The Influence of *NDRG1* Single Nucleotide Polymorphisms on Glioma Risk and Prognosis in Chinese Han Population

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Abstract

Background: glioma is a highly fatal malignant tumor with a high recurrence rate. We aimed to determine the association between single nucleotide polymorphisms (SNPs) of *NDRG1* and glioma risk and prognosis in the Chinese Han population.

Methods: 5 candidate SNPs were genotyped by Agena MassARRAY; logistic regression was used to analyze the association between SNPs and glioma risk; We used multi-factor dimensionality reduction to analyze the interaction of 'SNP-SNP'; the prognosis analysis was performed by log-rank test, Kaplan–Meier analysis and Cox regression model.

Results: our results showed that the rs3808599 was associated with the reduction of glioma risk in all participants (p = 0.024) and the participants ≤40 years old (p = 0.020). rs3802251 may reduce glioma risk in all participants (p = 0.008), the male (p = 0.033) or astrocytoma patients (p = 0.023). rs3779941 was associated with poor glioma prognosis in the all participants (p = 0.039) or astrocytoma patients (p = 0.038). We also found that the key factors for glioma prognosis may include surgical operation, radiotherapy and chemotherapy.

Conclusion: this study is the first to find that *NDRG1* gene polymorphisms may have a certain association with glioma risk or prognosis in the Chinese Han population.

1. Introduction

Glioma is a tumor that originates from neuroectodermal mesenchymal cells and accounts for about 40–50% of brain tumors. It is the most common intracranial malignant tumor (1). Glioma has a high recurrence rate and high mortality. And in the clinical treatment, it often appears insensitivity to radiotherapy or resistance to chemotherapy, which will lead to poor clinical treatment effects and poor prognosis (2). At present, the specific pathogenesis of glioma is not very clear. Therefore, glioma has always been one of the most difficult problems in neurosurgery. Studies have shown that in addition to the effects of high-dose ionizing radiation, genetic susceptibility genes may play a certain role in the pathogenesis of glioma (3). At present, some studies on the association between genetic polymorphisms and glioma have been reported worldwide (4–8). Although these studies have let us to gain some new insights into the pathogenesis of glioma, we have not found an effective, specific and unified method for prevention and treatment. Therefore, finding new and effective genetic markers is still very important, which will help us to judge the prognosis of glioma patients early and then conduct targeted interventions for treatment.

N-myc downstream regulated gene-1 (*NDRG1*) was cloned and isolated in 1997 for the first time and has been found in many cancers (9), such as pancreatic cancer (10), prostate cancer (11), esophageal squamous cell carcinoma (12). *NDRG1* has also been found to be involved in embryogenesis and development, cell growth and differentiation, lipid synthesis, stress response, immune function and myeloid formation (13). Most importantly, *NDRG1* may play an inhibitory role in the development of glioma and may be a potential prognostic indicator for glioma (14).

There is evidence that relatives of patients with glioma have a higher risk of glioma (15). And some studies have shown that the gene polymorphisms, one of genetic variation, is considered as a risk factor for glioma (16). The genome-wide association study of glioma has reported the association between gene polymorphisms and the risk of glioma, such as *CDKN2B*, *RTEL1*, *PHLDB1* et al. (17). However, no research on the association between *NDRG1* gene polymorphisms and glioma risk or patient prognosis has been found. Therefore, we explored the association between 5 candidate SNPs on *NDRG1* (rs2272646 A/G, rs3779941 C/A, rs3808599 G/C, rs2977497 T/C, rs3802251 C/T) and glioma risk or patient prognosis in Chinese Han population through the experimental design of 'case-control'.

2. Materials And Methods

2.1 Study subjects

In this study, 1061 participants were recruited at the First Affiliated Hospital of Xi'an Jiaotong University (Xi'an, China) during the same period, then we conducted a study on the association between *NDRG1* SNPs and the risk of glioma. At the same time, we also explored the impact of *NDRG1* SNPs on the prognosis of patients with glioma. 1061 participants included 558 glioma patients and 503 healthy individuals, none of them have genetic relationship. All glioma patients meet the WHO diagnostic criteria for central nervous system tumors, while no healthy individuals have a history of cancer or central nervous system disease. This study adopts the 'case-control' research method as a whole. In order to get the basic demographic and epidemiological information of all participants (age, gender, WHO grade, surgical operation, radiotherapy, chemotherapy, astrocytomas), we collected useful information through medical records, questionnaire surveys and follow-up. Finally, after obtaining the informed consent of all participants, we collected peripheral blood samples from each of them for subsequent DNA extraction (blood collection for glioma patients must be done before radiotherapy, chemotherapy, and surgery). The study has been approved by the ethics committee of the First Affiliated Hospital of Xi'an Jiaotong University, and the follow-up work was carried out after obtaining the informed consent of all patients.

2.2 Selection and genotyping of SNPs

Combining the relevant information of *NDRG1* gene polymorphisms in the dbSNP database, we selected candidate SNPs with an allele frequency ≥ 5%. Then, 5 SNPs on *NDRG1* were selected for our study (rs2272646 A/G, rs3779941 C/A, rs3808599 G/C, rs2977497 T/C, rs3802251 C/T). We extracted and purified the whole genome DNA according to the experimental procedures from the kit instructions (GoldMag Co. Ltd. Xi'an, China). Afterwards, the extracted DNA was stored in a low-temperature refrigerator (-80 °C) until needed for the next experiment. The primers required for this study were all designed by MassARRAY Assay Design software, and finally the MassARRAY (Agena, San Diego, CA, USA) system was used by us for genotyping.

In order to ensure the reliability and reproducibility of the experimental results, we randomly select 5% of DNA samples for repeatability testing. And the repetition rate of experimental results is > 99%.

2.3 Statistical analysis

The association between SNPs on NDRG1 **and the risk of glioma**: The difference in demographic characteristics in this study was tested by SPSS 17.0 statistical software. The *p* value represents whether it is statistically significant ($p < 0.05$: statistically significant). After testing whether all candidate SNPs meet the Hardy-weinberg balance (HWE), the correlation between the candidate SNPs and the risk of glioma was studied. The study included overall analysis and subgroup analysis (age, gender, astrocytomas). Using wild-type alleles as a reference, the plink 1.07 online tool software was used to estimate multiple genetic models (codominant, dominant, recessive, and logarithmic addition). The analysis results of this part were all estimated based on the odds ratio (OR) and 95% confidence interval (CI) obtained by the logistic regression model adjusted by age and gender (OR = 1: the factor has no effect on the occurrence of the disease; OR < 1: reduce the risk of disease; OR > 1: increase the risk of disease). Finally, we used multi-factor dimensionality reduction (MDR) to evaluate the interactions of candidate 'SNP-SNP' in the risk of glioma.

Prognosis analysis of 558 patients with glioma

The overall prognosis analysis is based on SPSS 17.0 software for statistical analysis. Univariate survival analysis used the Kaplan-Meier method to calculate the median survival time and 1-year, 2-year, and 3-year survival rates of patients. The Log-rank test was used to compare survival risks. The Cox hazard proportional regression model was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs), and then we evaluated the impact of *NDRG1* genotype on the overall survival and progression-free survival of glioma patients. We also used Kaplan-Meier method and Log-rank test to draw the corresponding survival curves of glioma patients.

All tests in this study were two-sided tests, and $p < 0.05$ was considered statistically significant.

3. Results

3.1 Sample overview

This study adopted a 'case-control' experimental design. The average age of glioma patients was 40.52 ± 18.08 years, including 307 males (55%) and 251 females (45%); the average age of healthy individuals was 40.75 ± 13.99 years, including 280 males (56%) and 223 females (44%). Table 1 summarizes the demographic (age and gender) and clinical information (WHO grade, astrocytoma, surgical operation, radiotherapy status, and chemotherapy status) of the participants. We found that there was no statistical difference between the case group and the control group in gender ($p = 0.853$) and age ($p = 0.817$).

Table 1
Characteristics of patients with glioma and healthy individuals.

Characteristics		Cases	Control	*p*
		n = 558	n = 503	
Age (years)	Mean ± SD	40.52 ± 18.08	40.75 ± 13.99	0.817
	> 40	289 (52%)	245 (49%)	
	≤ 40	269 (48%)	258 (51%)	
Gender	Male	307(55%)	280(56%)	0.853
	Female	251(45%)	223(44%)	
Astrocytoma	Yes	428 (77%)	-	
	No	130 (23%)		
WHO grade	I–II	352 (63%)	-	
	III–IV	206 (37%)		
Surgical operation	STR & NTR	175 (31%)	-	
	GTR	383 (69%)		
Radiotherapy	Conformal radiotherapy	145 (26%)	-	
	Gamma knife	356 (64%)		
	No	57 (10%)		
Chemotherapy	Yes	227 (41%)	-	
	No	331 (59%)		
WHO: World Health Organization;				
GTR: gross-total resection;				
NTR: near-total resection;				
STR: sub-total resection;				
$p < 0.05$: indicates statistical significance.				

3.2 Genotyping and candidate SNPs related information

5 candidate SNPs (rs2272646 A/G, rs3779941 C/A, rs3808599 G/C, rs2977497 T/C, rs3802251 C/T) on *NDRG1* were successfully genotyped. Detailed information about these five candidate SNPs was summarized in Table 2. All candidate SNPs were in line with HWE ($p > 5\%$). The results of HaploReg showed that the SNPs in this study may be regulated by many factors, including Enhancer histone marks, DNAse, Motifs changed, GRASP QTL hits, Selected eQTL Hits, Promoter histone marks.

Table 2
The basic information and HWE about the selected SNPs of *NDRG1*.

SNP ID	Chr: Position	Alleles (A/B)	MAF		HWE (*P* Value)	Haploreg 4.1
			Cases	Controls		
rs2272646	8: 134254051	A/G	0.319	0.301	0.523	Enhancer histone marks; DNAse; Motifs changed; GRASP QTL hits; Selected eQTL Hits.
rs3779941	8: 134257728	C/A	0.117	0.108	0.163	Enhancer histone marks; DNAse; Motifs changed.
rs3808599	8: 134267886	G/C	0.156	0.180	0.172	Enhancer histone marks; DNAse; Motifs changed; Selected eQTL Hits.
rs2977497	8: 134277855	T/C	0.414	0.444	0.651	Enhancer histone marks; DNAse; Motifs changed.
rs3802251	8: 134305599	C/T	0.392	0.448	0.787	Promoter histone marks; Enhancer histone marks; DNAse; Motifs changed.
SNP: single nucleotide polymorphism;						
MAF: minor allele frequency;						
HWE: Hardy—Weinberg equilibrium.						

3.3 Evaluation of the correlation between NDRG1 SNPs and glioma risk

Overall analysis

The association between SNPs on *NDRG1* and glioma risk under multiple genetic models was tested based on logistic regression, and the results were adjusted by age and gender (Table 3). The results showed that among the 5 candidate SNPs, rs3808599 or rs3802251 and the risk of glioma may have a certain association. Specifically, rs3808599 on *NDRG1* can reduce the risk of gliomas in homozygous (GG vs. CC, OR = 0.41, CI = 0.19–0.89, $p = 0.024$) and recessive models (GG vs. GC-CC, OR = 0.42, CI = 0.19–0.90, $p = 0.025$); rs3802251 on *NDRG1* can also reduce gliomas risk in allelic (C vs. T, OR = 0.79, CI = 0.67–0.94, $p = 0.008$), homozygous (CC vs. TT, OR = 0.63, CI = 0.44–0.90, $p = 0.011$), dominant (CC-CT vs. TT, OR = 0.73, CI = 0.56–0.95, $p = 0.017$), and log-additive models (OR = 0.79, CI = 0.66–0.94, $p = 0.008$). We did not find any evidence of the association between the remaining three candidate SNPs and glioma risk.

Table 3
Analysis of the association between glioma and SNPs of *NDRG1*.

SNP ID	Model	Genotype	Case	Control	Adjusted by age and gender	
					OR (95% CI)	p
rs2272646	Allele	A/G	356	299	1.09 (0.90–1.31)	0.367
	Homozygote	AA/GG	66	48	1.26 (0.84–1.90)	0.268
	Heterozygote	AG/GG	224	203	1.01 (0.78–1.31)	0.929
	Dominant	AA-AG/GG	290	251	1.06 (0.83–1.35)	0.641
	Recessive	AA/AG-GG	66	48	1.25 (0.85–1.86)	0.259
	Additive	-	-	-	1.08 (0.90–1.30)	0.385
rs3779941	Allele	C/A	131	109	1.09 (0.84–1.43)	0.512
	Homozygote	CC/AA	5	9	0.51 (0.17–1.54)	0.234
	Heterozygote	CA/AA	121	91	1.24 (0.92–1.68)	0.165
	Dominant	CC-CA/AA	126	100	1.18 (0.87–1.58)	0.286
	Recessive	CC/CA-AA	5	9	0.49 (0.16–1.48)	0.205
	Additive	-	-	-	1.09 (0.83–1.43)	0.518
rs3808599	Allele	G/C	174	181	0.84 (0.67–1.06)	0.139
	Homozygote	GG/CC	10	21	0.41 (0.19–0.89)	**0.024***
	Heterozygote	GC/CC	154	139	0.96 (0.74–1.27)	0.792
	Dominant	GG-GC/CC	164	160	0.89 (0.69–1.16)	0.393
	Recessive	GG/ GC-CC	10	21	0.42 (0.19–0.90)	**0.025***
	Additive	-	-	-	0.84 (0.67–1.06)	0.141
rs2977497	Allele	T/C	460	446	0.88 (0.74–1.05)	0.156
	Homozygote	TT/ CC	99	96	0.80 (0.56–1.14)	0.222
	Heterozygote	TC/ CC	262	254	0.80 (0.61–1.06)	0.116
	Dominant	TT-TC/ CC	361	350	0.80 (0.62–1.04)	0.096
	Recessive	TT/ TC-CC	99	96	0.92 (0.67–1.25)	0.581
	Additive	-	-	-	0.88 (0.74–1.05)	0.155
rs3802251	Allele	C/T	437	451	0.79 (0.67–0.94)	**0.008***
	Homozygote	CC/TT	85	99	0.63 (0.44–0.90)	**0.011***
	Heterozygote	CT/TT	267	253	0.77 (0.59–1.01)	0.062
	Dominant	CC-CT/TT	352	352	0.73 (0.56–0.95)	**0.017***
	Recessive	CC/ CT-TT	85	99	0.73 (0.53–1.01)	0.055
	Additive	-	-	-	0.79 (0.66–0.94)	**0.008***
SNP: single nucleotide polymorphisms;						
OR: odds ratio;						
CI: confidence interval;						
$p < 0.05$: indicates statistical significance.						

Age and Gender

The results showed (Table 4) that rs3808599 on *NDRG1* reduced the risk of glioma among the participants ≤ 40 years old under the homozygous model (GG vs. CC, OR = 0.30, CI = 0.11–0.83, $p = 0.020$) and the recessive model (GG vs. GC-CC, OR = 0.29, CI = 0.11–0.82, $p =$

0.019); the rs3802251 on *NDRG1* can also reduce the risk of glioma among males of the participants under heterozygous (CT vs. TT, OR = 0.69, CI = 0.47–1.00, $p = 0.049$) and dominant models (CC-CT vs. TT, OR = 0.68, CI = 0.48–0.97, $p = 0.0033$). We did not find evidence that there is an association between the five candidate SNPs and the risk of glioma in the female participants.

Table 4
The SNPs of *NDRG1* associated with risk of glioma in the subgroup tests (age and gender).

SNP ID	Model	genotype	Age, years				Gender			
			OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
			≤ 40		> 40		Female		Male	
rs2272646	Allele	A/G	1.17 (0.90–1.52)	0.240	1.02 (0.78–1.32)	0.897	1.00 (0.76–1.31)	0.977	1.17 (0.91–1.50)	0.216
	Homozygote	AA/GG	1.21 (0.68–2.14)	0.513	1.50 (0.81–2.78)	0.202	1.02 (0.55–1.89)	0.954	1.50 (0.86–2.60)	0.153
	Heterozygote	AG/GG	1.27 (0.88–1.85)	0.204	0.81 (0.56–1.16)	0.247	0.97 (0.66–1.43)	0.883	1.04 (0.74–1.48)	0.810
	Dominant	AA-AG/GG	1.26 (0.89–1.79)	0.197	0.91 (0.64–1.28)	0.582	0.98 (0.68–1.41)	0.916	1.13 (0.81–1.56)	0.471
	Recessive	AA/AG-GG	1.08 (0.63–1.87)	0.772	1.65 (0.91-3.00)	0.100	1.03 (0.57–1.86)	0.917	1.47 (0.86–2.50)	0.156
	Additive	-	1.15 (0.89–1.49)	0.279	1.05 (0.81–1.36)	0.737	1.00 (0.76–1.31)	0.976	1.16 (0.91–1.48)	0.234
rs3779941	Allele	C/A	0.95 (0.66–1.38)	0.803	1.29 (0.87–1.91)	0.210	1.10 (0.74–1.64)	0.642	1.09 (0.76–1.57)	0.644
	Homozygote	CC/AA	0.32 (0.08–1.22)	0.095	N/A	0.999	0.91 (0.22–3.71)	0.897	0.19 (0.02–1.62)	0.128
	Heterozygote	CA/AA	1.23 (0.79–1.92)	0.362	1.27 (0.83–1.94)	0.275	1.16 (0.73–1.83)	0.531	1.31 (0.87–1.97)	0.193
	Dominant	CC-CA/AA	1.08 (0.70–1.65)	0.732	1.30 (0.85–1.99)	0.221	1.14 (0.73–1.77)	0.573	1.21 (0.81–1.80)	0.351
	Recessive	CC/CA-AA	0.31 (0.08–1.17)	0.083	N/A	0.999	0.88 (0.22–3.59)	0.863	0.18 (0.02–1.53)	0.116
	Additive	-	0.95 (0.66–1.37)	0.784	1.33 (0.88–2.02)	0.175	1.10 (0.74–1.63)	0.649	1.09 (0.75–1.58)	0.643
rs3808599	Allele	G/C	0.78 (0.57–1.07)	0.127	0.92 (0.66–1.28)	0.622	0.88 (0.62–1.25)	0.481	0.81 (0.60–1.10)	0.180
	Homozygote	GG/CC	0.30 (0.11–0.83)	**0.020***	0.98 (0.26–3.76)	0.981	0.43 (0.13–1.47)	0.180	0.40 (0.15–1.08)	0.070
	Heterozygote	GC/CC	0.92 (0.68–1.50)	0.974	0.90 (0.61–1.32)	0.583	1.00 (0.67–1.51)	0.985	0.93 (0.65–1.34)	0.712

SNP: single nucleotide polymorphisms;

OR: odds ratio;

CI: confidence interval;

$p < 0.05$: indicates statistical significance.

SNP ID	Model	genotype	Age, years				Gender			
			OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
			≤ 40		> 40		Female		Male	
	Dominant	GG-GC/CC	0.87 (0.60–1.27)	0.462	0.90 (0.62–1.31)	0.594	0.94 (0.63–1.39)	0.745	0.86 (0.61–1.22)	0.395
	Recessive	GG/ GC-CC	0.29 (0.11–0.82)	**0.019***	1.01 (0.27–3.85)	0.984	0.43 (0.13–1.46)	0.178	0.41 (0.15–1.09)	0.074
	Additive	-	0.79 (0.57–1.08)	0.137	0.92 (0.65–1.29)	0.629	0.88 (0.62–1.25)	0.480	0.82 (0.60–1.10)	0.182
rs2977497	Allele	T/C	0.85 (0.66–1.08)	0.178	0.93 (0.73–1.18)	0.541	0.93 (0.72–1.21)	0.588	0.85 (0.67–1.07)	0.160
	Homozygote	TT/ CC	0.75 (0.45–1.25)	0.271	0.92 (0.56–1.53)	0.752	0.93 (0.54–1.59)	0.783	0.72 (0.45–1.16)	0.175
	Heterozygote	TC/ CC	0.69 (0.46–1.03)	0.072	0.90 (0.61–1.32)	0.591	0.79 (0.53–1.18)	0.246	0.81 (0.56–1.18)	0.277
	Dominant	TT-TC/ CC	0.71 (0.49–1.04)	0.075	0.91 (0.63–1.30)	0.593	0.82 (0.56–1.20)	0.313	0.79 (0.55–1.12)	0.180
	Recessive	TT/ TC-CC	0.94 (0.61–1.47)	0.793	0.98 (0.62–1.54)	0.932	1.07 (0.66–1.73)	0.790	0.82 (0.54–1.24)	0.343
	Additive	-	0.85 (0.66–1.08)	0.185	0.95 (0.74–1.22)	0.683	0.93 (0.72–1.21)	0.586	0.85 (0.67–1.07)	0.156
rs3802251	Allele	C/T	0.81 (0.64–1.04)	0.098	0.78 (0.61–0.99)	0.044*	0.78 (0.60–1.01)	0.059	0.80 (0.64–1.01)	0.064
	Homozygote	CC/TT	0.62 (0.38–1.03)	0.067	0.66 (0.39–1.11)	0.118	0.58 (0.34–0.99)	0.055	0.66 (0.41–1.07)	0.091
	Heterozygote	CT/TT	0.82 (0.55–1.22)	0.320	0.72 (0.49–1.05)	0.087	0.88 (0.59–1.32)	0.548	0.69 (0.47-1.00)	**0.049***
	Dominant	CC-CT/TT	0.75 (0.52–1.10)	0.144	0.70 (0.49–1.01)	0.056	0.79 (0.54–1.15)	0.222	0.68 (0.48–0.97)	**0.033***
	Recessive	CC/ CT-TT	0.71 (0.45–1.10)	0.122	0.80 (0.50–1.29)	0.356	0.62 (0.38–1.01)	0.053	0.83 (0.55–1.27)	0.397
	Additive	-	0.79 (0.62–1.02)	0.067	0.79 (0.61–1.02)	0.069	0.78 (0.60–1.01)	0.062	0.79 (0.63–1.01)	0.057

SNP: single nucleotide polymorphisms;

OR: odds ratio;

CI: confidence interval;

$p < 0.05$: indicates statistical significance.

Astrocytoma

The results showed (Table 5) that rs3802251 on *NDRG1* has a certain association with astrocytoma patients in allelic (C vs. T, OR = 0.81, CI = 0.67–0.97, $p = 0.023$), homozygous (CC vs. TT, OR = 0.67, CI = 0.46–0.99, $p = 0.043$), dominant (CC-CT vs. TT, OR = 0.75, CI = 0.57–0.99, $p =$

0.042), and log-additive models (OR = 0.81, CI = 0.68–0.98, $p = 0.031$), and it showed a risk reduction effect (OR < 1).

Table 5
The SNPs of *NDRG1* associated with risk of glioma in the subgroup tests (astrocytoma).

SNP ID	Model	genotype	Astrocytoma (astrocytoma in case group Vs. all controls)	
			OR (95% CI)	p
rs2272646	Allele	A/G	1.03 (0.85–1.26)	0.764
	Homozygote	AA/GG	1.19 (0.77–1.85)	0.435
	Heterozygote	AG/GG	0.94 (0.71–1.23)	0.642
	Dominant	AA-AG/GG	0.98 (0.76–1.28)	0.909
	Recessive	AA/AG-GG	1.23 (0.80–1.87)	0.343
	Additive	-	1.04 (0.85–1.26)	0.728
rs3779941	Allele	C/A	1.09 (0.82–1.45)	0.564
	Homozygote	CC/AA	0.70 (0.23–2.13)	0.535
	Heterozygote	CA/AA	1.20 (0.87–1.66)	0.276
	Dominant	CC-CA/AA	1.16 (0.84–1.59)	0.371
	Recessive	CC/CA-AA	0.68 (0.23–2.05)	0.493
	Additive	-	1.10 (0.82–1.46)	0.535
rs3808599	Allele	G/C	0.85 (0.67–1.09)	0.203
	Homozygote	GG/CC	0.50 (0.22–1.11)	0.086
	Heterozygote	GC/CC	0.96 (0.72–1.28)	0.778
	Dominant	GG-GC/CC	0.90 (0.68–1.19)	0.458
	Recessive	GG/ GC-CC	0.50 (0.23–1.11)	0.090
	Additive	-	0.86 (0.68–1.10)	0.229
rs2977497	Allele	T/C	0.85 (0.70–1.02)	0.079
	Homozygote	TT/ CC	0.75 (0.51–1.09)	0.130
	Heterozygote	TC/ CC	0.80 (0.60–1.07)	0.127
	Dominant	TT-TC/ CC	0.78 (0.59–1.03)	0.082
	Recessive	TT/ TC-CC	0.85 (0.61–1.20)	0.361
	Additive	-	0.85 (0.71–1.03)	0.094
rs3802251	Allele	C/T	0.81 (0.67–0.97)	**0.023***
	Homozygote	CC/TT	0.67 (0.46–0.99)	**0.043***
	Heterozygote	CT/TT	0.78 (0.58–1.05)	0.096
	Dominant	CC-CT/TT	0.75 (0.57–0.99)	**0.042***
	Recessive	CC/ CT-TT	0.78 (0.56–1.10)	0.156
	Additive	-	0.81 (0.68–0.98)	**0.031***
SNP: single nucleotide polymorphisms;				
OR: odds ratio;				
CI: confidence interval;				
$p < 0.05$: indicates statistical significance.				

WHO grade

The results showed (supplemental table 1) that there may be no association between the five candidate SNPs on *NDRG1* and the WHO grade of glioma in Chinese Han population.

MDR analysis: MDR analysis was used to evaluate the interactions between 'SNP-SNP'. Figure 1 can describe the interaction between 5 candidate SNPs. The blue line indicated that the candidate SNPs may have a redundant role in regulating the risk of glioma. All experimental results have been shown in Table 6: The best single-point model for predicting the risk of glioma is: rs3802251 (testing accuracy = 0.539, CVC = 10/10, $p = 0.0094$); the two-site model is: rs3779941, rs3802251 (testing accuracy = 0.511, CVC = 4/10, $p = 0.0003$); the three-site model is: rs3779941, rs3808599, rs3802251 (testing accuracy = 0.504, CVC = 4/10, $p < 0.0001$); the four-site model is: rs2272646, rs3808599, rs2977497, rs3802251 (testing accuracy = 0.511, CVC = 5/10, $p < 0.0001$); the five-site model is: rs2272646, rs3779941, rs3808599, rs2977497, rs3802251 (testing accuracy = 0.540, CVC = 10/10, $p < 0.0001$). Therefore, our analysis concluded that the impact of the five candidate SNPs on the risk of glioma may be interdependent.

Table 6
SNP–SNP interaction models analyzed by the MDR method.

Model	Training Bal. Acc	Testing Bal. Acc	OR (95% CI)	*p* value	CVC
rs3802251	0.539	0.539	1.42 (1.09–1.84)	**0.0094***	10/10
rs3779941, rs3802251	0.559	0.511	1.59 (1.23–2.04)	**0.0003***	4/10
rs3779941, rs3808599, rs3802251	0.575	0.504	1.82 (1.41–2.35)	**< 0.0001***	4/10
rs2272646, rs3808599, rs2977497, rs3802251	0.593	0.511	2.05 (1.59–2.63)	**< 0.0001***	5/10
rs2272646, rs3779941, rs3808599, rs2977497, rs3802251	0.610	0.540	2.38 (1.85–3.07)	**< 0.0001***	10/10
MDR: multifactor dimensionality reduction;					
Bal. Acc.: balanced accuracy;					
CVC: cross-validation consistency;					
OR: odds ratio;					
95% CI: 95% confidence interval.					
p values were calculated using χ^2 tests;					
$p < 0.05$: indicates statistical significance.					

3.4 Prognosis analysis of 558 patients with glioma

Overall: A follow-up survey was conducted on 558 glioma patients in this study, and the follow-up time was 1–36 months. Based on the follow-up records, we conducted a univariate analysis between overall survival (OS) or progression-free survival (PFS) and clinical factors in 558 glioma patients. These clinical factors include: gender, age, WHO grade, surgical operation, radiotherapy status, and chemotherapy status (Table 7 and Fig. 2). Our results showed that from the perspective of surgical resection methods, gliomas patients with total tumor resection (OS: log-rank $p < 0.001$, HR = 0.62; PFS: log-rank $p < 0.001$, HR = 0.60) had a better prognosis than patients with non-total resection, and the result was statistically significant ($p < 0.001$). For the radiotherapy, glioma patients who have undergone gamma knife radiotherapy were associated with an increased risk of PFS (PFS: log-rank $p = 0.039$, HR = 1.40, $p = 0.041$). For the chemotherapy, compared with glioma patients who have not undergone chemotherapy, patients after chemotherapy have a better prognosis (OS: log-rank $p < 0.001$, HR = 0.70, $p < 0.001$). However, we did not find any evidence that other clinical factors (gender, age, WHO grade) were related to the prognosis of glioma patients.

Table 7
Univariate analysis of the influence of clinical factors on glioma patient OS and PFS.

Factors		Total	Event	OS				PFS			
				Log-rank p	**SR (1-/3-year)**	**HR (95% CI)**	p	**Log-rank** p	**SR (1-/3-year)**	**HR (95% CI)**	p
Gender	Male	307	273	0.314	0.334/0.079	1.00		0.214	0.199/0.091	1.00	
	Female	251	226		0.315/0.090	1.09 (0.91–1.3)	0.356		0.149/0.093	1.11 (0.93–1.32)	0.266
Age	< 40 years	248	214	0.059	0.361/0.114	1.00		0.100	0.198/0.111	1.00	
	≥ 40 years	310	285		0.297/0.061	1.17 (0.98–1.40)	0.084		0.159/0.069	1.14 (0.96–1.37)	0.140
WHO grade	I–II	352	310	0.273	0.328/0.101	1.00		0.271	0.184/0.099	1.00	
	III–IV	206	189		0.320/0.066	1.10 (0.92–1.32)	0.315		0.164/0.069	1.10 (0.91–1.31)	0.324
Surgical operation	STR & NTR	175	173	**< 0.001***	0.206/-	1.00		**< 0.001***	0.012/-	1.00	
	GTR	383	326		**0.380/0.118**	**0.62 (0.52–0.76)**	**< 0.001***		**0.252/0.121**	**0.60 (0.49–0.72)**	**< 0.001***
Radiotherapy	No	57	46	0.346	0.456/-	1.00		0.061	0.204/-	1.00	
	Conformal radiotherapy	145	119		0.252/0.147	1.12 (0.80–1.58)	0.509		0.217/0.156	1.42 (1.00-2.01)	0.052
	Gamma knife	356	334		0.334/0.052	0.21 (0.89–1.65)	0.220		**0.158/0.048**	**1.40 (1.01–1.92)**	**0.041***
Chemotherapy	No	331	309	**< 0.001***	0.278/0.029	1.00		0.054	0.170/0.060	1.00	
	Yes	227	190		**0.395/0.143**	**0.70 (0.58–0.84)**	**< 0.001***		0.188/0.140	0.85 (0.71–1.02)	0.085

$p < 0.05$: indicates statistical significance;

Log-rank p values were calculated using the Chi-Square test

OS: overall survival;

PFS: progression free survival;

SR: survival rate;

HR: hazard ratio;

95% CI: 95% confidence interval.

Astrocytoma patients: The results showed that female astrocytoma patients have a potential association with progression-free survival (PFS: log-rank $p = 0.029$, HR = 1.23, $p = 0.050$). As shown in Table 8 and Fig. 3A and 3B, patients with total tumor resection had a better prognosis than patients with non-total resection (OS: log-rank $p < 0.001$, HR = 0.62, $p < 0.001$; PFS: log-rank $p < 0.001$, HR = 0.58, $p < 0.001$). For radiotherapy (Table 8 and Fig. 3C), compared with astrocytoma patients who are not undergoing radiotherapy, the results showed that no matter what kind of radiotherapy was given, it was associated with an increased risk of PFS in astrocytoma patients (log-rank $p = 0.031$, Conformal radiotherapy: HR = 1.59, $p = 0.023$; Gamma knife: HR = 1.50, $p = 0.029$). For chemotherapy, astrocytoma patients who have undergone chemotherapy have a better prognosis (OS: log-rank $p < 0.001$, HR = 0.62, $p < 0.001$). Table 8 have summarized the experimental results after univariate analysis.

Table 8
Univariate analysis of the influence of clinical factors on astrocytoma patient OS and PFS.

Factors		Total	Event	OS				PFS			
				Log-rank p	**SR (1-/3-year)**	**HR (95% CI)**	p	**Log-rank** p	**SR (1-/3-year)**	**HR (95% CI)**	p
Gender	Male	237	207	0.073	0.350/0.091	1.00		**0.029***	0.222/0.102	1.00	
	Female	191	173		0.304/0.071	1.18 (0.97–1.45)	0.101		**0.131/0.076**	**1.23 (1.00-1.50)**	**0.050***
Age	< 40 years	185	158	0.177	0.341/0.110	1.00		0.273	0.196/0.119	1.00	
	≥ 40 years	243	222		0.321/0.062	1.14 (0.93–1.40)	0.217		0.171/0.069	1.11 (0.90–1.36)	0.325
WHO grade	I–II	297	260	0.244	0.340/0.104	1.00		0.264	0.189/0.113	1.00	
	III–IV	131	120		0.305/0.049	1.13 (0.91–1.40)	0.286		0.165/0.057	1.12 (0.90–1.39)	0.317
Surgical operation	STR & NTR	133	132	**< 0.001***	0.211/-	1.00		**< 0.001***	0.008/-	1.00	
	GTR	295	248		**0.383/0.117**	**0.62 (0.50–0.77)**	**< 0.001***		**0.261/0.129**	**0.58 (0.47–0.72)**	**< 0.001***
Radiotherapy	No	44	35	0.337	0.500/-	1.00		**0.031***	0.524/-	1.00	
	Conformal radiotherapy	112	93		0.250/0.128	1.23 (0.83–1.82)	0.303		**0.218/0.137**	**1.59 (1.07–2.37)**	**0.023***
	Gamma knife	272	252		0.335/0.058	1.27 (0.89–1.82)	0.180		**0.162/0.063**	**1.50 (1.04–2.16)**	**0.029***
Chemotherapy	No	257	239	**< 0.001***	0.280/0.000	1.00		0.090	0.172/0.059	1.00	
	Yes	171	141		**0.404/0.143**	**0.68 (0.55–0.84)**	**< 0.001***		0.197/0.147	0.85 (0.69–1.05)	0.128

$p < 0.05$: indicates statistical significance;

Log-rank p values were calculated using the Chi-Square test

OS: overall survival;

PFS: progression free survival;

SR: survival rate;

HR: hazard ratio;

95% CI: 95% confidence interval.

SNPs and the prognosis of glioma patients (univariate analysis): We evaluated the impact of 5 candidate SNPs on the survival rate of glioma patients. The results are shown in Table 9 and Fig. 4, we found that rs3779941 has a potential impact on the OS and PFS of glioma patients (OS: log-rank $p = 0.006$; PFS: log-rank $p = 0.040$). At the same time, we also found an evidence that the genotype CC of rs3779941 was associated with the increased risk of OS in glioma patients (OS: HR = 3.07, 95% CI = 1.27–7.44, $p = 0.013$).

Table 9
Univariate analysis of the association between SNPs in *NDRG1* and glioma patient OS and PFS.

SNPs	Genotype	OS				PFS			
		Log-rank p	SR (1-/3-year)	HR (95% CI)	p	Log-rank p	SR (1-/3-year)	HR (95% CI)	p
rs2272646	GG	0.240	0.321/0.103	1.00		0.445	0.178/0.100	1.00	
	AG		0.311/0.051	1.09 (0.90–1.31)	0.390		0.146/0.057	1.04 (0.86–1.26)	0.676
	AA		0.394/0.120	0.87 (0.65–1.16)	0.334		0.277/-	0.88 (0.66–1.17)	0.376
rs3779941	AA	**0.006***	0.344/0.089	1.00		**0.040***	0.190/0.096	1.00	
	CA		0.273/-	1.20 (0.97–1.49)	0.090		0.134/-	1.22 (0.99–1.51)	0.068
	CC		0.000/-	**3.07 (1.27–7.44)**	**0.013***		-/-	1.91 (0.79–4.61)	0.153
rs3808599	CC	0.102	0.349/0.096	1.00		0.105	0.193/0.102	1.00	
	GC		0.273/0.062	1.19 (0.98–1.11)	0.089		0.138/0.051	1.19 (0.97–1.44)	0.089
	GG		0.200/-	1.43 (0.76–2.69)	0.264		0.100/-	1.38 (0.74–2.59)	0.316
rs2977497	CC	0.202	0.359/0.094	1.00		0.096	0.192/0.105	1.00	
	TC		0.311/0.096	1.05 (0.86–1.27)	0.661		0.183/0.090	1.03 (0.84–1.25)	0.783
	TT		0.303/0.032	1.23 (0.96–1.58)	0.108		0.131/-	1.27 (0.98–1.63)	0.066
rs3802251	TT	0.895	0.325/0.071	1.00		0.910	0.171/0.076	1.00	
	CT		0.326/0.100	0.96 (0.79–1.16)	0.679		0.187/0.096	0.97 (0.80_1.18)	0.787
	CC		0.324/0.079	0.99 (0.76–1.30)	0.960		0.158/-	1.02 (0.78_1.33)	0.882

p < 0.05: indicates statistical significance;

Log-rank p values were calculated using the Chi-Square test

OS: overall survival;

PFS: progression free survival;

SR: survival rate;

HR: hazard ratio;

95% CI: 95% confidence interval.

SNPs and the prognosis of glioma patients (multivariate analysis): After Cox multivariate analysis (multivariate: gender, age, WHO grade, radiotherapy, surgical operation, chemotherapy). The results showed that the rs3779941 polymorphism was associated with prognosis of glioma patients (Table 10). Specifically, the genotype CC of rs3779941 was a risk factor that increases the risk of OS in glioma patients, but there was no association with PFS (OS: HR = 2.59, 95% CI = 1.05–6.37, $p = 0.039$). There did not seem to be any association between the remaining candidate SNPs and the OS or PFS of glioma patients.

Table 10
Multivariate analysis of the association between SNPs of *NDRG1* and glioma patient OS and PFS (overall and astrocytoma).

SNPs	Genotype	OS		PFS	
		HR (95% CI)	p	**HR (95% CI)**	p
Overall analysis					
rs2272646	GG	1.00		1.00	
	AG	0.97 (0.8–1.17)	0.742	0.95 (0.78–1.15)	0.577
	AA	0.86 (0.64–1.16)	0.330	0.89 (0.66–1.20)	0.447
rs3779941	AA	1.00		1.00	
	CA	1.13 (0.91–1.40)	0.260	1.13 (0.92–1.41)	0.248
	CC	**2.59 (1.05–6.37)**	**0.039***	1.77 (0.72–4.35)	0.212
rs3808599	CC	1.00		1.00	
	GC	1.13 (0.93–1.38)	0.211	1.13 (0.93–1.38)	0.232
	GG	1.22 (0.64–2.330	0.538	1.16 (0.61–2.20)	0.656
rs2977497	CC	1.00		1.00	
	TC	1.05 (0.86–1.28)	0.625	1.01 (0.83–1.23)	0.911
	TT	1.19 (0.92–1.54)	0.184	1.20 (0.93–1.56)	0.156
rs3802251	TT	1.00		1.00	
	CT	1.04 (0.85–1.26)	0.705	1.06 (0.87–1.29)	0.565
	CC	1.04 (0.79–1.37)	0.775	1.06 (0.81–1.39)	0.688
Astrocytoma patients					
rs2272646	GG	1.00		1.00	
	AG	0.92 (0.74–1.14)	0.453	0.93 (0.74–1.15)	0.490
	AA	0.83 (0.59–1.17)	0.293	0.89 (0.63–1.25)	0.490
rs3779941	AA	1.00		1.00	
	CA	0.64 (1.06–0.83)	0.642	1.04 (0.81–1.34)	0.746
	CC	**2.63 (1.06–6.56)**	**0.038***	1.78 (0.72–4.42)	0.211
rs3808599	CC	1.00		1.00	
	GC	1.04 (0.83–1.31)	0.748	1.03 (0.82–1.29)	0.830
	GG	1.25 (0.63–2.50)	0.525	1.15 (0.58–2.28)	0.700
rs2977497	CC	1.00		1.00	
	TC	1.07 (0.85–1.35)	0.551	1.04 (0.83–1.31)	0.734

$p < 0.05$: indicates statistical significance;
Log-rank p values were calculated using the Chi-Square test
OS: overall survival;
PFS: progression free survival;
SR: survival rate;
HR: hazard ratio;
95% CI: 95% confidence interval.

SNPs	Genotype	OS		PFS	
	TT	1.08 (0.80–1.45)	0.636	1.12 (0.83–1.51)	0.467
rs3802251	TT	1.00		1.00	
	CT	1.04 (0.83–1.31)	0.728	1.06 (0.84–1.33)	0.628
	CC	1.07 (0.79–1.45)	0.660	1.10 (0.81–1.49)	0.535
$p < 0.05$: indicates statistical significance;					
Log-rank p values were calculated using the Chi-Square test					
OS: overall survival;					
PFS: progression free survival;					
SR: survival rate;					
HR: hazard ratio;					
95% CI: 95% confidence interval.					

SNPs and the prognosis of astrocytoma patients (multivariate analysis): Finally, we also performed the association analysis between *NDRG1* gene polymorphisms and the prognosis of astrocytoma patients. The results showed (Table 10) that the genotype CC of rs3779941 was a risk factor that increased the risk of OS in astrocytoma patients (OS: HR = 2.63, 95% CI = 1.06–6.56, $p = 0.038$), but there was no association with PFS. There did not seem to be any association between the remaining candidate SNPs and the OS or PFS of astrocytoma patients.

4. Discussion

Glioma is the tumor with the highest incidence and the worst prognosis among primary brain tumors, posing a great threat to human health. With the development of sequencing technology and genome-wide association studies (GWAS), more and more studies have proved that in addition to external factors such as high-dose ionizing radiation, genetic susceptibility genes also play a certain role in the occurrence and development of glioma (3, 18), such as *POLR3B*, *VTI1A*, *ZBTB16*, *ETFA*, etc. (19). Up to now, there is no report about the association between *NDRG1* gene polymorphisms and the occurrence and prognosis of glioma. However, studies have shown that *NDRG1* is necessary to inhibit the occurrence of glioma (20). This study was the first to explore the relationship between the 5 polymorphisms of *NDRG1* (rs2272646 A/G, rs3779941 C/A, rs3808599 G/C, rs2977497 T/C, rs3802251 C/T) and the genetic risk of glioma or the prognosis of patients in the Chinese Han population. And as far as we know, this study is the first to find the *NDRG1* SNPs (rs3779941, rs3808599, and rs3802251) are potentially associated with glioma susceptibility or prognosis. In addition, in the prognosis analysis of glioma patients, we found that surgical operation, radiotherapy, and chemotherapy are the key factors for the prognosis of glioma patients in the Chinese Han population.

NDRG1 has been found that it plays an important role in multiple regulatory mechanisms of tumor cells, including proliferation, invasion, migration, and apoptosis. At present, *NDRG1* has been proposed as a tumor suppressor gene in a variety of cancers, including breast cancer (21), colon cancer (22) and prostate cancer (23). And *NDRG1* is also necessary for inhibiting the occurrence of glioma (20, 24). Sun et al. found that the expression level of *NDRG1* in high-grade glioma tissue is relatively lower than that in normal brain tissue or low-grade glioma tissue (14). These research results prompted that *NDRG1* may be an internal regulator that can affect the occurrence and development of glioma, and the expression of *NDRG1* may play a very important role in the progression and prognosis of glioma.

In this study, we found that rs3808599 on *NDRG1* can reduce the risk of glioma in homozygous and recessive models, whether in the overall participants (homozygous: OR = 0.41; recessive: OR = 0.42) or in the participants ≤ 40 years old (homozygous: OR = 0.30; recessive: OR = 0.29); rs3802251 on *NDRG1* can significantly reduce the risk of glioma in the overall participants, male participants and astrocytoma patients under variety of genetic models; the prognostic analysis after the follow-up investigation found that rs3779941 on *NDRG1* was significantly associated with the prognosis of glioma patients in our study. At the same time, we also found the three candidate SNPs (rs3779941, rs3808599 and rs3802251), which are potentially related to the risk or prognosis of glioma in this study, are all located in the intron region. The results of HaploReg indicate that rs3779941 may be related to the regulation of enhancer histones, DNA enzymes and motif changes; rs3808599 may be related to the enhancement of self-histone regulation, DNA enzymes, motif changes, etc.; rs3802251 may be related to the regulation of promoter histone, the regulation of enhancer histone, the change of DNA enzyme and motif. The above results suggest that the three candidate SNPs on *NDRG1* may play a role in the occurrence and development of glioma. And there have been several studies suggesting that mutants located in the intron region can disrupt transcriptional regulatory motifs by affecting gene expression, which will affect the occurrence and development of diseases (25–27). More importantly, studies have shown that *NDRG1* can inhibit the proliferation and invasion of glioma cells, *NDRG1* is low expressed in glioma cells, and overexpressed *NDRG1* will inhibit the growth of glioma tumors in vivo (20).

Therefore, combined with the results of this study, we speculate that the polymorphic sites rs3808599, rs3802251 and rs3779941 on *NDRG1* may affect the risk or prognosis of glioma in the Chinese population by affecting the gene expression of *NDRG1*. But a deeper level of verification is needed to confirm this hypothesis.

There are inevitably several shortcomings in our research. On the one hand, enlarging the sample size and selection range is necessary in the following research. On the other hand, this study is only a preliminary research. Therefore, in order to clearly clarify the molecular mechanism of how the *NDRG1* SNPs affect the risk or prognosis of glioma, we need to further verify the functions of these variants (rs3779941, rs3808599, and rs3802251) to strongly confirm the results of this study. Despite the above-mentioned deficiencies in this study, the results provide a theoretical basis for the study of glioma risk in the Chinese Han population.

5. Conclusion

In summary, the results of this study showed that the *NDRG1* gene polymorphisms have a potential association with the risk or prognosis of glioma in the Chinese Han population, which provides new ideas for the risk assessment and prognosis evaluation of glioma in the Chinese Han population.

Declarations

Ethics approval and consent to participate

This study was conducted under the standard approved by the ethics committee of the First Affiliated Hospital of Xi'an Jiaotong University. And conformed to the ethical principles for medical research involving humans of the World Medical Association Declaration of Helsinki. All participants signed informed consent forms before participating in this study.

Consent to publication

All authors agreed to publish the manuscript.

Data availability statement

The datasets used and analyzed in the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no conflict of interest.

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Authors' contribution statement

Conceptualization, Shiwen Guo; methodology: Pengfei Hou, Lu Gao and Yongqiang Shi; software: Weiyang Mi, Gang Zhang and Ning Wang; data curation: Wei Dai, Lin Wei and Yongzhi Shi; writing, review and editing: Nan Li and Hangyu Shi. All authors have read and approved the manuscript.

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Figures

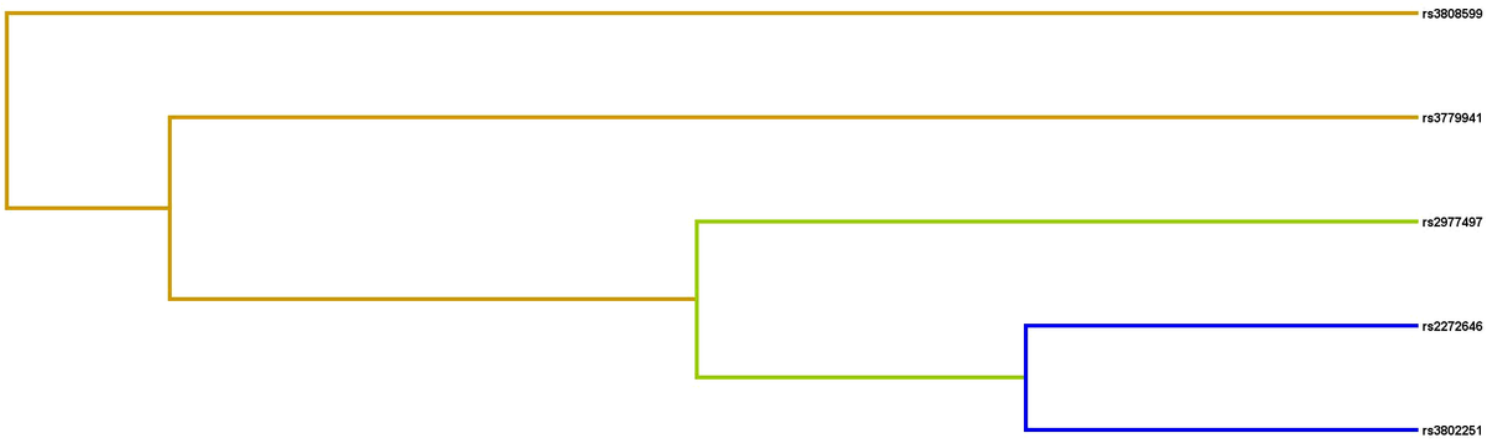

Figure 1

Dendrogram analysis of SNP-SNP interaction (NDRG1). The colors in the tree diagram represent synergy (yellow) or redundancy (blue).

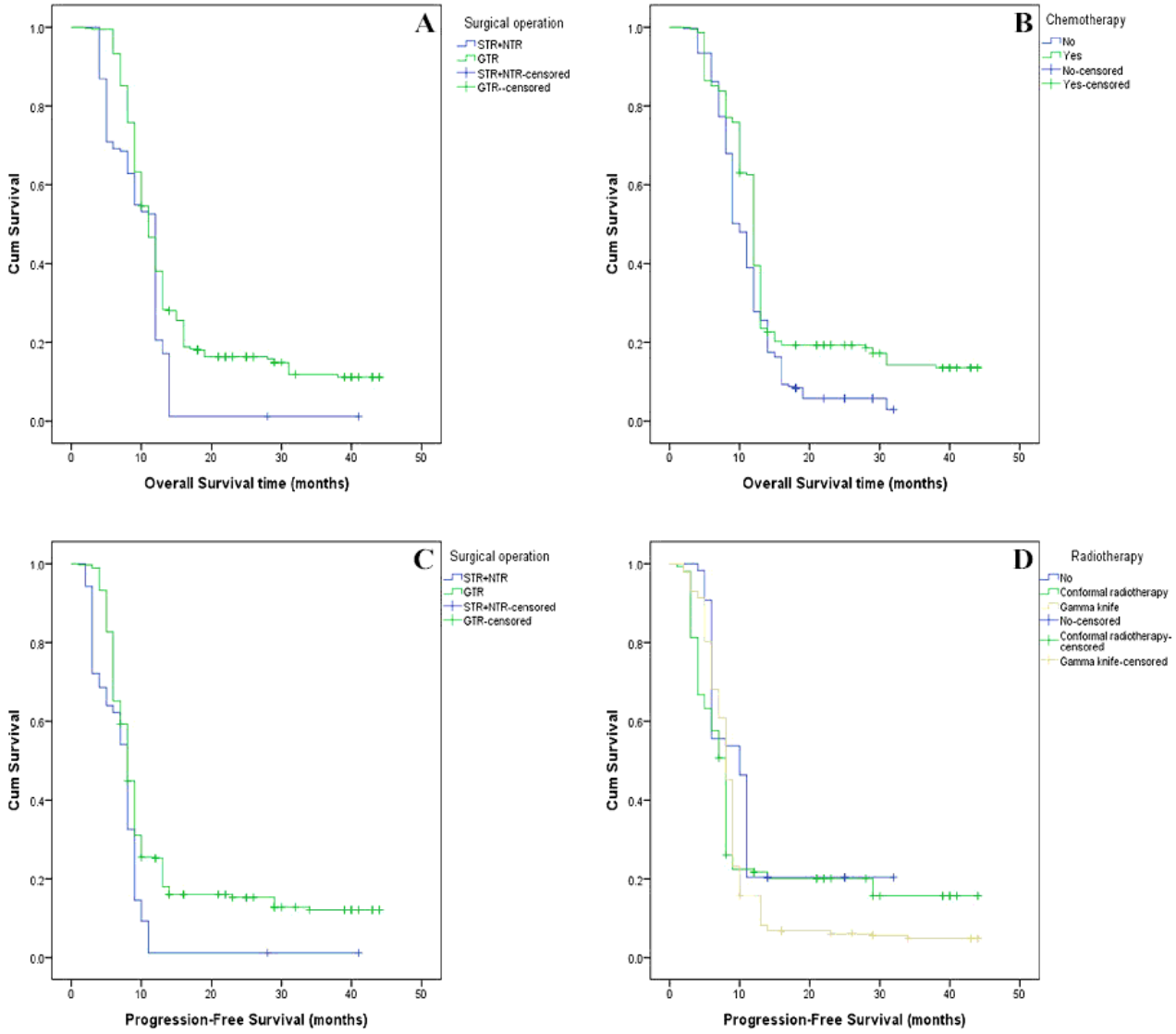

Figure 2

Kaplan–Meier curves for overall survival and progression-free survival according to the glioma patients with different clinical factors. (A: OS according to surgical operation; B: OS according to chemotherapy status; C: PFS according to surgical operation; D: PFS according to radiotherapy status).

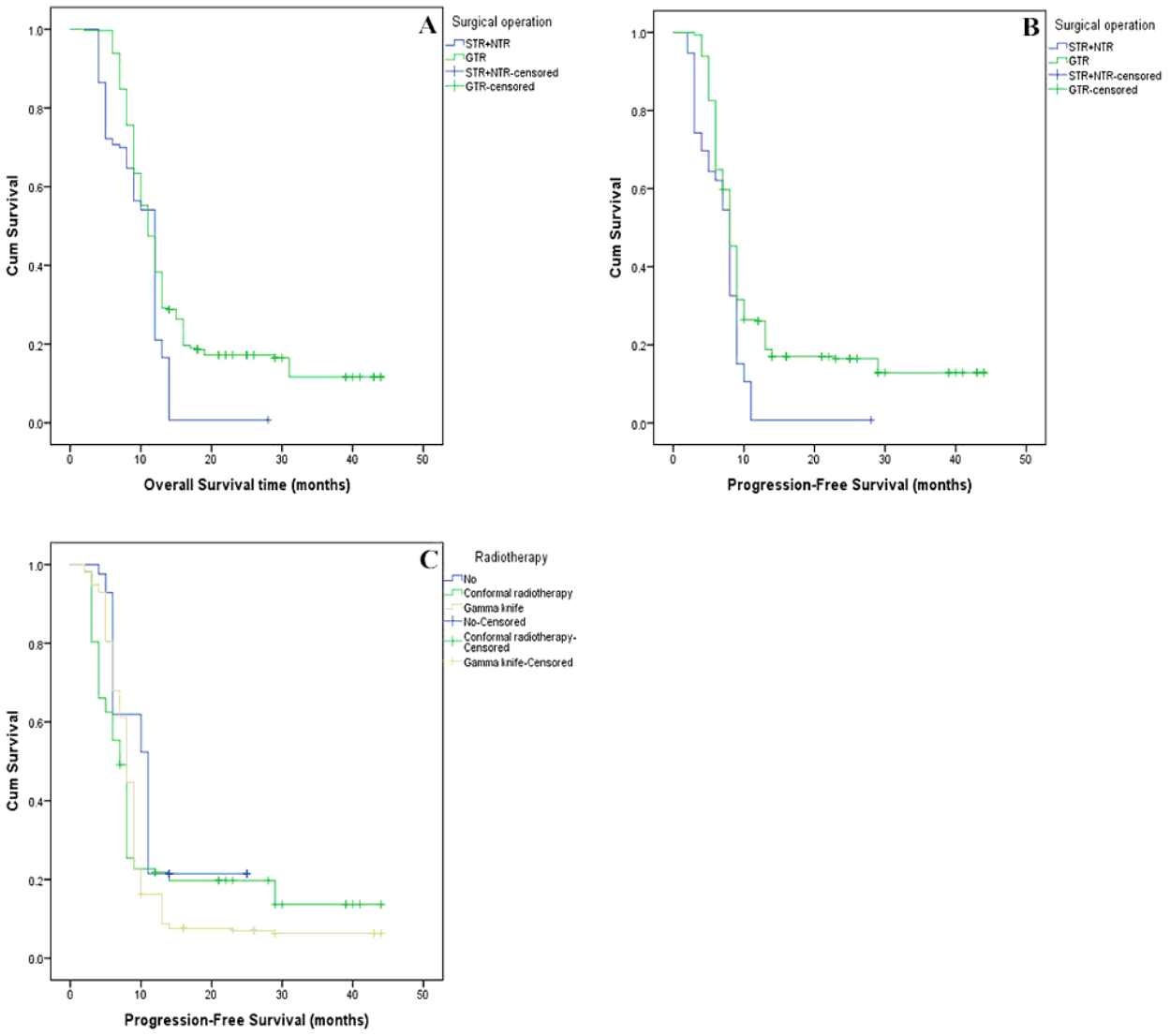

Figure 3

Kaplan–Meier curves for overall survival and progression-free survival according to the astrocytoma patients with different clinical factors. (A: OS according to surgical operation; B: PFS according to surgical operation; C: PFS according to radiotherapy status).

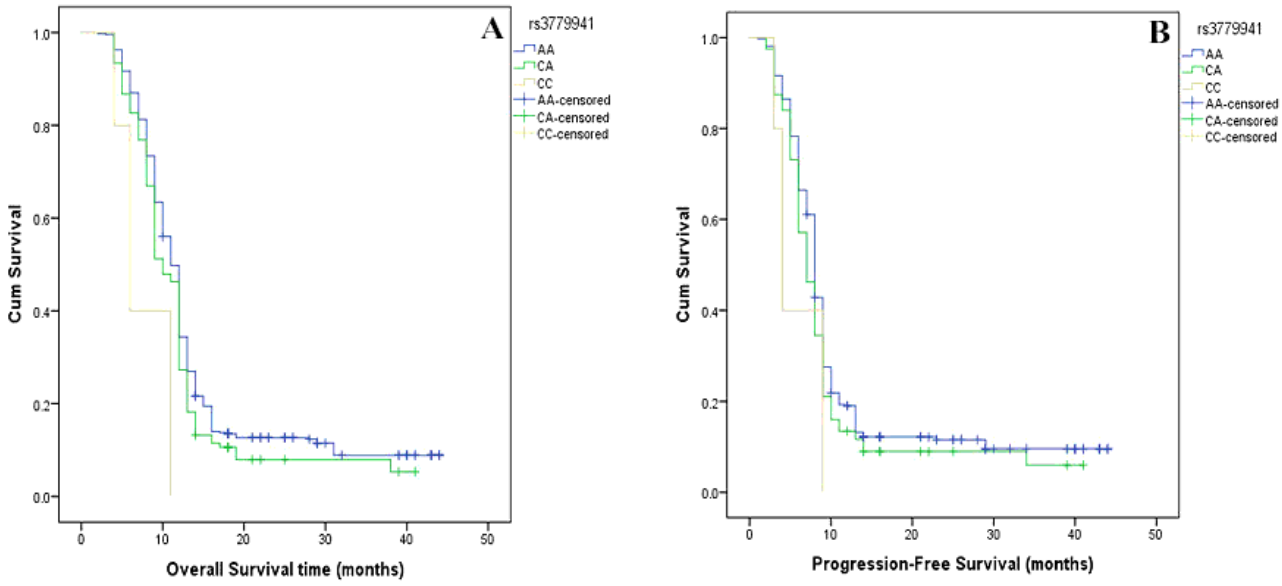

Figure 4

Glioma patient survival based on NDRG1 rs3779941 polymorphism. Kaplan–Meier survival curves are plotted for overall and progression free survival. (A: OS based on NDRG1 rs3779941 polymorphism; B: PFS based on NDRG1 rs3779941 polymorphism).

Supplementary Files

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- Supplementaltable.docx