from ERCC5, PNKY, ERCC1, SIRT1, XPA, XRCC3 and XRCC5, such as rs873601, rs2444933, rs3740051, rs1869641, rs1051685 and so on. The rs873601 has been reported to be associated with cancer susceptibility [30]. The rs3740051 plays an important role in the development of pituitary adenoma [31]. The transporter genes polymorphisms of rs1869641 have been reported to show significant relation to chemotherapy response [32]. The rs1051685 was reported to associated with the response and survival in relapsed or refractory multiple myeloma patients [33]. Based on the previous study, we aim to find the new biomarkers to predict the efficacy in lung cancer patients, which can make forward to a more intensive guidance in the clinical diagnosis and treatment.

Material and Methods

Research objects and treatment procedures

 doi:10.20944/preprints202310.0897.v1

All the subjects enrolled were selected by the following conditions: (1) Patients who were in diagnosed of lung cancer for the first time at Xiangya Hospital of Central South University or Hunan province of Cancer Hospital (Changsha, Hunan, China) between August 2009 and January 2013; (2) Patients didn't receive surgery treatment before palatinum-based chemotherapy. (3) All the patients should receive at least 2 periods of platinum-based chemotherapy. The clinical characteristics of the enrolled subjects are listed in **Table 1**. All the patients should write the approved informed consent before they participated in this study. The investigation protocol was approved by the Ethics Committee of Xiangya School of Medicine, Central South University, with a registration number of CTXY-110008-1.

Table 1. Clinical characteristic of lung cancer patients.

Patient characteristics	N (%)
Total no. of patients	345
Histology	
Adenocarcinoma	112(32.5)
Squamous cell	111(32.2)
Small cell	99(28.7)
Age	
≤56	172(49.9)
＞56	173(50.1)
Clinical stage	
I/II/LD	41(11.9)
III/IV/ED	298(86.4)
Smoking status	
Non-smoker	122(35.4)
Smoker	223(64.6)
Gender	
Male	285(82.6)
Female	60(17.4)
Metastasis	
No	61(17.7)
Yes	149(34.2)
Chemotherapy regimens	
Platinum/gemcitabine	109(31.6)
Platinum/paclitaxel	59(17.1)
Platinum/navelbine	8(2.3)
Platinum/etoposide	77(22.3)
Platinum/irinotecan	8(2.3)

Data collection

The deadline for patients recruited was July 15, 2019. Their survival data were collected by telephone follow-up or residence registration. The endpoint criteria were progress-free survival (PFS) and overall survival (OS). The progress-free survival (PFS) was according to the date diagnosed of lung cancer and the date of the first local recurrence or metastases in the last follow-up. The overall survival (OS) time was calculated form the time between diagnosed of lung cancer and the date of the last follow-up or death. Patients without progression will be defined as censor when analyzed. As researchers, the polymorphisms of the patients were unknown before the sequencing analysis.

SNP selecting, DNA extraction and genotyping

There were 17 common SNPs of *DNA* damage and repair genes selected in our study (**Table 2**). The candidate SNPs were located from 5 kb upstream of the first exon to the downstream of the last

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 13 October 2023 doi:10.20944/preprints202310.0897.v1

exon respectively. We used Haploview version 4.2 to choose the Haplotype tagging SNPs. And all the selected SNPs must satisfy the condition that the minor allele frequency (MAF)>0.05 in the HapMap CHB population. The DNA we used for genotyping was separated from a 5ml external blood sample using FlexiGene DNA Kit (Qiagen, Hilden, Germany). And all the samples were stored at 4°C before using. Genotyping was conducted by Sequenom's MassARRAY system (Sequenom, San Diego, California, USA).

Table 2. The 17 polymorphisms examined in this study.

Gene	Locus	dbSNP	Call Rate(%)	Polymorphism	MAF
ERCC1	19q13.32	rs12984195	97.97	T>C	3.70
		rs117128015	100.00	C>T	8.00
ERCC5	13q33.1	rs873601	99.13	G>A	49.11
PNKY	6q16.1	rs1869641	98.84	G>A	22.22
		rs1883306	93.91	T>G	38.53
		rs2444933	99.13	A>G	31.62
SIRT1	10q21.3	rs3758391	97.39	T>C	24.46
		rs3740051	96.52	A>G	33.41
		rs4746720	99.13	T>C	46.67
		rs12778366	95.65	T>C	22.09
XPA	9q22.33	rs3176751	98.84	G>C	20.61
		rs3176752	98.84	C>A	21.44
XRCC3	14q32.33	rs3212117	98.84	C>A	5.28
		rs3212121	98.55	A>G	4.24
XRCC5	2q35	rs1051677	98.84	T>C	22.43
		rs2440	98.55	C>T	34.03
		rs1051685	99.13	A>G	12.14

Statistical analysis

We used Cox proportional hazard models to analyze the differences in the variables, as histology, age, clinical stage, smoking status, gender and metastasis between the PFS and OS. We used forward stepwise method of Cox proportional hazard models to find the covariates. Variables which were significantly associated with OS or PFS were considered as the covariates in the specific subgroup. And then, we fit the covariates into multivariate logistic regression model to adjust the covariates, through the command of --covar in PLINK. The p value was 2-sided and $p<0.05$ will be considered as statistically significant. All association analyses were conducted by three models including additive, dominant, and recessive. The additive model is for the additive effects of SNPs. It means that, if D is a minor allele and d is the major allele, the additive model means DD *versus* Dd *versus* dd. Dominant and recessive models are tests for the minor allele with two of the classes pooled. The dominant model means (DD, Dd) *versus* dd, and the recessive model means DD *versus* (Dd, dd). The aforementioned statistical analyses were performed using PLINK (ver 1.07, http://pngu.mgh.harvard.edu/purcell/plink/) and SPSS 18.0 (SPSS Inc, Chicago, Illinois, USA)

Results

Distribution of characteristics in lung cancer patients and prognosis analysis

The demographic characteristics and prognosis consequences for the 345 lung cancer patients were provided in **Table 3**. The majority of these patients were NSCLC (67.5%), compared with SCLC (28.7%). The median age was 56 years old. Most of them were diagnosed at advanced time, III/IV/ED (86.4%), contrast to I/II/LD (11.9%). More than half of the patients were smokers (64.6%) with a non-smoking proportion (35.4%). Most patients were male (82.6%) versus female (17.4%). The patients with metastasis were 43.2%, and without metastasis were 17.7%. The median survival time of overall

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 13 October 2023 doi:10.20944/preprints202310.0897.v1

survival (MST-OS) is 4.42 year, and the median survival time of progression free survival (MST-PFS) is 3.16 year. The other statistics of the clinical outcomes in the above subgroups were also summarized in table 3.

Table 3. Distribution of characteristics in lung cancer patients and prognosis analysis.

Variables	Patients N(%)	Death N(%)	MST-OS (year)	MST-PFS (year)
Lung cancer	345	279	4.42	3.16
NSCLC	233(67.5)	188(67.4)	4.56	3.25
SCLC	99(28.7)	80(28.7)	4.17	3.10
Age				
≤56	172(49.9)	142(50.9)	4.48	2.95
＞56	173(50.1)	137(49.1)	4.36	3.80
Clinical stage				
I/II/LD	41(11.9)	31(11.1)	3.14	4.05
III/IV/ED	298(86.4)	243(87.1)	4.55	3.21
Smoking status				
Non-smoker	122(35.4)	97(34.8)	4.77	4.60
Smoker	223(64.6)	182(65.2)	4.26	2.61
Gender				
male	285(82.6)	229(82.1)	4.39	2.93
female	60(17.4)	50(17.9)	4.57	4.47
Metastasis				
No	61(17.7)	51(18.3)	3.84	2.28
Yes	149(43.2)	121(43.4)	4.53	3.94

MST, median survival time; OS, overall survival; PFS, progression free survival; NSCLC, non-small lung cancer; SCLC, small cell lung cancer; LD, Limitation Period; ED, Extensive period.

Association between the polymorphisms and prognosis in the lung cancer patients

As we analyzed, the genomic polymorphisms *ERCC5* rs873601 (G>A) was significantly associated with the overall survival (OS) of lung cancer patients in recessive model (p=0.031). Which means patients carry the *ERCC5* rs873601 GG genotype had a shorter MST-OS than the patients who have the *ERCC5* rs873601 GA or AA genotypes (MST-OS: 3.28, 4.88, 4.02 years, respectively) **(Table 4)**. In conclusion, patients who carry the allele A of *ERCC5* rs873601 are the protective allele in the prognosis of lung cancer treated with platinum-based chemotherapy **(Figure 1)**.

Table 4. Association of the ERCC5 rs873601 polymorphisms and OS in lung cancer patients.

Gene	Polymorphisms	Genotype	MST(year)	Additive		Dominant		Recessive	
				BETA (95%CI)	*p* value	BETA (95%CI)	*p* value	BETA (95%CI)	*p* value
ERCC5	**rs873601**	G G	3.28	-0.37(-0.75,0.01)	0.061	-0.30(-0.91,0.32)	0.348	-0.70(-1.34,-0.07)	0.031*
		G A	4.88						
		A A	4.02						

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 13 October 2023 doi:10.20944/preprints202310.0897.v1

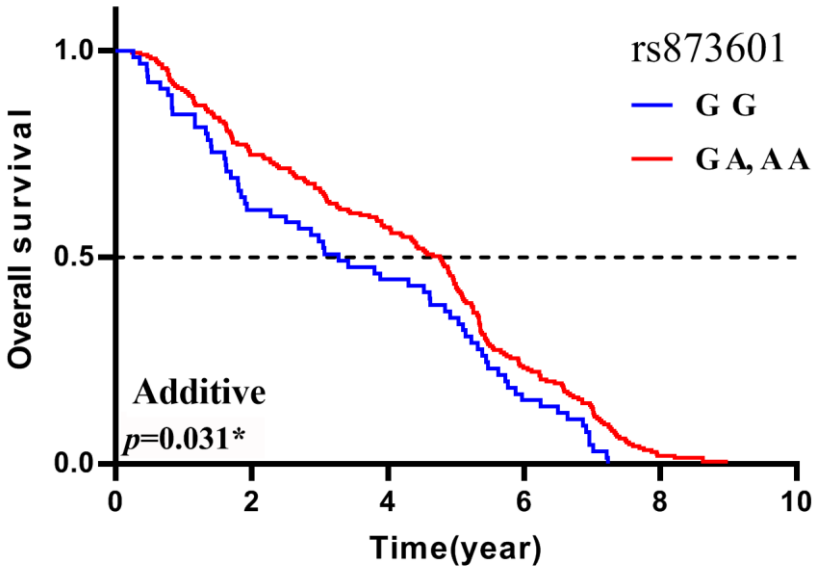

Figure 1. The *ERCC5* rs873601 polymorphisms are significantly associcated with the prognosis in lung cancer patients treated with platinum-based chemotherapy, and the A variant allele of *ERCC5* rs873601 are protective alleles. Patients carry the AA or GA genotypes have a longer MST-OS than GG (p=0.031*).

Stratification analyses of Association between polymorphisms and prognosis in lung cancer patients

To further elucidate the association between these SNPs and the prognosis in lung cancer patients, we also performed subgroup analysis based on age, gender, smoking status, histology, clinical stage and metastasis. As shown in **Table 5**, the *ERCC5* rs873601 was related to overall survival in additive and recessive model in age>56 years lung cancer patients (Additive model: *p*=0.032; Recessive model: *p*=0.004) and smoker patients in additive and recessive model (Additive model: *p*=0.048; Recessive model: *p*=0.018). The *PNKY* rs2444933 was significantly associated with the overall survival in age≤56 (Additive model: *p*=0.043; Recessive model: *p*=0.036), metastasis (Additive model: *p*=0.019; Recessive model: *p*=0.035), non-smoking (Recessive model: *p*=0.042) and III/IV/ED (Additive model: *p*=0.040) patients. What's more, the *STIR1* rs3740051 polymorphisms in SCLC (Additive model: *p*=0.018; Dominant model: *p*=0.023) and metastasis (Additive model: *p*=0.048) patients was significantly associated with the overall survival (**Figure 2**).

Table 5. Stratification analyses of Association between polymorphisms and OS or PFS in lung cancer patients.

OS/PFS	Gene	Polymorphisms	Subgroup	Additive		Dominant		Recessive	
				BETA (95%CI)	*p* value	BETA (95%CI)	*p* value	BETA (95%CI)	*p* value
OS	*ERCC5*	rs873601	age>56	-0.57(-1.08,-0.05)	0.032*	-0.35(-1.15,0.46)	0.399	-1.32(-2.22,-0.43)	0.004*
			smokers		0.048*		0.347		0.018*
	PNKY	rs2444933	age≤56	-0.46(-0.91,-0.01)	0.043*	-0.35(-1.08,0.38)	0.140	-0.93(-1.69,-0.17)	0.036*
			metastasis		0.019*		0.063		0.035*
			non-smoker	-0.63(-1.24,-0.02)	0.188	-0.59(-1.37,0.19)	0.501	-1.62(-3.11,-0.12)	0.042*
			III/IV/ED		0.040*		0.097		0.072
	STIR1	rs3740051	SCLC	-0.84(-1.53,-0.15)	0.018*	-0.81(-1.66,0.04)	0.023*	-1.94(-3.72,-0.15)	0.133
			metastasis		0.048*		0.104		0.089
PFS	*ERCC5*	rs873601	SCLC	-0.51(-1.25,0.24)	0.031*	-0.31(-1.21,0.59)	0.027*	-2.07(-4.05,-0.10)	0.230

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 13 October 2023 doi:10.20944/preprints202310.0897.v1

PNKY	rs2444933	SCLC	-0.49(-0.95,-0.03)	0.070	-0.48(-1.05,0.09)	0.394	-1.10(-2.30,0.09)	0.007*
	rs1869641	SCLC		0.133		0.408	-1.39(-3.18,0.40)	0.028*
XRCC5	rs1051685	Non-metastasis	-0.97(-1.75,-0.18)	0.037*	-1.27(-2.34,-0.20)	0.037*	-1.15(-2.46,0.16)	
			-0.62(-1.23,-0.01)		-0.71(-1.55,0.14)		-0.87(-2.28,0.54)	
			-0.88(-1.67,-0.09)		-1.38(-2.58,-0.18)		-2.80(-4.77,-0.83)	
			-0.80(-1.66,0.05)		-0.49(-1.60,0.63)		-2.83(-5.32,-0.34)	
			-0.76(-1.75,0.22)		-0.54(-1.83,0.74)			
			-2.08(-3.99,-0.17)		-2.08(-3.99,-0.17)			

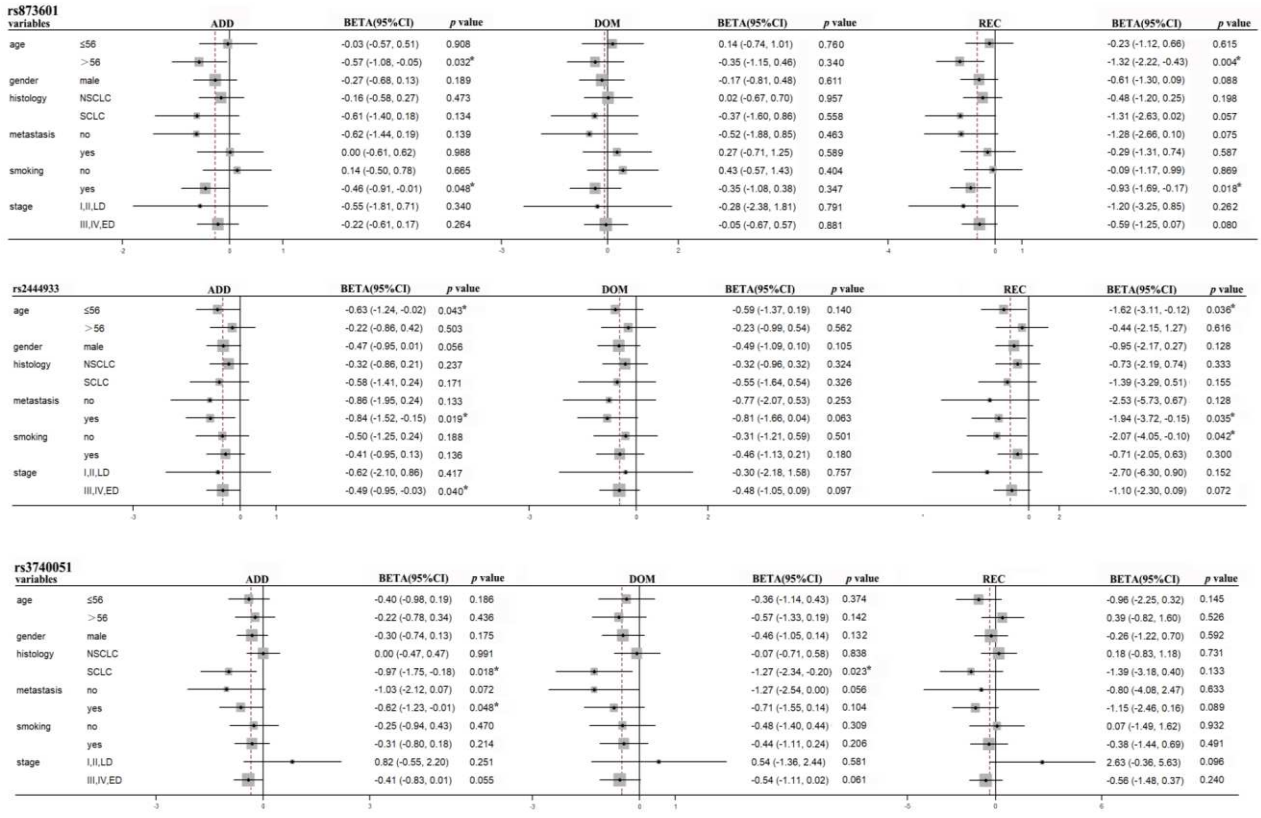

Figure 2. The polymorphisms of *ERCC5* rs873601, *PNKY* rs2444933 and *STIR1* rs1051685 were related with the overall survival (OS) significantly. The *ERCC5* rs873601 polymorphisms were significantly associated with the overall survival (OS) in age>56 and smoking patients. The variants of *PNKY* rs2444933 were related with the prognosis significantly in age≤56, metastasis, non-smoker and clinical in III/IV/ED patients. The polymorphisms of *STIR1* rs3740051 were significantly associated with the overall survival in SCLC and metastasis patients.

We also analyzed the association between the genomic polymorphisms with progress free survival (PFS) in subgroups. The polymorphisms of *ERCC5* rs873601 (Additive model: p=0.031; Dominant model: p=0.027), *PNKY* rs2444933 (Recessive model: p=0.007) and *PNKY* rs1869641 (Recessive model: p=0.028) were significantly associated with the PFS in SCLC patients. The *XRCC5* rs1051685 were significantly associated with the PFS in non-metastasis patients in additive and dominant models (Additive model: p=0.037; Dominant model: p=0.037) (**Figure 3**).

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 13 October 2023 doi:10.20944/preprints202310.0897.v1

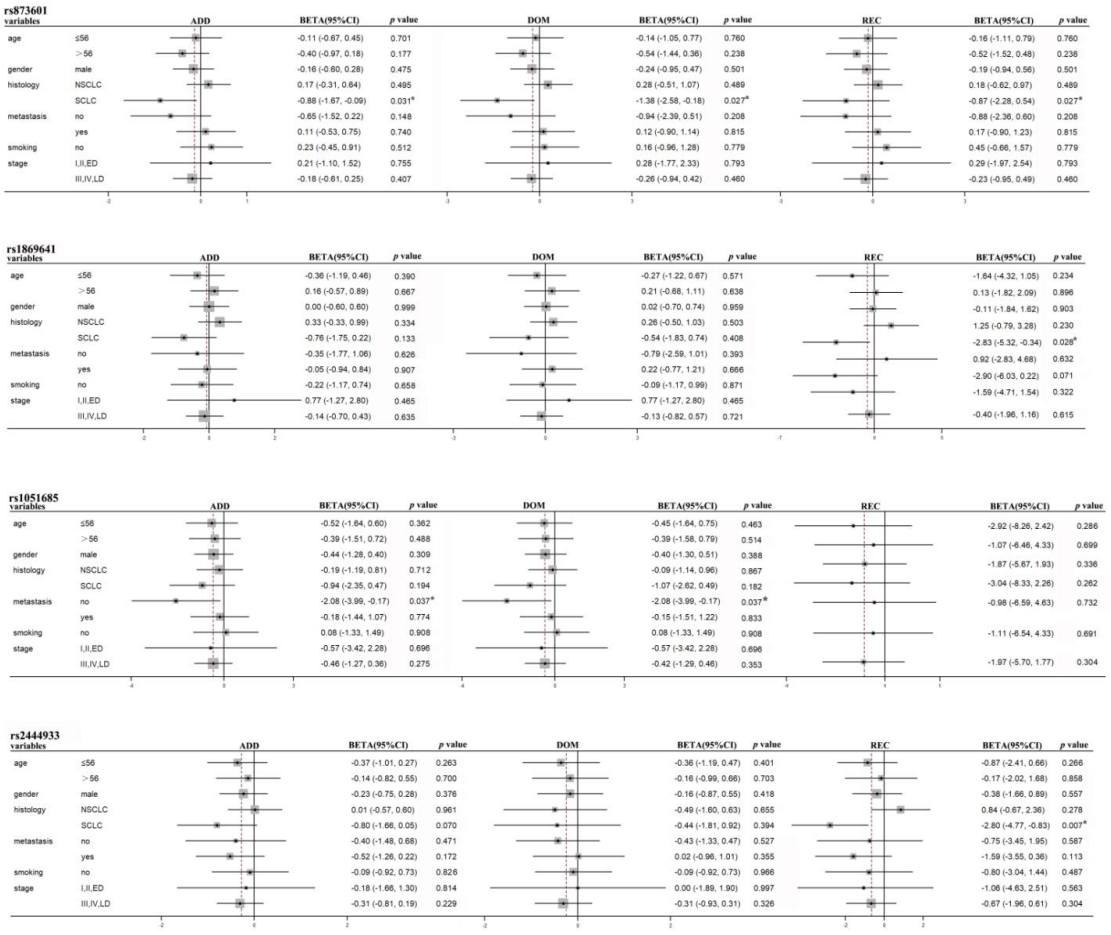

Figure 3. The polymorphisms of *ERCC5* rs873601, *PNKY* rs2444933, rs1849641 and *XRCC5* rs1051685 were significantly with the progress free survival (PFS) significantly. The *ERCC5* rs873601, *PNKY* rs2444933 and rs1869641 polymorphisms were significantly associated with the progress free survival (PFS) in SCLC patients. The variants of *XRCC5* rs1051685 were related with the prognosis significantly in non-metastasis patients.

As we showed in **Figure 4**, the main finding of our study was the polymorphisms of *ERCC5* rs873601 play an important role in the prognosis of lung cancer patients treated with platinum-based chemotherapy. The mechanism of which is also valuable to be discussed. The rs873601 is a 3_prime_UTR_variant in ERCC5, it may affect the translation of mRNA of ERCC5, the RNA-binding protein (RBP) and the protein-to-protein interaction. ERCC5 can regulate the NER pathway of DNA damage and repair, which have been reported to be significantly associated with the prognosis of lung cancer patients treated with platinum-based chemotherapy. ERCC5 may be a potential therapeutic target in the treatment of lung cancer patients, which is valuable to be further investigated.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 13 October 2023 doi:10.20944/preprints202310.0897.v1

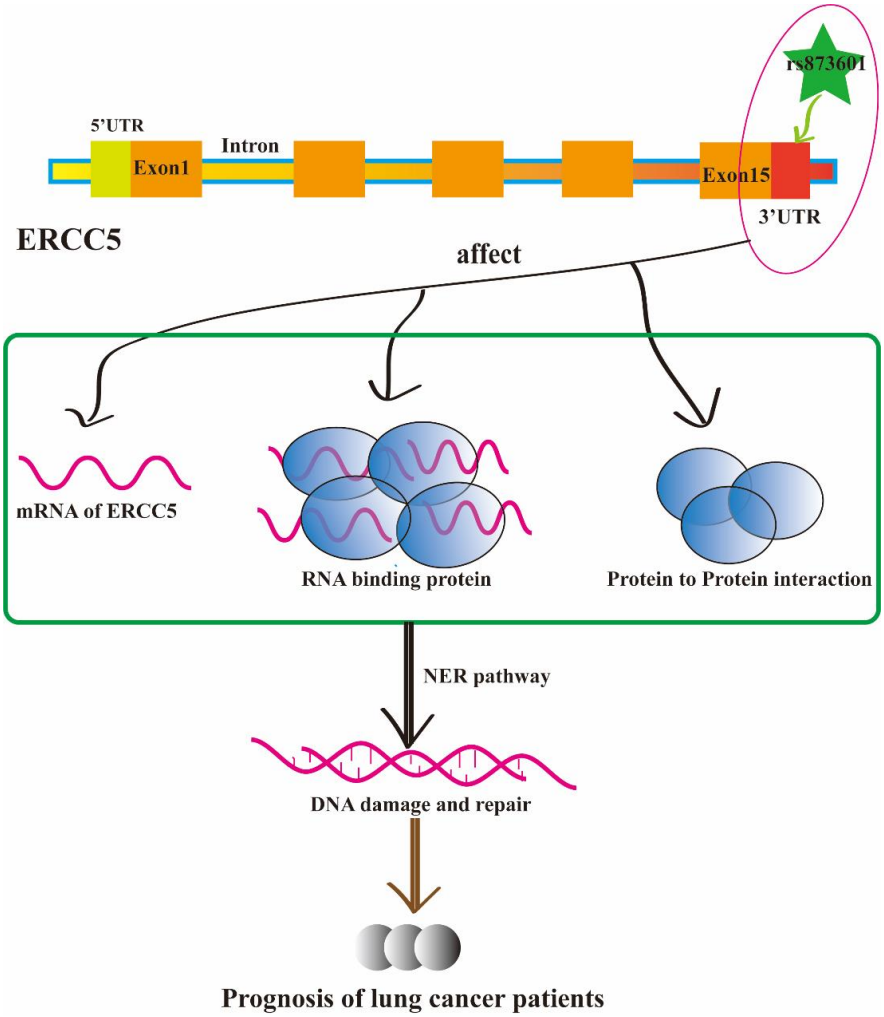

Figure 4. The polymorphisms of ERCC5 rs873601 can affect the prognosis of lung cancer patients. Rs873601 is a mutation located in the 3'UTR of ERCC5, it can affect the mRNA of ERCC5 to translation protein. It can also regulate the RNA-binding protein and the protein-to-protein interaction of ERCC5. These may have an influence in the DNA damage and repair in NER pathway, which is a vital regulator in the prognosis of lung cancer patients treated with platinum-based chemotherapy.

Discussion

As a crucial member of DNA damage and repair system, there are plenty of reports about *ERCC5* and lung cancer. The *ERCC5* polymorphisms of rs2016073, rs4771436, rs11069498 and rs4150330 were significantly associated with NSCLC risk, the *ERCC5* rs4771436 was also significantly correlated with the reduced risk of toxicity in Chineses NSCLC patients [34]. In the other investigation, *ERCC5* rs4771436 and rs1047768 genotypes were reported to be associated with an increased risk of lung cancer patients [20]. What's more, there was a study in North Indians found that the *ERCC5* rs751402 polymorphisms was significantly related to the risk in NSCLC patients [35]. In other population of coal-mining region, the genomic variants of *ERCC5* rs17655 was associated with lung cancer risk significantly [36]. There were also investigations about *ERCC5* and lung cancer prognosis, *ERCC5* (rs2094258 and rs2296147) was reported to be related with progression-free survival (PFS) in NSCLC patients treated with platinum-based chemotherapy [37]. It has been also found that the *ERCC5* rs751402 genotype was associated with the treatment response in patients with advanced non-small-cell lung cancer treated with platinum-based chemotherapy [38]. The SNPs of *ERCC5* in Nucleotide Excision Repair (NER) pathway genes were correlated with toxicity treated with double chemotherapy in advanced NSCLC patients [39]. These all mean that the polymorphisms in DNA repair

 doi:10.20944/preprints202310.0897.v1

genes are significantly related to the risk of lung cancer, and play an important role in the occurrence of lung cancer.

As we all know, Human Epidermal growth factor Receptor 2 (*HER2*/*ERBB2*) and Epidermal Growth Factor Receptor (*EGFR*) are two crucial biomarkers in the prognosis of lung cancer [40, 41]. These biomarkers are often used for screening, detection, diagnosis, prognosis, prediction and monitoring of cancer development [42]. It has been reported that the adverse drug reaction (ADR) in HER2 (+) patients with Grade 3 or 4 was significantly higher than that in the control group in NSCLC patients [43]. EGFR tyrosine kinase inhibitors (TKI) is an important treatment regimen for lung cancer patients, however, up to 50% of patients treated with first- and second-generation TKIs develop an EGFR exon 20 T790M mutation at the time of progression, which may lead to a treatment failure in these patients [44]. To find the new biomarkers for lung cancer patients is of great importance. ERCC5 as an important component in the repair pathway of platinum-induced damage, plays an important role in the prognosis of lung cancer patients [45]. The polymorphisms of ERCC5 have been reported to be associated with the risk of NSCLC [46]. ERCC5 may become a potential therapeutic target for the treatment in lung cancer patients, as important as HER2 and EGFR.

We also found the *PNKY* rs2444933 and rs1869641 were associated with the prognosis in lung cancer patients through the stratified analysis. Most report of *PNKY* was about its function in brain, there are several investigations about its role in cancer. It has been found that *PNKY* can inhibit the binding of miR124 to Polypyrimidine Tract-Binding Protein 1 (*PTBP1*) and maintained the homeostasis of choroidal vascular function [47]. *PNKY* may control the resistance of platinum-based chemotherapy through the regulation of the maintain of choroidal vascular. *STIR1* rs3740051 and *XRCC5* rs1051685 polymorphisms were associated with the prognosis significantly in lung cancer patients treated with platinum-based chemotherapy. *STIR1* was reported to be related with immune evasion, which may be essential to maintain their stability [48]. *STIR1* may play an important role in lung cancer survival through its regulation in immune evasion. *XRCC5* was overexpressed in lung adenocarcinoma, it may be a risk factor and it can also predict a poor prognosis in lung adenocarcinoma patients [49]. The other investigation also found that *XRCC5* was independent risk factors affecting the prognosis of lung adenocarcinoma patients [50]. It was also reported that the transcriptional overexpression of *XRCC5* showed significant correlation with a shorter patients' outcome in advanced lung cancer patients [51].

Our study investigated the association between the polymorphisms of DNA repair gene, *PNKY* and *STIR1* with the prognosis in Chinese lung cancer patients treated with platinum-based chemotherapy. And we also stratified these polymorphisms in age, gender, smoking, histology, clinical stage and metastasis. However, there were several limitations in our study. First, the simple size of our study was not large enough, we just enrolled 345 patients in our project. Second, the biological function mechanisms of these SNPs need further study in vitro. Finally, the validation of our results needs replication studies with other independent subjects.

In conclusion, the variants of *ERCC5* rs873601 was significantly associated with the prognosis in lung cancer patients treated with platinum-based chemotherapy. Patients carry the *ERCC5* rs873601 A allele may have a longer overall survival (OS) than G allele. The genotypes of *ERCC5* rs873601 may be an attractive biomarker used to predict the prognosis of lung cancer patients treated with platinum-based chemotherapy.

Acknowledgments: This work was supported by the National Natural Science Foundation of China (82173901), Major Project of Natural Science Foundation of Hunan Province (Open competition, 2021 JC0002), and Major Science and Technology Program of Changsha（kh2003010)**.**

Disclosure Statement: The authors declare that they have no conflict of interest.

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin*. 2022; 72: 7-33.
2. Roy-Chowdhuri S. Molecular Pathology of Lung Cancer. *Surg Pathol Clin*. 2021; 14: 369-377.
3. Vrana D. Advances in the therapy of small cell lung cancer. *Klin Onkol*. 2021; 34: 66-70.
4. Miller M, Hanna N. Advances in systemic therapy for non-small cell lung cancer. *BMJ*. 2021; 375: n2363.
5. Schulz C. [Advances in Lung Cancer Treatment]. *Dtsch Med Wochenschr*. 2021; 146: 1283-1286.
6. Park S, Lee H, Lee B, et al. DNA Damage Response and Repair Pathway Alteration and Its Association With Tumor Mutation Burden and Platinum-Based Chemotherapy in SCLC. *J Thorac Oncol*. 2019; 14: 1640-1650.
7. Ge F, Huo Z, Li C, et al. Lung cancer risk in patients with multiple sclerosis: a Mendelian randomization analysis. *Mult Scler Relat Disord*. 2021; 51: 102927.
8. Yin JY, Zhang JT, Zhang W, Zhou HH, Liu ZQ. eIF3a: A new anticancer drug target in the eIF family. *Cancer Lett*. 2018; 412: 81-87.
9. Zou T, Yin J, Zheng W, et al. Rho GTPases: RAC1 polymorphisms affected platinum-based chemotherapy toxicity in lung cancer patients. *Cancer Chemother Pharmacol*. 2016; 78: 249-258.
10. He J, Wang Z, Wang Y, et al. The Effects of WISP1 Polymorphisms on the Prognosis of Lung Cancer Patients with Platinum-Based Chemotherapy. *Pharmgenomics Pers Med*. 2021; 14: 1193-1203.
11. Schumacher B, Pothof J, Vijg J, Hoeijmakers JHJ. The central role of DNA damage in the ageing process. *Nature*. 2021; 592: 695-703.
12. Ashour ME, Mosammaparast N. Mechanisms of damage tolerance and repair during DNA replication. *Nucleic Acids Res*. 2021; 49: 3033-3047.
13. Kay J, Thadhani E, Samson L, Engelward B. Inflammation-induced DNA damage, mutations and cancer. *DNA Repair (Amst)*. 2019; 83: 102673.
14. Paull TT. DNA damage and regulation of protein homeostasis. *DNA Repair (Amst)*. 2021; 105: 103155.
15. Pilger D, Seymour LW, Jackson SP. Interfaces between cellular responses to DNA damage and cancer immunotherapy. *Genes Dev*. 2021; 35: 602-618.
16. Dai CH, Li J, Chen P, Jiang HG, Wu M, Chen YC. RNA interferences targeting the Fanconi anemia/BRCA pathway upstream genes reverse cisplatin resistance in drug-resistant lung cancer cells. *J Biomed Sci*. 2015; 22: 77.
17. Gorbunova V, Seluanov A, Mao Z, Hine C. Changes in DNA repair during aging. *Nucleic Acids Res*. 2007; 35: 7466-7474.
18. Muniesa-Vargas A, Theil AF, Ribeiro-Silva C, Vermeulen W, Lans H. XPG: a multitasking genome caretaker. *Cell Mol Life Sci*. 2022; 79: 166.
19. Kiyohara C, Yoshimasu K. Genetic polymorphisms in the nucleotide excision repair pathway and lung cancer risk: a meta-analysis. *Int J Med Sci*. 2007; 4: 59-71.
20. Lan X, Li Y, Wu Y, Li X, Xu L. The Association of ERCC1 and ERCC5 Polymorphisms with Lung Cancer Risk in Han Chinese. *J Cancer*. 2022; 13: 517-526.
21. Liu D, Wu J, Shi GY, Zhou HF, Yu Y. Role of XRCC1 and ERCC5 polymorphisms on clinical outcomes in advanced non-small cell lung cancer. *Genet Mol Res*. 2014; 13: 3100-3107.
22. Pradhan S, Sarma H, Mattaparthi VSK. Investigation of the probable homo-dimer model of the Xeroderma pigmentosum complementation group A (XPA) protein to represent the DNA-binding core. *J Biomol Struct Dyn*. 2019; 37: 3322-3336.
23. Yuan M, Yu C, Yu K. Association of human XPA rs1800975 polymorphism and cancer susceptibility: an integrative analysis of 71 case-control studies. *Cancer Cell Int*. 2020; 20: 164.
24. Mei C, Hou M, Guo S, et al. Polymorphisms in DNA repair genes of XRCC1, XPA, XPC, XPD and associations with lung cancer risk in Chinese people. *Thorac Cancer*. 2014; 5: 232-242.
25. Song X, Wang S, Hong X, et al. Single nucleotide polymorphisms of nucleotide excision repair pathway are significantly associated with outcomes of platinum-based chemotherapy in lung cancer. *Sci Rep*. 2017; 7: 11785.
26. Su Y, Zhang H, Xu F, Kong J, Yu H, Qian B. DNA Repair Gene Polymorphisms in Relation to Non-Small Cell Lung Cancer Survival. *Cell Physiol Biochem*. 2015; 36: 1419-1429.
27. Chen J, Wu L, Wang Y, et al. Effect of transporter and DNA repair gene polymorphisms to lung cancer chemotherapy toxicity. *Tumour Biol*. 2016; 37: 2275-2284.
28. Piljic Burazer M, Mladinov S, Matana A, Kuret S, Bezic J, Glavina Durdov M. Low ERCC1 expression is a good predictive marker in lung adenocarcinoma patients receiving chemotherapy based on platinum in all TNM stages - a single-center study. *Diagn Pathol*. 2019; 14: 105.
29. Grenda A, Blach J, Szczyrek M, et al. Promoter polymorphisms of TOP2A and ERCC1 genes as predictive factors for chemotherapy in non-small cell lung cancer patients. *Cancer Med*. 2020; 9: 605-614.
30. Huang J, Liu X, Tang LL, et al. XPG gene polymorphisms and cancer susceptibility: evidence from 47 studies. *Oncotarget*. 2017; 8: 37263-37277.
31. Liutkeviciene R, Vilkeviciute A, Morkunaite G, Glebauskiene B, Kriauciuniene L. SIRT1 (rs3740051) role in pituitary adenoma development. *BMC Med Genet*. 2019; 20: 185.

32. Wang Y, Yin JY, Li XP, et al. The association of transporter genes polymorphisms and lung cancer chemotherapy response. *PLoS One*. 2014; 9: e91967.
33. Cibeira MT, de Larrea CF, Navarro A, et al. Impact on response and survival of DNA repair single nucleotide polymorphisms in relapsed or refractory multiple myeloma patients treated with thalidomide. *Leuk Res*. 2011; 35: 1178-1183.
34. Wang Z, Xu B, Lin D, et al. XRCC1 polymorphisms and severe toxicity in lung cancer patients treated with cisplatin-based chemotherapy in Chinese population. *Lung Cancer*. 2008; 62: 99-104.
35. Bhat GR, Sethi I, Bhat A, et al. Genetic evaluation of the variants using MassARRAY in non-small cell lung cancer among North Indians. *Sci Rep*. 2021; 11: 11291.
36. Minina VI, Bakanova ML, Soboleva OA, et al. Polymorphisms in DNA repair genes in lung cancer patients living in a coal-mining region. *Eur J Cancer Prev*. 2019; 28: 522-528.
37. Perez-Ramirez C, Canadas-Garre M, Molina MA, Robles AI, Faus-Dader MJ, Calleja-Hernandez MA. Contribution of genetic factors to platinum-based chemotherapy sensitivity and prognosis of non-small cell lung cancer. *Mutat Res Rev Mutat Res*. 2017; 771: 32-58.
38. He C, Duan Z, Li P, Xu Q, Yuan Y. Role of ERCC5 promoter polymorphisms in response to platinum-based chemotherapy in patients with advanced non-small-cell lung cancer. *Anticancer Drugs*. 2013; 24: 300-305.
39. Zhang L, Gao G, Li X, et al. Association between single nucleotide polymorphisms (SNPs) and toxicity of advanced non-small-cell lung cancer patients treated with chemotherapy. *PLoS One*. 2012; 7: e48350.
40. Landi L, Cappuzzo F. HER2 and lung cancer. *Expert Rev Anticancer Ther*. 2013; 13: 1219-1228.
41. Leonetti A, Sharma S, Minari R, Perego P, Giovannetti E, Tiseo M. Resistance mechanisms to osimertinib in EGFR-mutated non-small cell lung cancer. *Br J Cancer*. 2019; 121: 725-737.
42. Sharma B, Kanwar SS. Phosphatidylserine: A cancer cell targeting biomarker. *Semin Cancer Biol*. 2018; 52: 17-25.
43. Diao WY, Ding CL, Yuan BY, Li Z, Sun N, Huang JB. Clinical Characteristics and Prognosis of HER2 Gene Phenotype in Patients with Non-Small Cell Lung Cancer. *Int J Gen Med*. 2021; 14: 9153-9161.
44. Baraibar I, Mezquita L, Gil-Bazo I, Planchard D. Novel drugs targeting EGFR and HER2 exon 20 mutations in metastatic NSCLC. *Crit Rev Oncol Hematol*. 2020; 148: 102906.
45. Abdalkhalek ES, Wakeel LME, Nagy AA, Sabri NA. Variants of ERCC5 and the outcome of platinum-based regimens in non-small cell lung cancer: a prospective cohort study. *Med Oncol*. 2022; 39: 152.
46. Zienolddiny S, Campa D, Lind H, et al. Polymorphisms of DNA repair genes and risk of non-small cell lung cancer. *Carcinogenesis*. 2006; 27: 560-567.
47. Shi L, Han X, Liu C, et al. Long Non-Coding RNA PNKY Modulates the Development of Choroidal Neovascularization. *Front Cell Dev Biol*. 2022; 10: 836031.
48. Liu T, Yang Q, Wei W, Wang K, Wang E. Toll/IL-1 receptor-containing proteins STIR-1, STIR-2 and STIR-3 synergistically assist Yersinia ruckeri SC09 immune escape. *Fish Shellfish Immunol*. 2020; 103: 357-365.
49. Fan Y, Gao Z, Li X, Wei S, Yuan K. Gene expression and prognosis of x-ray repair cross-complementing family members in non-small cell lung cancer. *Bioengineered*. 2021; 12: 6210-6228.
50. Zhang QX, Yang Y, Yang H, et al. The roles of risk model based on the 3-XRCC genes in lung adenocarcinoma progression. *Transl Cancer Res*. 2021; 10: 4413-4431.
51. Saviozzi S, Ceppi P, Novello S, et al. Non-small cell lung cancer exhibits transcript overexpression of genes associated with homologous recombination and DNA replication pathways. *Cancer Res*. 2009; 69: 3390-3396.