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Original Article

Effect of *ERCC2* rs13181 and rs1799793 polymorphisms and environmental factors on the prognosis of patients with lung cancer

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Abstract: Purpose: The 5-year survival rate of patients with lung cancer in China is < 20%, and predicting their prognosis is difficult. Here, we investigated the association between two common non-synonymous single-nucleotide polymorphisms (SNPs) in the excision repair cross-complementing 2 (*ERCC2*) genes (rs13181 and rs1799793) and the prognosis of patients with lung cancer. Methods: Genomic DNA was extracted from the blood samples of 839 patients with lung cancer and genotyped using the SNPscan technique. The association between patient prognosis and the *ERCC2* genotype was analyzed using a multivariate Cox proportional hazards model adjusted for multiple potential confounders. Results: The presence of *ERCC2* rs13181 T>G significantly increased the risk of death (adjust hazard ratio (HR) = 1.29, 95% CI: 1.06-1.56, P = 0.009). Patients with the rs13181 TG genotype (adjust HR = 1.34, 95% CI: 1.08-1.65, P = 0.007) and rs13181 dominant mode TG+GG (adjust HR = 1.33, 95% CI: 1.08-1.63, P = 0.007) had significantly worse overall survival. Moreover, stratified analyses showed that patients with the TG and TG+GG rs13181 genotypes who were male, elderly (≥60 years), had a history of smoking, or without family history of malignant tumors had a significantly increased risk of death. In patients with adenocarcinoma lung cancer (ADC), the rs1799793 genotype CT (adjust HR = 1.49, 95% CI: 1.06-2.09, P = 0.023) and dominant model CT+TT (adjust HR = 1.45, 95% CI = 1.04-2.02, P = 0.027) were associated with an increased risk of death. Conclusion: *ERCC2* rs13181 and rs1799793 SNPs may be significant prognostic factors for the risk of death among patients with lung cancer.

Keywords: *ERCC2*, rs13181, rs1799793, single-nucleotide polymorphism, lung cancer, prognosis

Introduction

Despite advances in the diagnosis and treatment of lung cancer in recent decades, reliably predicting prognosis remains challenging, particularly in China, where the five-year survival rate is lower than 20% [1, 2]. Establishing accurate prognostic indicators is crucial for improving survival among patients with lung cancer, whose prognosis depends on several factors [3]. Single-nucleotide polymorphisms (SNPs), the most common form of genetic variation in humans, can affect gene expression and predict prognosis in patients with lung cancer [4-8]. In addition, smoking is an important factor associated with the risk and prognosis of lung cancer. Approximately 80-90% of lung cancer cases are caused by smoking; however, only 15% of smokers develop lung cancer. Both heredity and the living environment affect the prognosis of patients with lung cancer [3]. In a study of 104 patients with early-stage lung cancer who were treated by surgery and 107 patients with advanced lung cancer who were

administered chemotherapy, *Jiang* [9] suggested that smoking and the rs776746 SNP of *CYP3A5* were risk factors for poor prognosis among patients with lung cancer administered chemotherapy and for a lower survival rate among those undergoing surgery. These results indicated that both the risk and prognosis of lung cancer is influenced by the interaction between environmental risk factors and individual genetic factors [10-12].

Nucleotide excision repair (NER) is an important multifunctional DNA repair system that can remove exogenous or endogenous factors, induce DNA damage or interchain addition, and maintain cell function and genomic integrity [13-16]. The excision repair cross-complementing 2 (*ERCC2*) genes encodes an ATP-dependent DNA helicase that mediates DNA spin unfolding to initiate NER, and is a key factor in DNA transcription and the NER pathway [17-19]. Lys751Gln (rs13181) and Asp312Asn (rs1799793) are non-synonymous SNPs with a 0.5% allele frequency each in the coding region of *ERCC2*, which may regulate the DNA repair ability by altering the protein amino acid sequence [20, 21]. *ERCC2* rs13181 and rs1799793 SNPs have been shown to affect the prognosis and survival of patients with esophageal [22], gastric [23], and colorectal cancers [24] and are associated with poor curative efficacy in patients with lung cancer being administered platinum-based chemotherapy [25].

Previous studies of *ERCC2* rs13181 and rs1799793 SNPs have focused on evaluating their predictive role in the curative efficacy of patients with advanced lung cancer being administered platinum-based combination chemotherapy. The association between the above loci and prognosis of lung cancer in different stages has not been reported. We collected peripheral blood samples from patients with a confirmed diagnosis of lung cancer before treatment initiation and performed genotyping and patient follow-up. The relationship between *ERCC2* rs13181 and rs1799793 SNPs and the prognosis and survival of patients with lung cancer was evaluated.

Patients and methods

Study group

From January to November 2009, 888 patients with primary lung cancer were enrolled, of whom 536 were from Changhai Hospital affiliated with the Naval Military Medical University (Second Military Medical University), and the other 352 were from the Taizhou Institute of Health Sciences, Fudan University. Inclusion criteria were as follows: patients diagnosed with primary lung cancer by histopathological examination and without a history of malignancy in other organs; there were no age or gender limitations. The clinical data of the patients were obtained from medical records, and follow-up data were collected through telephone interviews. This study was approved by the ethics committee of the School of Life Sciences, Fudan University. Informed consent was obtained from each participant.

SNP selection and genotyping

All enrolled patients donated 5 mL of blood before their treatment was initiated. The genomic DNA was extracted using the Qiagen Blood DNA Extraction Kit (Qiagen, Hilden, Germany). Genotyping was performed using a 2 × 48-plex SNPscan TM kit (cat. no. G0104; Genesky Biotechnologies, Shanghai, China) [26-28]. SNPscan is a proprietary multiplex SNP genotyping system that allows simultaneous genotyping of 48/96/144/192 SNPs per sample in a single tube/sample. SNPscan uses a highly specific ligation reaction to discriminate alleles. Genotyping quality was determined using a detailed procedure consisting of an over 95% successful call rate, duplicate calling of genotypes, internal positive control samples, and Hardy-Weinberg equilibrium (HWE) testing. Laboratory personnel who performed the genotyping assays were blinded to the patients' clinical information.

Statistical analyses

HWE was tested using Pearson's chi-square test. Overall survival (OS) was calculated from the date of sample collection to the date of either death from any cause or last follow-up visit. The median survival time was estimated using the Kaplan-Meier method, and group differences were tested using the log-rank test. Univariate and multivariate Cox regression analyses were used to estimate the hazard ratio (HR) and its 95% confidence interval (CI) with and without adjustment for age and sex. Four genetic models (allele, genotype, dominant, and recessive) of the SNPs were applied in Cox regression analyses. Stratified analyses

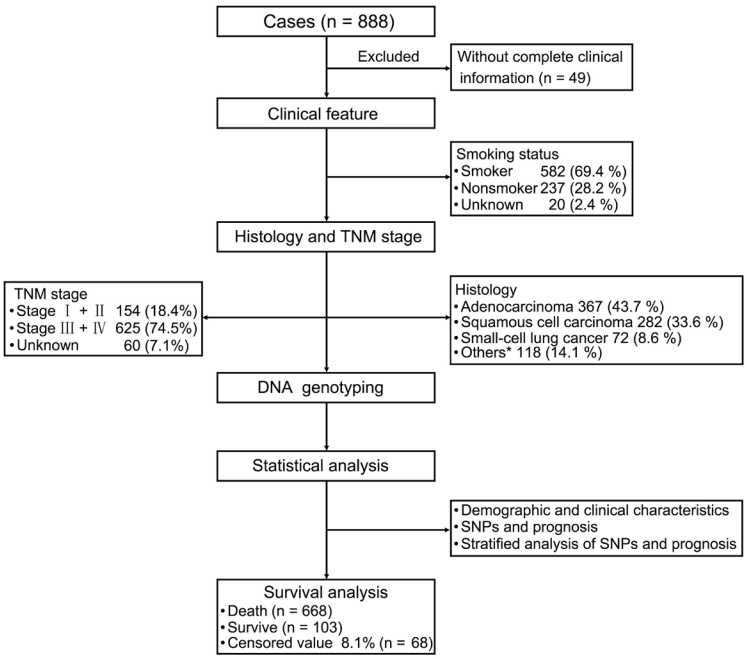

Figure 1. Patient's demographic and clinical characteristics. We evaluated patients with lung cancer, clinical features, and analysis strategies. For the 839 patients with primary lung cancer (excluding 49 patients because of insufficient clinical information), we evaluated their clinical features including smoking status, TNM stage, and histology. Statistical analysis of demographic and clinical characteristics, SNPs, and prognosis. Stratified analysis of SNPs and prognosis. *Other carcinomas include adenosquamous carcinoma, large cell carcinoma, carcinosarcoma, and mucoepidermoid carcinoma.

were performed by age, sex, smoking status, family history of malignant cancer, TNM stage, and histologic type of lung cancer. All tests were two sided and $P < 0.05$ was considered as statistically significant. All statistical analyses were performed using R version 3.6.2 (Vienna, Austria).

Results

Demographic and clinical characteristics and analysis of prognosis

The follow-up period was from the start of enrollment until the end of 2019. After excluding 49 patients because of incomplete clinical information, data from 839 patients were analyzed. The study sample was an ethnically homogenous group of Han Chinese, of whom 668 died, 103 survived (12.3%) for longer than five years, 68 (8.1%) were lost to follow-up, 610 (72.7%) were male, 524 (62.5%) were aged ≥60 years, 582 (69.4%) had a history of smoking, and 302 (36%) had a family history of malignant cancer. Further, 367 (43.7%) patients were diagnosed with adenocarcinoma, 282 (33.6%) with squamous cell carcinoma, 72 (8.6%) with small-cell lung cancer, and 118 (14.1%) with other types of cancer. There were 154 (18.4%) patients diagnosed with stage I and stage II disease, and 625 (74.5%) patients had stage III and stage IV disease (**Figure 1**).

Association between patients' characteristics and lung cancer outcomes

We performed multivariate Cox regression analysis to assess the associations between clinical characteristics and prognosis among patients with lung cancer. As shown in **Table 1**, the median survival time was significantly lower among males compared to females (34.27 vs. 40.17 months; $P = 0.01$); among patients aged ≥60 years compared with those aged <60 years (33.2 vs. 40.87 months; $P = 0.003$); and among smokers compared with non-smokers (33.9 vs. 41.03 months; $P < 0.001$). Patients with advanced tumor stage had a significantly shorter median survival time compared with patients with early-stage tumors (29.4 vs. 113.93 months; $P < 0.001$).

Association between ERCC2 polymorphisms and prognosis of lung cancer

There were 677 TT, 122 TG, and 7 GG genotypes at rs13181 of *ERCC2*, with a genotype detection rate of 96.07% (**Table 2**). The genotype frequency at rs13181 T/G of *ERCC2* was consistent with HWE ($P = 0.426$). There were 736 CC, 99 TC, and 3 TT genotypes at rs1799793 of *ERCC2*, with a genotype detection rate of 99.9%. The genotype frequency at rs1799793 C/T of *ERCC2* was consistent with HWE ($P = 0.883$), indicating that the investigated population was in a genetic balance, i.e., the population survey data were credible. 1476 T genes and 136 G genes were detected at the

Table 1. Distribution of characteristics in Chinese patients with lung cancer (n = 839) and prognosis analysis

Variables	n (%)	MST	log rank p
All	839	36.73	
Gender			0.01
Female	229 (27.3%)	40.17	
Male	610 (72.7%)	34.27	
Age			0.003
Age <60	315 (37.5%)	40.87	
Age ≥60	524 (62.5%)	33.20	
Smoking status			<0.001
Nonsmoker	237 (28.2%)	41.03	
Smoker	582 (69.4%)	33.90	
Unknown	20 (2.4%)	67	
Family history of malignant cancer			0.462
Yes	302 (36%)	33.63	
No	537 (64%)	38.03	
Histology			0.211
ADC	367 (43.7%)	38.80	
SCC	282 (33.6%)	33.63	
SCLC	72 (8.6%)	33.90	
Others*	118 (14.1%)	36.20	
TNM Stage			<0.001
Stage I+II	154 (18.4%)	113.93	
Stage III+IV	625 (74.5%)	29.40	
Unknown	60 (7.1%)	66.43	

*Other carcinomas include adenosquamous carcinoma, large cell carcinoma, carcinosarcoma, and mucoepidermoid carcinoma. MST, median survival time; CI, confidence interval.

rs13181 locus of *ERCC2*. The frequency of alleles T and G were 90.97% (1159/1274) and 9.03% (115/1274) in the death group respectively, and the allele frequency difference between the two groups was significant (P = 0.009). Compared with TT, the risk of death was higher among individuals with genotypes TG and the dominant model TG+GG (adjust HR for TG = 1.34; 95% CI: 1.08-1.65, P = 0.007; adjust HR for TG+GG = 1.33; 95% CI: 1.08-1.63, P = 0.007) (**Table 2**).

Association between ERCC2 polymorphisms and prognosis of lung cancer stratified by patient characteristics

We observed that among male patients, the rs13181 G allele increased the prognostic risk of death relative to the T allele (P = 0.008) (**Table 3**). Compared with genotype TT, genotype TG increased the risk of death (P = 0.015) (**Table 4**), as did the dominant genotype TG+GG (P = 0.010) (**Table 6**). Among older patients (age ≥60 years), the rs13181 G allele increased the prognostic risk of death relative to the T allele (P = 0.002) (**Table 3**). Compared with genotype TT, genotype TG increased the risk of death (P = 0.003) (**Table 4**), as did the dominant genotype TG+GG (P = 0.002) (**Table 6**). Among patients who were smokers, the rs13181 G allele increased the prognostic risk of death relative to T (P = 0.003) (**Table 3**). Compared with genotype TT, genotype TG increased the risk of death (P = 0.012) (**Table 4**), as did the dominant genotype TG+GG (P = 0.005) (**Table 6**). Compared with genotype T/T+T/G, recessive genotype G/G increased the risk of death (P = 0.009) (**Table 7**). In patients without a family history of malignant cancer, rs13181 genotype TG (P = 0.020) (**Table 4**) and the dominant genotype TG+GG (P = 0.038) (**Table 6**) increased the prognostic risk of death compared with genotype TT. For patients with ADC, rs1799793 T allele increased the prognostic risk of death relative to C (P = 0.036) (**Table 3**). Compared with genotype CC, genotype CT increased the risk of death (P = 0.023) (**Table 5**), as did the dominant genotype CT+TT (P = 0.027) (**Table 6**). Among patients who were smokers, rs1799793 recessive genotype T/T increased the risk of death (P = 0.014), compared with C/C+C/T (**Table 7**).

Discussion

In this study, we evaluated the relationship between the rs13181 and rs1799793 SNPs in *ERCC2* and prognostic risk of death using blood samples from 839 Chinese patients with lung cancer. We found that *ERCC2* rs13181 T>G increased the prognostic risk of death in patients with lung cancer. Further stratified analyses showed that the risk of death increased significantly in men, the elderly (60 years and

Table 2. Association between ERCC2 polymorphisms and prognosis in Chinese patients with lung cancer

SNP	Model	Death/Survive	HR (95% CI)	P	HR[a] (95% CI)	P[a]
rs13181	Allele					
	T (ref)	1159/317	1		1	
	G	115/21	1.27 (1.05-1.54)	0.015	1.29 (1.06-1.56)	0.009
	Genotype					
	T/T (ref)	528/149	1		1	
	T/G	103/19	1.32 (1.07-1.63)	0.010	1.34 (1.08-1.65)	0.007
	G/G	6/1	1.11 (0.50-2.50)	0.793	1.17 (0.52-2.64)	0.698
	Dominate					
	T/T (ref)	528/149	1		1	
	T/G+G/G	109/20	1.31 (1.06-1.61)	0.011	1.33 (1.08-1.63)	0.007
	Recessive					
	T/T+T/G (ref)	631/168	1		1	
	G/G	6/1	1.07 (0.48-2.40)	0.868	1.12 (0.50-2.53)	0.776
rs1799793	Allele					
	C (ref)	1244/327	1		1	
	T	90/15	1.06 (0.86-1.32)	0.583	1.03 (0.83-1.28)	0.758
	genotype					
	C/C (ref)	580/156	1		1	
	C/T	84/15	1.06 (0.84-1.34)	0.603	1.04 (0.82-1.31)	0.759
	T/T	3/0	1.12 (0.36-3.51)	0.846	1.04 (0.33-3.30)	0.942
	Dominate					
	C/C (ref)	580/156	1		1	
	C/T+T/T	87/15	1.06 (0.85-1.34)	0.587	1.04 (0.83-1.30)	0.754
	Recessive					
	C/C+C/T (ref)	664/171	1		1	
	T/T	3/0	1.11 (0.36-3.48)	0.856	1.04 (0.33-3.28)	0.948

[a]Adjusted by age, gender. ref, reference.

older), those with a history of smoking, and those without a family history of malignant cancer.

This study also stratified the above analyses by epidemiological factors such as pathological type, disease stage, and smoking status and explored the impact of the above two loci on the prognosis of patients with lung cancer. However, previous studies of the correlation between the rs13181 and rs1799793 SNPs and prognosis of patients with lung cancer are relatively limited and mainly focused on the pharmacogenomics of platinum-based combination chemotherapy [29-36]. A study by *Wu* [25] included 353 patients with advanced lung cancer who were initially treated with platinum-based combination chemotherapy and whose blood-derived SNPs were genotyped before the initial treatment. The response to platinum-based chemotherapy was evaluated after first-line cycles of chemotherapy based on Response Evaluation Criteria in Solid Tumors guidelines (Version 1.1) [37]. However, *Perez-Ramirez* [38] found that *ERCC2* rs13181 and rs1799793 SNPs were not correlated with the clinical efficacy of platinum chemotherapy in 141 Spanish patients with lung cancer.

NER plays an extremely important role in maintaining genome integrity and preventing mutation. Its effect is regulated by the transcription initiation factor TFIIH, which has ATP-dependent helicase activity. *ERCC2* is an integral member of the core transcription factor IIH via p44, which, if mutated, prevents the interaction between its protein product and p44, thereby reducing the activity of helicase and affecting the repair capacity of DNA [19, 39]. *ERCC2* rs13181 and rs1799793 are common non-syn-

Table 3. Association between ERCC2 polymorphisms in allele model and prognosis in Chinese patients with lung cancer

Variables	rs13181						rs1799793					
	Death/Survive		HR (95% *CI*)	P	HR[a] (95% CI)	P[a]	Death/Survive		HR (95% CI)	P	HR[a] (95% CI)	P[a]
	T (ref)	G					C (ref)	T				
Gender												
Male	874/197	82/15	1.33 (1.06-1.67)	0.014	1.36 (1.08-1.70)	0.008	936/205	66/11	1.05 (0.82-1.35)	0.693	1.04 (0.81-1.34)	0.737
Female	285/120	33/6	1.19 (0.83-1.71)	0.341	1.14 (0.79-1.64)	0.483	308/122	24/4	1.08 (0.71-1.64)	0.712	1.00 (0.65-1.52)	0.990
Age (year)												
≥60	754/164	78/8	1.44 (1.14-1.82)	0.002	1.44 (1.14-1.82)	0.002	809/166	63/8	0.99 (0.77-1.29)	0.964	0.99 (0.76-1.28)	0.929
<60	405/153	37/13	1.05 (0.75-1.47)	0.781	1.05 (0.75-1.47)	0.772	435/161	27/7	1.08 (0.73-1.60)	0.711	1.06 (0.72-1.58)	0.761
Smoking status												
Yes	850/173	80/13	1.41 (1.12-1.77)	0.004	1.42 (1.13-1.79)	0.003	908/180	64/10	1.04 (0.81-1.35)	0.738	1.03 (0.80-1.33)	0.820
No	288/129	32/7	1.20 (0.83-1.73)	0.332	1.16 (0.80-1.67)	0.432	314/131	24/5	1.08 (0.71-1.63)	0.729	1.03 (0.68-1.57)	0.887
Family history of malignant cancer												
Yes	425/99	45/7	1.28 (0.94-1.74)	0.121	1.30 (0.95-1.77)	0.100	450/105	42/5	1.10 (0.80-1.51)	0.553	1.12 (0.81-1.53)	0.496
No	734/218	70/14	1.24 (0.97-1.59)	0.083	1.25 (0.97-1.59)	0.081	794/222	48/10	1.01 (0.75-1.36)	0.946	0.95 (0.70-1.27)	0.709
Histology												
ADC	491/171	45/9	1.23 (0.90-1.67)	0.195	1.27 (0.93-1.73)	0.135	507/176	45/6	1.45 (1.06-1.96)	0.018	1.39 (1.02-1.89)	0.036
SCC	414/77	36/7	1.24 (0.88-1.74)	0.225	1.21 (0.86-1.71)	0.267	452/81	24/5	0.76 (0.50-1.15)	0.198	0.76 (0.50-1.15)	0.195
TNM stage												
Stage I+II	138/143	12/9	1.24 (0.68-2.24)	0.482	1.43 (0.79-2.62)	0.241	142/149	10/7	1.10 (0.58-2.09)	0.773	1.14 (0.59-2.17)	0.702
Stage III+IV	923/158	99/12	1.20 (0.98-1.48)	0.085	1.20 (0.98-1.48)	0.084	1005/162	73/8	1.02 (0.80-1.29)	0.879	1.00 (0.79-1.27)	0.990

[a]Adjusted by age, gender. CI, confidence interval; HR, hazard ratio; ref, reference.

Table 4. Association between ERCC2 rs13181 SNPs in genotype model and prognosis in Chinese patients with lung cancer

Variables	Death /survive			T/G VS. T/T				G/G VS. T/T			
	T/T (ref)	T/G	G/G	HR (95% CI)	P	HR[a] (95% CI)	P[a]	HR (95% CI)	P	HR[a] (95% CI)	P[a]
Gender											
male	399/92	76/13	3/1	1.34 (1.05-1.71)	0.020	1.36 (1.06-1.74)	0.015	1.70 (0.55-5.31)	0.359	2.06 (0.66-6.44)	0.216
female	129/57	27/6	3/0	1.32 (0.87-1.99)	0.197	1.30 (0.86-1.97)	0.216	0.91 (0.28-2.93)	0.872	0.77 (0.24-2.51)	0.667
Age (year)											
≥60	344/78	66/8	6/0	1.53 (1.17-1.99)	0.002	1.49 (1.14-1.94)	0.003	1.32 (0.59-2.96)	0.505	1.48 (0.65-3.38)	0.349
<60	184/71	37/11	0/1	1.12 (0.79-1.60)	0.527	1.12 (0.79-1.60)	0.531	-	-	-	-
Smoking status											
yes	388/80	74/13	3/0	1.36 (1.06-1.75)	0.015	1.38 (1.07-1.77)	0.012	4.98 (1.59-15.63)	0.006	4.89 (1.56-15.35)	0.007
no	131/62	26/5	3/1	1.41 (0.93-2.16)	0.109	1.38 (0.90-2.11)	0.141	0.79 (0.25-2.49)	0.685	0.75 (0.24-2.37)	0.623

Family history of malignant cancer											
yes	194/46	37/7	4/0	1.20 (0.84-1.71)	0.308	1.23 (0.86-1.75)	0.253	2.03 (0.75-5.48)	0.161	2.02 (0.74-5.51)	0.171
no	334/103	66/12	2/1	1.38 (1.06-1.81)	0.016	1.37 (1.05-1.78)	0.020	0.55 (0.14-2.22)	0.401	0.60 (0.15-2.43)	0.473
Histology											
ADC	225/81	41/9	2/0	1.30 (0.93-1.82)	0.127	1.38 (0.98-1.93)	0.064	0.91 (0.22-3.76)	0.901	0.82 (0.20-3.42)	0.787
SCC	191/36	32/5	2/1	1.27 (0.87-1.85)	0.214	1.22 (0.84-1.79)	0.299	1.17 (0.29-4.73)	0.824	1.32 (0.32-5.40)	0.703
Stage											
Stage I+II	64/67	10/9	1/0	1.42 (0.73-2.79)	0.303	1.79 (0.90-3.58)	0.097	-	-	-	-
Stage III+IV	417/74	89/10	5/1	1.22 (0.97-1.54)	0.089	1.21 (0.96-1.52)	0.103	1.24 (0.51-2.99)	0.635	1.33 (0.55-3.22)	0.528

[a]Adjusted by age, gender. CI, confidence interval; HR, hazard ratio; ref, reference.

Table 5. Association between ERCC2 rs1799793 SNPs in genotype model and prognosis in Chinese patients with lung cancer

Variables	Death/Survive			C/C VS. C/T				C/C VS. T/T			
	C/C (ref)	C/T	T/T	HR (95% CI)	P	HR[a] (95% CI)	P[a]	HR (95% CI)	P	HR[a] (95% CI)	P[a]
Gender											
male	437/97	62/11	2/0	1.00 (0.76-1.30)	0.986	0.99 (0.76-1.30)	0.954	6.31 (1.56-25.58)	0.010	5.17 (1.27-21.05)	0.022
female	143/59	22/4	1/0	1.25 (0.80-1.96)	0.331	1.18 (0.75-1.85)	0.482	-	-	-	-
Age (year)											
≥60	376/79	57/8	3/0	0.99 (0.75-1.31)	0.933	0.98 (0.74-1.30)	0.887	1.04 (0.33-3.27)	0.941	1.06 (0.33-3.37)	0.920
<60	204/77	27/7	-	1.08 (0.72-1.64)	0.699	1.07 (0.71-1.61)	0.751	-	-	-	-
Smoking status											
yes	424/85	60/10	2/0	0.99 (0.75-1.30)	0.928	0.97 (0.74-1.28)	0.855	6.72 (1.66-27.25)	0.008	5.80 (1.42-23.65)	0.014
no	146/63	22/5	1/0	1.20 (0.77-1.88)	0.424	1.17 (0.74-1.83)	0.499	-	-	-	-
Family history of malignant cancer											
yes	206/50	38/5	2/0	-	-	-	-	-	-	-	-
no	374/106	46/10	1/0	1.09 (0.80-1.49)	0.580	1.01 (0.74-1.38)	0.964	-	-	-	-
Histology											
ADC	234/85	39/6	3/0	1.52 (1.08-2.14)	0.016	1.49 (1.06-2.09)	0.023	1.29 (0.40-4.11)	0.668	1.13 (0.35-3.64)	0.844
SCC	214/38	24/5	-	0.74 (0.48-1.14)	0.177	0.74 (0.48-1.14)	0.174	-	-	-	-
TNM stage											
Stage I+II	67/71	8/7	1/0	1.23 (0.59-2.57)	0.581	1.30 (0.62-2.73)	0.486	-	-	-	-
Stage III+IV	468/77	69/8	2/0	0.97 (0.75-1.25)	0.812	0.95 (0.74-1.23)	0.697	5.85 (1.45-23.69)	0.013	5.02 (1.23-20.40)	0.024

[a]Adjusted by age, gender. CI, confidence interval; HR, hazard ratio; ref, reference.

Table 6. Association between ERCC2 polymorphisms in dominant model and prognosis in Chinese patients with lung cancer

Variables	rs13181						rs1799793					
	Death/Survive		HR (95% CI)	P	HR[a] (95% CI)	P[a]	Death/Survive		HR (95% CI)	P	HR[a] (95% CI)	P[a]
	T/T (ref)	T/G+G/G					C/C (ref)	C/T+T/T				
Gender												
male	399/92	79/14	1.35 (1.06-1.72)	0.015	1.37 (1.08-1.75)	0.010	437/97	64/11	1.02 (0.79-1.34)	0.855	1.02 (0.78-1.33)	0.895
female	129/57	30/6	1.26 (0.85-1.88)	0.255	1.22 (0.82-1.82)	0.326	143/59	23/4	1.16 (0.75-1.81)	0.500	1.08 (0.69-1.69)	0.726
Age (year)												
≥60	344/78	72/8	1.51 (1.17-1.94)	0.002	1.49 (1.15-1.92)	0.002	376/79	60/8	0.99 (0.75-1.30)	0.947	0.98 (0.75-1.30)	0.905
<60	184/71	37/12	1.09 (0.76-1.55)	0.635	1.09 (0.76-1.55)	0.635	204/77	27/7	1.08 (0.72-1.64)	0.699	1.07 (0.71-1.61)	0.751
Smoking status												
yes	388/80	77/13	1.40 (1.10-1.79)	0.007	1.42 (1.11-1.81)	0.005	424/85	62/10	1.02 (0.78-1.33)	0.909	1.00 (0.77-1.31)	0.991
no	131/62	29/6	1.31 (0.87-1.95)	0.195	1.27 (0.84-1.90)	0.254	146/63	23/5	1.14 (0.73-1.77)	0.563	1.10 (0.71-1.71)	0.677
Family history of malignant cancer												
yes	194/46	41/7	1.25 (0.89-1.75)	0.194	1.28 (0.91-1.80)	0.158	206/50	40/5	1.06 (0.75-1.48)	0.752	1.07 (0.76-1.51)	0.680
no	334/103	68/13	1.33 (1.02-1.72)	0.035	1.32 (1.02-1.72)	0.038	374/106	47/10	1.05 (0.77-1.43)	0.749	0.98 (0.71-1.33)	0.875
Histology												
ADC	225/81	43/9	1.28 (0.92-1.78)	0.149	1.34 (0.96-1.86)	0.088	234/85	42/6	1.50 (1.08-2.09)	0.016	1.45 (1.04-2.02)	0.027
SCC	191/36	34/6	1.26 (0.88-1.82)	0.212	1.23 (0.85-1.78)	0.273	214/38	24/5	0.74 (0.48-1.14)	0.177	0.74 (0.48-1.14)	0.174
TNM stage												
Stage I+II	64/67	11/9	1.33 (0.70-2.53)	0.385	1.60 (0.83-3.09)	0.159	67/71	9/7	1.16 (0.58-2.33)	0.676	1.21 (0.60-2.44)	0.594
Stage III+IV	417/74	94/11	1.22 (0.98-1.53)	0.081	1.22 (0.97-1.52)	0.087	468/77	71/8	0.99 (0.77-1.28)	0.958	0.97 (0.76-1.25)	0.828

[a]Adjusted by age, gender. CI, confidence interval; HR, hazard ratio; ref, reference.

Table 7. Association between ERCC2 polymorphisms in recessive model and prognosis in Chinese patients with lung cancer

Variables	rs13181						rs1799793					
	Death/Survive		HR (95% CI)	P	HR[a] (95% CI)	P[a]	Death/Survive		HR (95% CI)	P	HR[a] (95% CI)	P[a]
	T/T+T/G (ref)	G/G					C/C+C/T (ref)	T/T				
Gender												
male	475/105	3/1	1.63 (0.52-5.08)	0.399	1.96 (0.62-6.12)	0.249	499/108	2/0	6.31 (1.56-25.57)	0.010	5.17 (1.27-21.06)	0.022
female	156/63	3/0	0.88 (0.27-2.82)	0.824	0.74 (0.23-2.41)	0.623	165/63	1/0	0.44 (0.058-3.27)	0.420	0.36 (0.048-2.70)	0.321
Age (year)												
≥60	410/86	6/0	1.25 (0.56-2.80)	0.593	1.40 (0.61-3.19)	0.423	433/87	3/0	1.05 (0.33-3.27)	0.939	1.06 (0.34-3.37)	0.916
<60	211/82	0/1	-	-	-	-	231/84	-	-	-	-	-
Smoking status												
yes	462/93	3/0	4.73 (1.51-14.82)	0.008	4.63 (1.47-14.52)	0.009	484/95	2/0	6.73 (1.66-27.28)	0.008	5.82 (1.43-23.73)	0.014
no	157/67	3/1	0.75 (0.24-2.38)	0.629	0.71 (0.23-2.26)	0.566	168/68	1/0	0.52 (0.071-3.80)	0.519	0.45 (0.062-3.32)	0.436
Family history of malignant cancer												
yes	231/53	4/0	1.98 (0.73-5.32)	0.178	1.95 (0.72-5.31)	0.191	244/55	2/0	7.84 (1.90-32.34)	0.004	7.17 (1.72-29.94)	0.007
no	400/115	2/1	0.52 (0.13-2.12)	0.364	0.57 (0.14-2.32)	0.431	420/116	1/0	0.38 (0.053-2.76)	0.341	0.38 (0.052-2.76)	0.338
Histology												
ADC	266/90	2/0	0.88 (0.21-3.62)	0.860	0.79 (0.19-3.28)	0.745	273/91	3/0	1.24 (0.39-3.95)	0.714	1.08 (0.33-3.49)	0.897
SCC	223/41	2/1	1.13 (0.28-4.57)	0.860	1.30 (0.32-5.32)	0.716	238/43	-	-	-	-	-
TNM stage												
Stage I+II	74/76	1/0	-	-	-	-	75/78	1/0	0.78 (0.10-5.81)	0.808	0.75 (0.094-5.94)	0.783
Stage III+IV	506/84	5/1	1.20 (0.50-2.90)	0.686	1.29 (0.53-3.12)	0.572	537/8	2/0	5.88 (1.45-23.77)	0.013	5.06 (1.24-20.56)	0.024

[a]Adjusted by age, gender. CI, confidence interval; HR, hazard ratio; ref, reference.

onymous SNPs whose specific functions have been identified in the *ERCC2* coding sequence and affect the function of the NER pathway by regulating mRNA expression. *ERCC2* rs13181 T>G and rs1799793 C>T are missense mutations, which may alter the amino acid sequence of proteins and regulate their capacity for DNA damage repair [20, 25, 30].

Among smokers in this study, rs13181 mutation carriers had a higher risk of death. Smoking is generally recognized as a risk factor related to the occurrence and poor prognosis of lung cancer. More than 20 compounds in smoke are classified as lung carcinogens, as they can cause permanent mutations by forming DNA adducts and causing DNA double-strand breaks, as well as interfere with DNA repair function, resulting in a higher risk of lung cancer and worse cancer prognosis [40-43]. Among smokers, the extensive DNA damage caused by tobacco can even completely mask the slight differences in the DNA repair capacity caused by genetic polymorphisms [44, 45]. Smoking is considered the most important environmental factor influencing lung cancer. Other known environmental factors include occupational exposure to carcinogens and air pollution [46, 47]. In this study, the risk of death differed by gender among patients with lung cancer, and being male was a prognostic factor for poor lung cancer survival. Smoking and the SNPs may have jointly affected the prognosis of patients with lung cancer. In addition, the influence of other environmental factors on the prognosis of patients with lung cancer should also be considered in future studies.

In a study of 2724 male and 1894 female patients with lung cancer in Minnesota, USA conducted from 1997 to 2002, *Visbal* [48] found that men had a significantly higher risk of death compared to women following a diagnosis of lung cancer (adjusted relative risk: 1.20, 95% CI: 1.11-1.30). Smoking is a critical factor, as more men smoke and are likely to be heavier smokers than women [46, 49]. In this study, the prognostic risk of death among elderly rs13181 G carriers was significantly higher, possibly because of the long-term accumulation of DNA damage over time, which in turn is due to the loss of NER function caused by rs13181 T>G [50].

Our study showed that the rs1799793 SNP of *ERCC2* was not associated with the prognosis of patients with lung cancer overall, but the risk of death was significantly increased in patients with ADC with the mutant T allele. Previous studies revealed that the rs1799793 T allele might cause a decrease in NER function, thereby reducing the survival time of patients with lung cancer. However, this study did not stratify the different histologic type of lung cancer, and thus the relationship between rs1799793 SNPs and ADC was unknown [25]. Notably, a large number of studies have observed no association between the rs1799793 SNP and clinical outcomes among patients with lung cancer being administered platinum-based chemotherapy [34, 38]. rs1799793 is located in the Arch transcription domain of *ERCC2*, and its SNP mainly affects its transcriptional activity rather than its DNA repair capacity, which may explain why rs1799793 affects patient survival but not chemotherapy efficacy [38]. A study of 360 patients with gastric cancer in North America showed that the rs1799793 mutant genotype TT was associated with a worse prognosis in patients with poorly differentiated tumors [51]; similar results were obtained in our study.

Previous studies used genome-wide association studies, which can detect millions of SNPs across the whole genome and identify associations between SNPs and complex diseases. However, the size and complexity of the data were difficult to manage and some important genes in this pathway may have been missed [52]. The candidate-gene associations explored in this study had the advantages of a limited number of candidate genes and low number of false-positive cases, enhancing the accuracy of the analyses, providing reliable estimates, and solving the problem of the insufficient association between single genes and cancer in previous studies [53]. However, this study also had some limitations. First, the relatively small sample size restricted the analysis of recessive models and may have led to unstable estimates in stratified analyses. The subjects were of Han Chinese ethnicity, limiting the ability to generalize the results to other populations. Future studies of a larger number of patients are required to evaluate the association between *ERCC2* rs13181 and rs1799793 SNPs and lung cancer survival. Second, the number of SNPs analyzed in the present study was limited, although the correlation between rs13181 and the prognosis of lung cancer was clearly determined. DNA repair is a process of prote-

in synergy, which requires multiple DNA repair pathways, and further studies of SNPs in candidate genes should be performed. Finally, although we obtained significant results, additional clinical studies are needed to verify our results; moreover, the exact biological functions and mechanisms of rs13181 and rs1799793 SNPs of ERCC2 on prognostic survival of patients with lung cancer should be further analyzed.

In summary, our results demonstrate that *ERCC2* rs13181 T>G and rs1799793 C>T increase the prognostic risk of death among patients with lung cancer, with the former playing a more significant role depending on gender, age, and smoking status. These findings have potential clinical significance for predicting the prognosis of patients with lung cancer and formulating new therapeutic strategies.

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Disclosure of conflict of interest

None.

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