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Original Article

Genetic variants of *BCL2* gene predict clinical outcomes of non-small-cell lung cancer patients treated with platinum-based chemotherapy in a Chinese population

Xi Ding[1*], Ji Qian[2*], Yang Yang[3], Wen Xu[4], Di Liu[5], Bo Su[1]

[1]Central Laboratory, Departments of [4]Respiratory Medicine, [5]Thoracic Surgery, Shanghai Pulmonary Hospital, School of Medicine, Tongji University, Shanghai, China; [2]Cancer Institute, Shanghai Cancer Center, Department of Oncology, Shanghai Medical College; State Key Laboratory of Genetic Engineering and MOE Key Laboratory of Contemporary Anthropology, School of Life Sciences and Taizhou Institute of Health Sciences, Fudan University, Shanghai, China; [3]Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao-Tong University, Shanghai, China. [*]Equal contributors.

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Abstract: Platinum agents induce cancer cell death through BCL2-dependent intrinsic apoptotic pathway and are commonly used as anti-tumor drug. In this study, we evaluated whether single nucleotide polymorphism (SNPs) of BCL2 can affect the overall survival (OS) and progression-free survival (PFS) in non-small-cell lung cancer (NSCLC) patients treated with platinum-based chemotherapy. We genotyped 48 SNPs of BCL2 gene by Illumina Custom Designed Chip in 972 advanced NSCLC patients treated with platinum-based chemotherapy. We evaluated the relationship between genotype/haplotype/diplotype and OS/PFS by COX regression analysis. As a result, five SNPs, rs949037, rs3810027, rs4987739, rs4987726 and rs7226979, were significantly associated with overall survival time in 972 NSCLC patients after platinum-based chemotherapy. rs1381547 and rs8083946 were associated with progression-free survival. As representative, the G allele of rs949037 was associated with longer OS in NSCLC patients with platinum-based chemotherapy. Patients with GG or AG genotype showed a 19.9 months mOS vs AA genotype 14.2 months mOS (HR: 1.38, 95% CI: 1.11-1.72, P=0.004). In further analysis, rs949037 was found to predominantly contribute to the OS of patients with platinum-tubulin-targeting drugs, moreover, the GG genotype of rs949037 showed an 8.5 months longer OS compared with the unfavorable AA genotype (mOS: 21.36 vs 12.83, HR=0.70, 95% CI: 0.52-0.94, P=0.000). To conclude, polymorphisms of BCL2 gene may have an impact on the OS of platinum-based chemotherapy in NSCLC patients, which may be prognostic biomarkers of chemotherapy if validated in larger studies.

Keywords: BCL2, polymorphism, overall survival, advanced non-small cell cancer, chemotherapy

Introduction

Lung cancer is the leading cause of cancer mortality worldwide [1], and NSCLC (non-small-cell lung cancer) accounts for nearly 80% of total lung cancer deaths [2]. In China, NSCLC has become the most fatal cancer and most patients with NSCLC are detected at advanced stages [3], which cannot be treated with surgery. Over the past two decades, Platinum-based chemotherapy has become the major chemotherapeutic modality for a variety of cancer types, and the cornerstone treatment for patients with advanced NSCLC. However, the response rates to platinum-based regiments are low (less than 30%) in NSCLC treatment, compared with a 70% response rate in other cancers such as ovarian, testicular, and head and neck cancer patients [4, 5]. Furthermore, there has been substantially different response in patients with similar tumor stage and treated with similar chemotherapy, suggesting different genetic susceptibility to chemotherapy [6]. Therefore, it is valuable to find biomarkers to select patients who are likely to benefit from platinum-based chemotherapy, which may contribute to realize individualized treatment for cancer patients in the future.

A number of promising pharmcogenetic candidates have been identified for prediction of chemotherapy efficacy and toxicity [7]. In recent years, researchers have focused on apoptosis signaling pathway as a potential target for tumor therapies. Animal models proved that activated apoptotic signal may be in favor of keeping high therapeutic efficiency of anticancer agents *in vivo* [8-10]. At the meantime, upregulated expression of inhibitors of apoptosis may have stimulating effect on tumor growth of cancer patients [11].

BCL2 family members, through intrinsic pathway, are able to regulate apoptosis induced by external stimulus such as DNA damage or anticancer agents including platinum drugs [12-14]. *BCL2* was the first one to be found in this family, and its association with cancer development has been extensively studied.

The expression of *BCL2* has been reported as an indicator of better survival in NSCLC [15]. Some studies focusing on the polymorphism of the *BCL2* gene provided evidence that SNP of this gene may be associated with some diseases. For example, the rare AA genotype of the SNP -938C>A (located in the P2 region of BCL2 gene) has been found to be in relation with susceptibility of head and neck squamous cell carcinoma (HNSCC) [16], another study reported that the AA genotype is associated with high risk of breast cancer development, and the A allele is related with lower BCL2 expression in breast cancer cell line [17]. However, the A allele displayed to be associated with increased BCL2 expression and its role is converse in some other studies [15, 18, 19]. Researches on another SNP (rs956572) of BCL2 also demonstrate the polymorphism of this gene may change the expression or function of the gene, thus influence the risk for some disease development. The preclinical data indicate that the variant genotype AA is associated with lower expression of mRNA and protein [20]. Moreover, it has been found that genetic variant in rs956572 may be associated with the risk for development of bipolar disorder [21], and compared to the G allele, A allele of SNP rs956572 may reduce the volume of gray matter (GM) in left ventral striatum [22].

Although the result may conflict in different studies, but there is no doubt that polymorphism of the gene may influence the expression and function of the protein. Based on the assumption that genetic variations of BCL2 gene may link to prognosis for NSCLC patients through apoptosis regulation, in this population-based study, we try to systematically analyze the relationship between polymorphisms of the BCL2 gene and treatment response of NSCLC patients after receiving platinum-based chemotherapy.

Materials and methods

Patient recruitment

We recruited 972 newly diagnosed non-small cell lung cancer patients with stage IIIA-IV, including 663 from Shanghai Chest Hospital, Shanghai Zhongshan Hospital and Shanghai Changhai hospital between March 2005 and January 2010 and other patients were from Shanghai Pulmonary Hospital between June 2010 and May 2013. The recruitment criteria has been previously described in details [23]. Informed consent was obtained from all patients and the study was approved by the appropriate Ethics committees of participating institution.

Date collection

Clinical data (sex, age, smoking history, clinical stage, and tumor histology) and peripheral blood samples for genotyping have been collected at the entry time of the study.

Tumor response was evaluated according to the RECIST after first 2 chemotherapy cycle, including CR (complete response), PR (partial response), SD (stable disease) and PD (progressive disease). The CR and PR evaluation were considered as ORR (objective response rate) and CR/PR/SD were included into DCR (disease control rate).

Overall survival (OS) and time to progress-free survival (PFS) were calculated from the day when patients begin to receive the chemotherapy treatment to the date of death (any cause) and the date of objective disease progression respectively. If there is no record of date of death or objective progression, we censored at the date last known to be alive or their objective tumor assessment. The complete medical record (including progress notes of the treating oncologist and treating nurses) was available

and reviewed to collect these data. The investigators were blinded to the genotype status of the patients.

Chemotherapy regimens

All the patients enrolled in this study were inoperable, and received first-line platinum-based chemotherapy (definitive chemoradiotherapy was excluded): cisplatin 75 mg/m^2 or carboplatin AUC 5, both administered on day 1 every 3 weeks, in combination with navelbine 25 mg/m^2 on days 1 and 8 every 3 weeks, gemcitabine 1250 mg/m^2 on days 1 and 8 every 3 weeks, paclitaxel 175 mg/m^2 on day 1 every 3 weeks, or docetaxel 75 mg/m^2 on day 1 every 3 weeks. Few patients were given other platinum-based treatment. All chemotherapeutic drugs were administered intravenously, and patients were treated for two to six cycles.

SNP selection and genotyping

The human *BCL2* gene is located at chromosome 18q21.3 [24]. The genotype data of this gene region (including 2 kb upstream) from the CHB population were downloaded from phase II HapMap SNP database (http://www.hapmap.org/), We selected Tagging SNPs of BCL2 gene by the Haploview Software (http://www.broadinstitute.org/haploview) using a minor allele frequency (MAF) cut-off of 0.05 and r^2 threshold of 0.8.

Genomic DNA was extracted using the QIAamp DNA Maxi Kit (Qiagen GmbH). All SNPs selected were genotyped using iSelect HD BeadChip (illumina), with quality control criteria as follows: genotyping call rate of SNP>0.95; MAF>0.05; GenCall score >0.2. All SNPs were genotyped successfully except 6 probes failed in beadchip synthesis process. The rest 42 tagging-SNPs had call rates above 0.95. GenomeStudioV2010 and GeneMap software were used to analyze the data and prepare reports. SNPinfo (http://snpinfo.niehs.nih.gov/) was used to predict the function of SNPs.

Statistical analysis

Deviation from Hardy-Weinberg equilibrium was checked using the Chi-Square goodness-of-fit test. Phase 2.1 software (Version 2.0.2) was used to estimate the individual haplotypes frequencies based on the Bayesian algorithm and the database of 42 SNPs.

Haploview software was selected to access the D' and r^2 for each pair of SNPs, using standard haploview parameters, and haploview blocks were defined by the four-gamete rule.

The associations with clinical variables and genetic polymorphisms/haplotype to PFS/OS were explored by univariate cox regression analysis and adjusted by multivariate cox regression analysis. Kaplan-Meier analysis by log rank was used to assess the cumulative death/disease progression probability on significant SNPs in our study. χ^2 test was used to analyze the relationship between SNP and tumor response to chemotherapy. All statistical analyses were performed by SPSS 20.0 software (SPSS Inc., Chicago, IL). All *p* values reported were two-sided, and a level <0.05 was considered statistically significant.

Results

We recruited 972 patients for the study, who were at stage III or IV NSCLC and received first-line platinum-based chemotherapy. The main patient characteristics, and their associations with overall survival (OS) and progress-free survival (PFS) were summarized in Supplementary Table 2. The observed allele frequency of the 42 tag-SNPs and the test of Hardy-Weinberg equilibrium (*P*>0.05) were summarized (Supplementary Table 1). The study group consists of 71.0% female and 29% male with a median age 58 years. 57.9% patients had a smoking history and 90.4% of the 972 patients were PS 1. The tumor histology was classified as 63.0% adenocarcinoma, 21.9% squamous cell, 2.0% adenosquamous cell and 12.6% other NSCLC. All patients were diagnoses as advanced NSCLC, and 62.6% were stage IV. The classification of chemotherapy was 62.9% platinum-tubulin targeting drugs (paclitaxel, docetaxel, navelbine), 24.1% platinum-gemcitabine and 13.1% other combinations.

The association with clinical characteristics to OS/PFS was analyzed by univariate Cox's regression analysis (Supplementary Table 2). In terms of therapeutic efficacy, five factors (gender, smoking, age, clinical stage and tumor histology) may have impact on OS, and only PS (for

Table 1. Prognostic factors for OS/PFS in 972 NSCLC patients after platinum-based chemotherapy by univariate/multivariate Cox's regression analysis

			Univariate		Multivariate	
Variables	N	mOS/mPFS (95% CI)	HR (95% CI)	*P* value	HR (95% CI)	*P* value
OS						
Gender				0.003*		0.056
Male	690	18.07 (16.49-19.64)				
Female	282	22.50 (18.95-26.05)	0.78 (0.66-0.92)		0.79 (0.62-1.01)	
Age				0.003*		0.002*
<58	502	21.30 (19.25-23.35)				
≥58	470	17.17 (15.30-19.04)	1.25 (1.08-1.44)		1.26 (1.09-1.47)	
Smoking				0.012*		0.745
Nonsmoker	405	21.23 (19.04-23.43)				
Ever smoker	563	17.93 (16.13-19.74)	1.21 (1.04-1.40)		1.03 (0.83-1.27)	
Stage						
IIIa	76	23.03 (14.56-31.51)	0.75 (0.57-0.99)	0.045*	0.67 (0.50-0.90)	0.007*
IIIb	283	19.10 (17.14-21.06)	1.02 (0.57-0.99)	0.842	1.00 (0.85-1.18)	0.980
IV	608	19.07 (16.95-21.19)	R	0.113	R	0.022*
Histology						
Adenocarcinoma	612	20.23 (18.40-22.07)	R	0.093	R	0.249
Squamous cell	213	16.63 (13.11-20.16)	1.20 (1.01-1.44)	0.044*	1.14 (0.93-1.39)	0.209
Adenosquamo carcinoma	19	15.30 (4.87-25.73)	1.21 (0.70-2.11)	0.491	1.24 (0.71-2.15)	0.455
Others	122	18.30 (14.71-21.89)	1.24 (0.99-1.54)	0.063	1.24 (0.98-1.56)	0.075
rs4987726					NA	NA
GG	779	19.53 (18.00-21.07)	R	0.016*		
AG	173	19.03 (16.42-21.65)	1.17 (0.97-1.40)	0.099		
AA	20	12.60 (9.94-15.26)	1.84 (1.14-2.99)	0.013*		
Dominant model				0.030*	NA	NA
AA+AG	193	17.97 (15.51-20.42)				
GG	779	19.53 (18.00-21.07)	0.82 (0.69-0.98)			
Recessive model				0.018*		0.021*
AA	20	12.60 (9.94-15.26)				
AG+GG	952	19.37 (18.07-20.66)	0.56 (0.35-0.90)		0.54 (0.32-0.91)	
rs949037					NA	NA
GG	406	21.73 (19.56-23.91)	0.88 (0.76-1.03)	0.121		
AG	443	18.63 (16.70-20.57)	R	0.005*		
AA	123	14.20 (11.64-16.76)	1.20 (1.03-1.64)	0.027*		
Dominant model				0.004*		0.001*
GG+AG	849	19.93 (18.58-21.29)				
AA	123	14.20 (11.64-16.76)	1.38 (1.11-1.72)		1.46 (1.17-1.82)	
Recessive model				0.021*	NA	NA
GG	406	21.73 (19.56-23.91)				
AG+AA	566	17.27 (15.75-18.79)	1.19 (1.03-1.38)			
rs49877739					NA	NA
GG	885	19.30 (17.87-20.73)	R	0.000*		
AG	85	19.10 (14.77-23.43)	1.08 (0.84-1.40)	0.536		
AA	2	1.97	25.38 (6.19-104.17)	0.000*		
Dominant model				0.395	NA	NA
AA+AG	87	19.03 (15.19-22.88)				
GG	885	19.30 (17.87-20.73)	0.90 (0.70-1.15)			

Recessive model				0.000*		0.001*
AA	2	1.967				
AG+GG	970	19.27 (17.93-20.60)	0.04 (0.01-0.16)		0.08 (0.02-0.34)	
rs17685559					NA	NA
GG	902	19.43 (18.05-20.81)	R	0.003*		
AG	65	17.13 (13.40-20.77)	1.38 (1.04-1.83)	0.027*		
AA	5	8.73 (0.29-17.18)	3.22 (1.33-7.77)	0.009*		
Dominant model				0.007*		0.077
AA+AG	70	16.63 (11.03-22.23)				
GG	902	19.43 (18.05-20.81)	0.69 (0.53-0.91)		0.77 (0.57-1.03)	
recessive model				0.011*	NA	NA
AA	5	8.73 (0.29-17.18)				
AG+GG	967	19.27 (17.97-20.56)	0.32 (0.13-0.77)			
rs3810027					NA	NA
GG	311	20.67 (17.04-24.29)	0.79 (0.66-0.93)	0.005*		
CG	497	18.23 (16.69-19.78)	R	0.013*		
CC	164	22.17 (18.94-25.40)	0.85 (0.70-1.03)	0.104		
Dominant model				0.016*		0.009*
CC+CG	661	19.07 (17.66-20.48)				
GG	311	20.67 (17.04-24.29)	0.82 (0.70-0.96)		0.80 (0.68-0.95)	
Recessive model				0.468	NA	NA
CC	164	22.17 (18.94-25.40)				
CG+GG	808	18.93 (17.43-20.44)	1.07 (0.89-1.29)			
rs7226979						
AA	280	19.53 (17.37-21.70)	0.90 (0.76-1.07)	0.239	0.88 (0.74-1.05)	0.164
AG	473	18.83 (16.63-21.04)	R	0.074	R	0.044*
GG	219	19.43 (15.94-22.93)	0.81 (0.67-0.97)	0.026*	0.79 (0.65-0.96)	0.016*
Dominant model				0.679	NA	NA
GG+AG	692	19.10 (17.27-20.93)				
AA	280	19.53 (17.37-21.70)	0.97 (0.82-1.14)			
Recessive model				0.053	NA	NA
GG	219	19.43 (15.94-22.93)				
AG+AA	753	19.07 (17.49-20.65)	1.19 (1.00-1.42)			
PFS						
ECOG PS				0.000*		0.000*
1	814	9.33 (8.06-10.60)				
2	73	5.43 (3.41-7.46)	1.66 (1.25-2.20)		1.72 (1.29-2.29)	
rs1381547					NA	NA
AA	366	7.80 (6.28-9.32)	1.24 (1.03-1.50)	0.024*		
AG	388	10.27 (8.58-11.96)	R	0.007*		
GG	138	6.70 (4.57-8.83)	1.43 (1.12-1.83)	0.004*		
Dominant model				0.178	NA	NA
GG+AG	526	9.47 (7.78-11.16)				
AA	366	7.80 (6.28-9.32)	1.13 (0.95-1.34)			
Recessive model				0.026*		0.019*
GG	138	6.70 (4.57-8.83)				
AG+AA	754	9.47 (8.19-10.75)	0.78 (0.62-0.97)		0.76 (0.61-0.96)	
rs8083946						
AA	374	7.33 (5.96-8.70)	1.21 (1.01-1.45)	0.036*	NA	NA
AG	418	9.83 (8.51-11.15)	R	0.075		

GG	104	9.10 (5.64-12.56)	0.97 (0.74-1.29)	0.851		
Dominant model				0.023*		0.034*
GG+AG	522	9.80 (8.38-11.22)				
AA	374	7.33 (5.96-8.70)	1.22 (1.03-1.45)		1.21 (1.01-1.44)	
Recessive model				0.387	NA	NA
GG	104	9.10 (5.64-12.56)				
AG+AA	792	9.13 (7.99-10.28)	1.12 (0.86-1.47)			

The listed factors showed statistical significance after univariate Cox's regression analysis and were further included into multivariate Cox's regression analysis. For SNPs with significant dominant model and recessive model in univariate analysis, the one with smaller *P* value was considered for further multivariate analysis. Abbreviations: PS: performance status; mOS: median overall survival time (months). mPFS: median progression-free survival time (months). HR: hazard ratio. *P: P<0.05. R: reference. NA: not available.

the small number, treatment canceled) may influence PFS (**Table 1**).

Association between individual SNPs and OS/PFS

All 42 SNPs were analyzed by univariate Cox's Regression Analysis to explore the association with OS/PFS (Supplementary Table 3). In univariate analysis, 6 SNPs of *BCL2* (rs949037, rs3810027, rs4987726, rs4987739, rs1768-5559, rs7226979) showed significant association with OS and 2 SNPs of *BCL2* (rs1381547, rs8083946) were associated with the PFS (all *P*<0.05) (**Table 1**).

The characteristics and individual SNPs showing significant association with OS/PFS were included into multivariate Cox's regression analysis. As a result, the G allele of rs4987726 was associated with a 6.7 months longer OS (AG+GG vs AA, P=0.021, HR=0.54, 95% CI=0.32-0.91). The G allele of rs949037 was associated with a 5.7 months longer OS (AA vs AG+GG, P=0.001, HR=1.46, 95% CI=1.17-1.82). The G allele of rs4987739 (AA vs AG+GG, P=0.001, HR=0.08, 95% CI=0.02-0.34) was also associated with a longer OS. The C allele of rs3810027 led to a shortened OS (CC+CG vs GG, P=0.013, HR=1.23, 95% CI=1.04-1.45). For rs7226979, the GG or AA homozygotes showed a relatively longer mOS than AG heterozygotes, but no significance was found in common genetic analysis.

In terms of PFS, the A allele of rs1381547 (GG vs AG+AA, P=0.019, HR=0.76, 95% CI=0.61-0.96) and the G allele of rs8083946 (GG+AG vs AA, P=0.034, HR=1.21, 95% CI=1.01-1.44) led to a longer PFS (taken at 18 months). Details were shown in **Table 1** and **Figure 1**.

rs949037 affects OS in patients with platinum-tubulin-targeting drugs predominantly

We further analyzed the related SNPs in subtype of therapy to gain a deeper understanding in effect on therapy efficacy. For rs949037, we found that it predominantly affected the therapy efficacy of patients treated with platinum-based tubulin-targeting drugs. In the subtype of tubulin-targeting drugs, GG genotype of rs-949037 showed an 8.5 months longer OS compared with the unfavorable AA genotype (mOS: 12.83, 95% CI: 10.35-15.32, P=0.000) (**Figure 2B**). In analysis of relationship with tumor response, the G allele of rs949037 also showed a higher ORR (GG+AG: 17.9% *vs* AA: 11.8%, *P*=0.253) and DCR (GG+AG: 81.0% *vs* AA: 76.3%, *P*=0.354), although no statistical significance was observed (**Table 3**).

For the other related SNPs, rs3810027 had similar results in all study cases and each subtype of chemotherapy. rs4987726 and rs49-87739 were not further analyzed because of the potential random error resulting from few cases in subtype. rs7226979 was not considered to further analyze for its insignificance in common genetic models.

Haploview analysis

In this present study, *BCL2* gene has 9 blocks in total, and the arrangement on SNPs was showed in **Figure 3**. We execute the same approach on haplotype/diplotype analysis. Details were shown in Supplementary Table 4.

Haploview analysis on OS and PFS

For the 5 SNPs (rs949037, rs4987726, rs49-87739, rs3810027, rs7226979) which were strongly influence the outcome of OS, rs949037

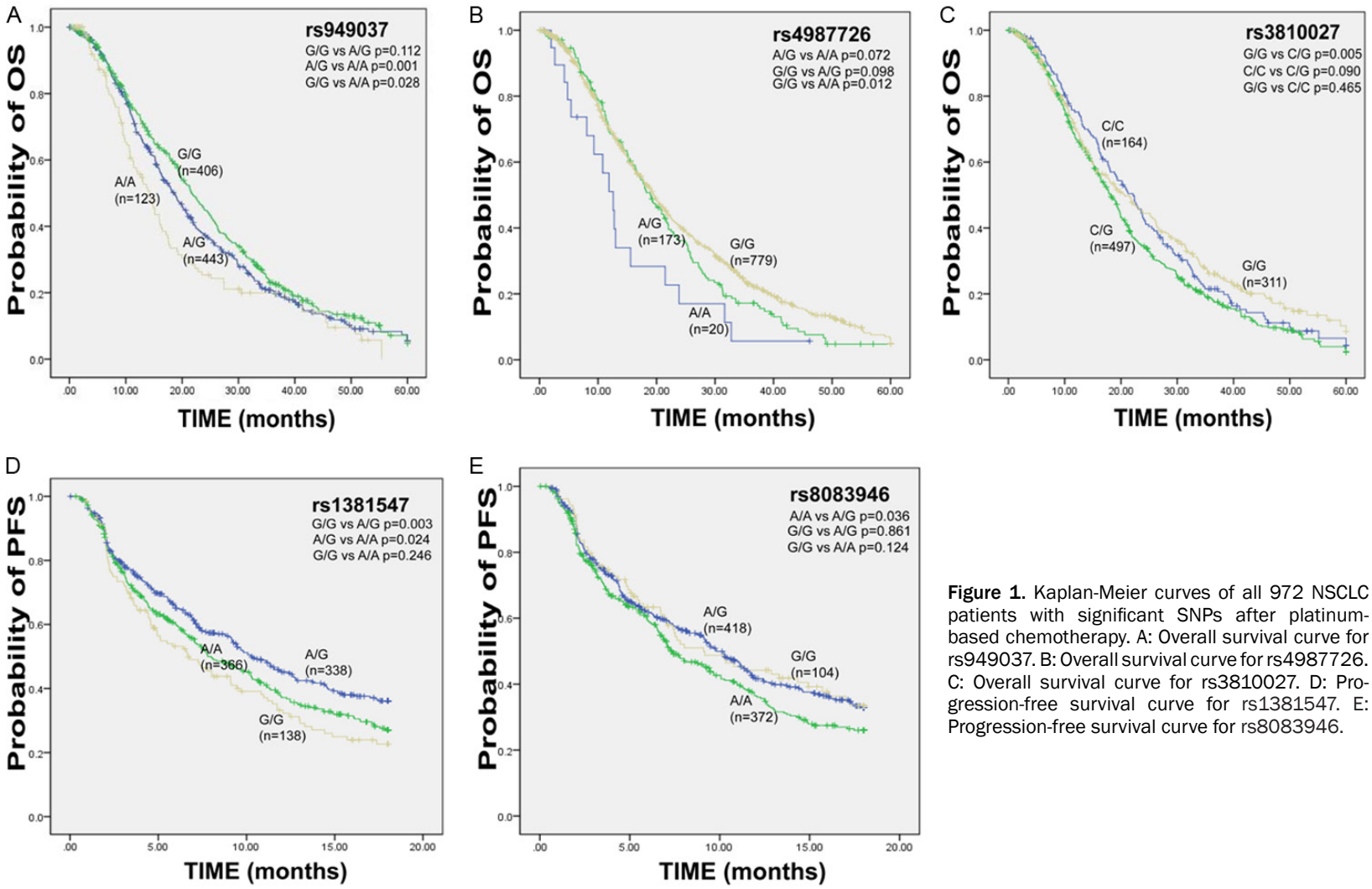

Figure 1. Kaplan-Meier curves of all 972 NSCLC patients with significant SNPs after platinum-based chemotherapy. A: Overall survival curve for rs949037. B: Overall survival curve for rs4987726. C: Overall survival curve for rs3810027. D: Progression-free survival curve for rs1381547. E: Progression-free survival curve for rs8083946.

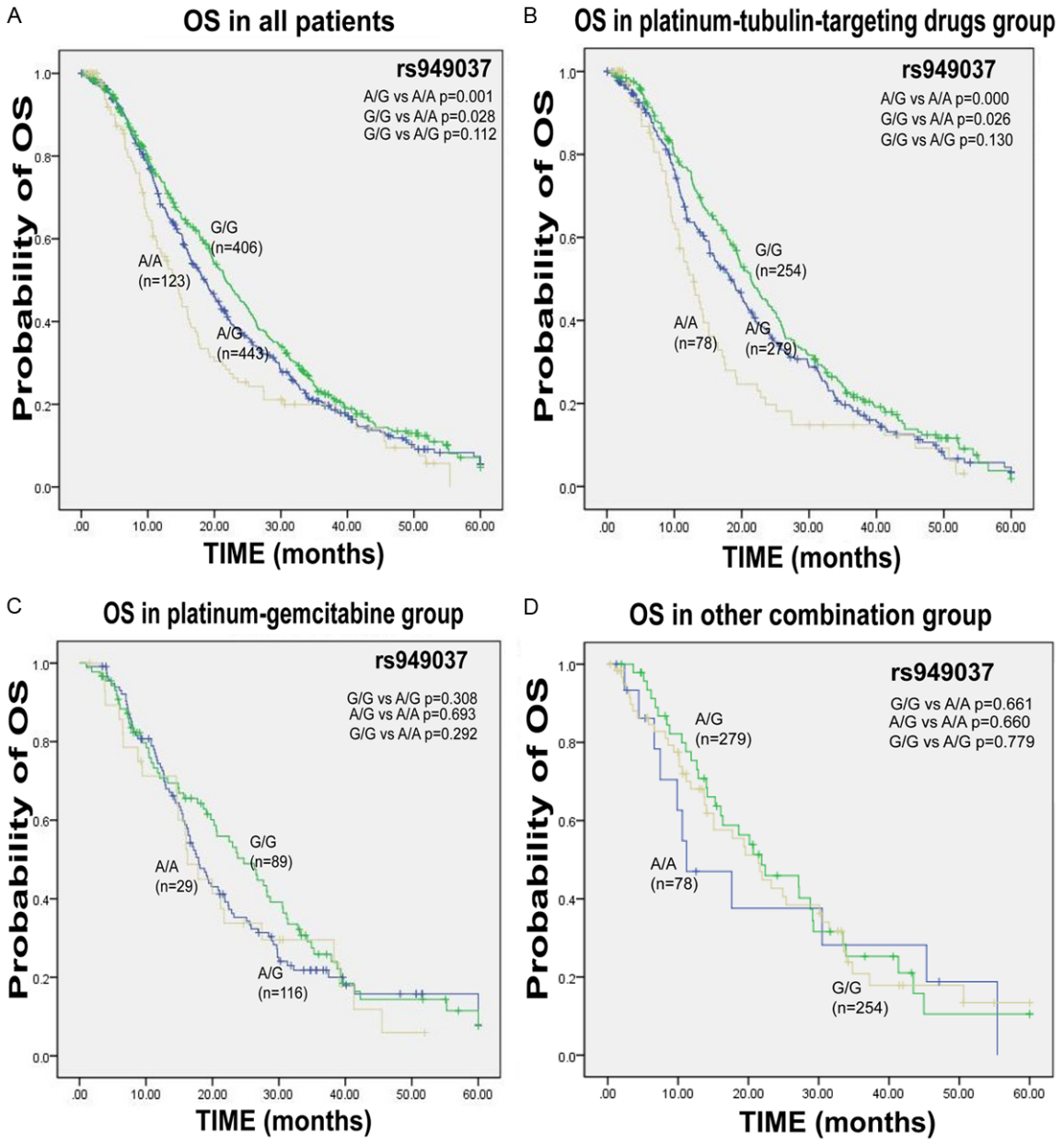

Figure 2. Kaplan-Meier curves for NSCLC patients with rs949037 genotypes in subtypes of different chemotherapy doublet regimens. A: Overall survival curve for all NSCLC patients. B: Overall survival curve for patients treated with platinum-tubulin-targeting drugs. C: Overall survival curve for patients treated with platinum-gemcitabine. D: Overall survival curve for patients treated with other combinations.

located in block9, rs3810027 located in block5 and rs7226979 located in block7 of *BCL2* in our study. A haplotype of block9 had impact on OS and CGC haplotype had a longer OS (5 months longer OS than CAC, P=0.006, HR= 0.83, 95% CI=0.73-0.95). While adjusted for the related covariates in multivariate analysis, the values changed little and showed the same result (**Table 2**). For diplotype, only block9 of BCL2 correlated with OS (Supplementary Table 4).

For the PFS related SNPs (rs1381547, rs-8083946), only rs8083946 located in block6 of BCL2. In further analysis of haplotype and OS/PFS, the haplotype of block6 had little impact on OS. Neither haplotype nor diplotype had significant impact on PFS.

Discussion

BCL2 gene, which encodes a protein with a MW (moculer weight) of 26000 that located on the

Table 2. Association between clinical characteristics, haplotypes and OS in 972 NSCLC patients after platinum-based chemotherapy by univariate/multivariate Cox's regression analysis

		Univariate		Multivariate	
Variables	mOS (95% CI)	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Gender			0.000*		0.030*
Male	18.07 (16.96-19.18)				
Female	22.50 (19.99-25.01)	0.78 (0.66-0.92)		0.83 (0.70-0.98)	
Age			0.000*		0.000*
<58	21.30 (19.85-22.75)				
≥58	17.17 (15.85-18.48)	1.25 (1.08-1.44)		1.25 (1.12-1.40)	
PS			0.013*		0.033*
1	19.40 (18.37-20.43)				
2	17.90 (12.03-23.77)	1.26 (1.05-1.52)		1.23 (1.02-1.49)	
Smoking			0.000*		0.758
Nonsmoker	21.23 (19.67-22.79)				
Ever smoker	17.93 (16.67-19.20)	1.21 (1.04-1.40)		1.02 (0.87-1.18)	
Stage					
IIIA	23.03 (17.04-29.02)	0.98 (0.88-1.10)	0.778	0.67 (0.55-0.83)	0.000
IIIB	19.10 (17.72-20.49)	0.74 (0.60-0.91)	0.005*	1.01 (0.90-1.14)	0.839
IV	19.07 (17.57-20.57)	R	0.013*	R	0.001*
Histology					
Adenocarcinoma	20.23 (18.93-21.53)	R	0.005*	R	0.038*
Squamous cell	16.63 (14.14-19.13)	1.20 (1.06-1.37)	0.004*	1.12 (0.97-1.29)	0.115
Adeno-squamous cell	15.30 (7.93-22.67)	1.21 (0.82-1.79)	0.330	1.18 (0.79-1.74)	0.423
Other	18.30 (15.76-20.84)	1.24 (1.06-1.45)	0.009*	1.26 (1.07-1.50)	0.007*
Therapy					
Platinum-tubulin targeting	19.03 (17.81-20.26)	R	0.048*	R	0.026*
Platinum-gemcitabine	19.77 (17.96-21.57)	0.89 (0.78-1.00)	0.055	0.93 (0.82-1.05)	0.240
Other combinations	20.67 (17.84-23.50)	0.85 (0.73-1.01)	0.058	0.79 (0.67-0.94)	0.009*
Block1					
AA	20.40 (18.98-21.82)	R	0.126	R	0.110
AG	17.73 (16.43-19.04)	1.13 (1.00-1.26)	0.042*	1.14 (1.01-1.29)	0.036*
GG	20.00 (17.77-22.24)	1.06 (0.92-1.23)	0.429	1.05 (0.90-1.22)	0.551
Block6					
GAGA	19.07 (17.01-21.13)	R	0.035*	R	0.011*
AAGA	19.40 (17.81-20.99)	1.03 (0.90-1.18)	0.653	1.15 (0.99-1.33)	0.067
GGGA	19.30 (17.32-21.28)	0.97 (0.84-1.11)	0.628	1.03 (0.89-1.19)	0.719
GGGG	20.33 (18.17-22.49)	0.99 (0.83-1.17)	0.862	1.10 (0.92-1.32)	0.284
Other	15.70 (9.70-21.70)	1.49 (1.15-1.94)	0.003*	1.58 (1.21-2.07)	0.001*
Block9					
CAC	16.39 (15.22-17.51)	R	0.000*	R	0.000*
CGC	21.77 (19.80-23.73)	0.83 (0.73-0.95)	0.006*	0.85 (0.74-0.98)	0.022*
AGA	19.67 (18.24-21.09)	0.86 (0.75-0.98)	0.025*	0.86 (0.74-1.00)	0.053
CGA	19.77 (16.82-22.72)	0.86 (0.73-1.03)	0.104	0.84 (0.70-1.00)	0.051
Other	6.33 (3.56-9.11)	6.91 (2.57-18.57)	0.000*	6.76 (2.49-18.33)	0.000*

Abbreviations: PS: performance status; mOS: median overall survival time (months). HR: hazard ratio. *P: P<0.05. R: reference.

intracellular membranes, can inhibit apoptosis in response to various death-inducing signal. To our knowledge, this is the first study to assess the relationship between the genetic polymor-

Table 3. Association between dominant model of rs949037 and chemotherapy response in advanced NSCLC patients treated with platinum-tubulin-targeting chemotherapy

Genotype	ORR			DCR		
	n/N	χ^2	*p*	n/N	χ^2	*p*
GG+AG	17.9% (93/520)	1.717	0.253	81.0% (421/520)	0.907	0.354
AA	11.8% (9/76)			76.3% (58/76)		

Abbreviations: ORR: objective response rate. DCR: disease control rate.

phism of *BCL2* gene and outcome of patients after platinum-based chemotherapy systematically. In our study, we found that 5 SNP of *BCL2* (rs949037, rs4987726, rs4987739, rs3810027, rs7226979) may strongly influence the overall survival of patients. For rs4987739, the AA genotype was consisted of just 2 samples, and for rs7226979, no significance was found in further analysis of common genetic models. So, no much more attention was paid to these two SNPs in consideration of possible sample bias. As representative, the G allele of rs949037 was associated with a longer survival. We may infer that the polymorphisms of the 5 SNP are associated with the ability of apoptosis of individual patient, which may be activated by the platinum agents. And the interaction of SNP and platinum agents may affect the response of individual patient treated with platinum-based chemotherapy.

Including rs949037, the SNPs which showed significance in our study belong to intron and are tag SNPs located at the *BCL2* gene regions. Patients' susceptibility to chemotherapy treatment related with no functional SNP remains unclear. Previous studies suggest variation SNPs in intron can influence gene function in two major ways: first, the polymorphism of the intron may produce splicing variants, the polymorphism on the splice site may induce the variety of final m-RNA product. Another major way by which intronic regions may influence gene action is by endogenons production of small RNAs, such as micro-RNAs.

We made function predictions to explore the way in which the introns in our study are likely to change the function or structure of the protein (http://snpinfo.niehs.nih.gov/). As mentioned above, rs949037 located on block9 of *BCL2,* which consists of rs12478289, rs949037 and rs2279115. In further haploview analysis, the haplotype of block9 also appeared to affect OS. In SNP function prediction, rs2279115 of *BCL2* functions in transcription factor binding site (TFBS) (http://snpinfo.niehs.nih.gov/), which means an important role in gene expression. And we can infer that, these SNPs may be in strong LD with functionally important in regulation of biological function and expression of *BCL2* gene and protein, thus further affect the chemotherapy efficacy through *BCL2*-depedent apoptosis pathway.

rs949037, which is emphatically reported in our study, has also been investigated in other pathologies. Nicole ZH [25] has found that the homozygous variant for rs949037 was related with favorable outcome of patients with TBI (traumatic brain injury), and the homozygous wild-genotype may increase the risk of death at 3 months. The Tsnp locates in the large intron2 region towards the 5' end of *BCL2* gene. The size of intron2 may be an indication that it has a functional role [26], potentially related to mRNA stability or processing. For the four tagRNAs, it's the first time to reveal they may play a functional role in the outcome of NSCLC patients treated with platinum-based chemotherapy.

We identified some *BCL2* SNPs that are likely to be associated with clinical outcomes of platinum-based chemotherapy in advanced NSCLC patients using a relatively large sample size. Particularly for SNPs of rs949037, rs4987726, rs4987739, rs3810027 and rs7226979, they were found to remain statistically significant in association with OS, which is the major strength of our study.

However, we must acknowledge the limitation of this study. First, the SNPs included here were tagging SNPs, and their functional importance has not been investigated yet. Further study is necessary to elucidate biological role of the polymorphisms, such as rs949037 and rs3810027 in functional experiments. Secondly, several other proteins such as BAD, BAX, have been proved to be important co-factors, which collaborate with *BCL2* in regulating of intrinsic apoptosis pathway. A recent study on SNP

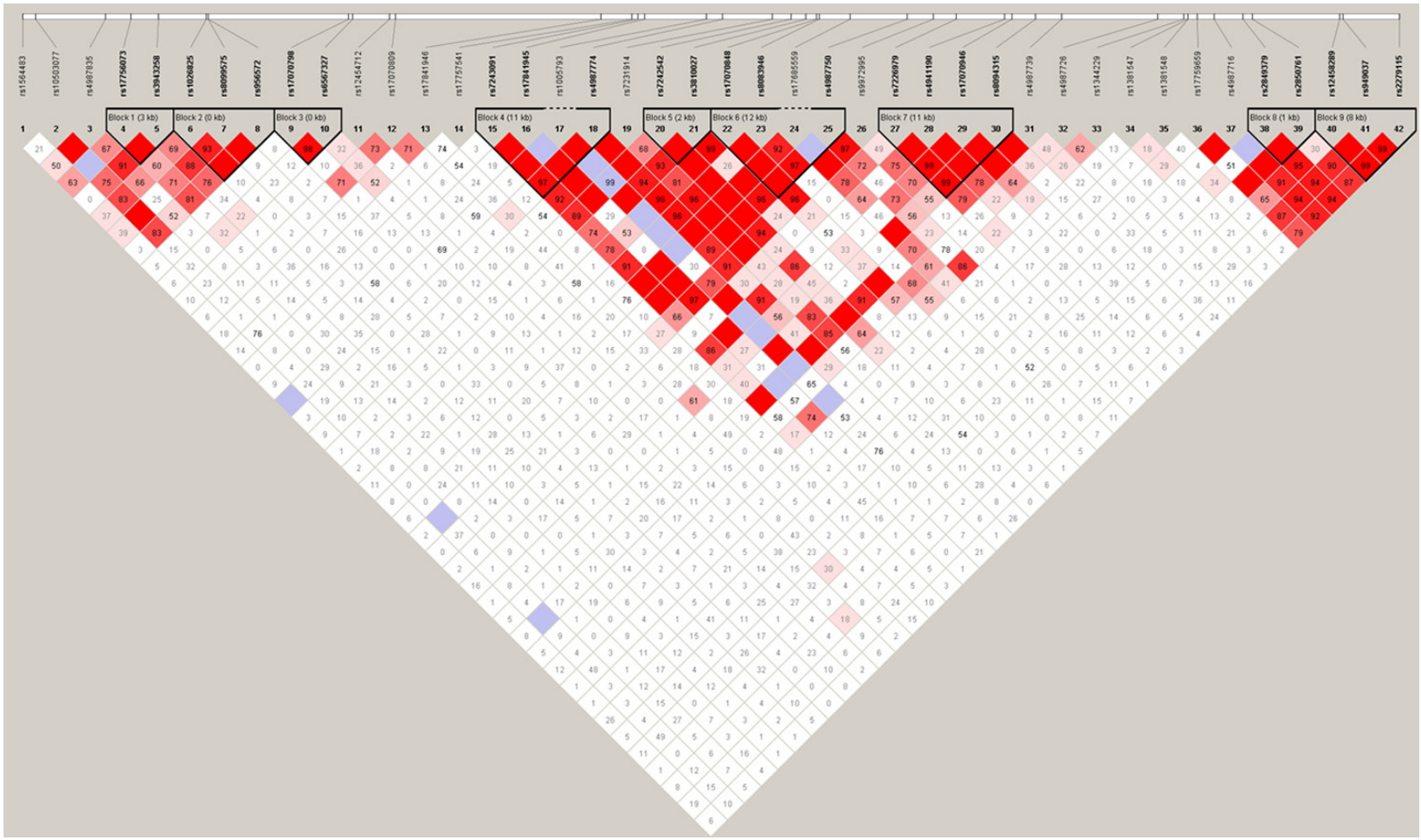

Figure 3. The blocks of BCL-2 calculated in our study.

locating at the promotor region, which regulates both *BCL2* and *BAX*, revealed its association with chemotherapy response in NSCLC [27]. *BCL2* family members, which consist of antiapoptotic members, multi-domain proapoptotic members and proapoptotic BH3-only proteins [13, 28-31], can control the integrity of the outer mitochondrial membrane (OMM) and thus the balance of proapoptotic and antiapoptotic *BCL2* family members is critical in determining cellular susceptibility to apoptosis. For example, chronic lymphocytic leukemic (CLL) cells not only express high levels of *BCL2* but also high levels of Bim, which is constitutively bound by *BCL2 [32]*. However, the current study is performed at a single-gene level, which did not take into account possible gene-gene interactions. Thirdly, rs1381547 and rs8083946 were found to be associated with progression-free survival, but further analysis was not conducted because the difference was not much significant relatively. The relative toxicities were not shown in this study. And the last, this study was based on the population of Chinese, the result can be more reliable and credible if conducted in the world's population.

Conclusion

To summarize, we found that SNPs of *BCL2* gene may play an important role in modulating platinum-based chemotherapeutic efficacy in advanced NSCLC patients. In particular, polymorphism of rs949037 was associated with OS and affected patients with platinum-tubulin-targeting therapy largely. If validated, these SNPS could be used as useful biomarkers to predict clinical outcomes of NSCLC patients treated with platinum-based chemotherapy in the future. Prospective studies in larger scale are still needed.

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Disclosure of conflict of interest

None.

Address correspondence to: Bo Su, Central Laboratory, Shanghai Pulmonary Hospital, School of Medicine, Tongji University, No. 507, Zhengmin Road, Shanghai 200433, P. R. China. Tel: +86 021 65115006; E-mail: su_bo_s@hotmail.com

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Supplementary Table 1. Summary of studied genes, polymorphisms and corresponding properties of BCL2

Gene=BCL2	SNP	Genotyping rate (%)	MAF[&]	MAF[§]
	rs1564483	100.0	0.378	0.336
	rs2279115	99.5	0.433	0.378
	rs2062011	99.4	0.386	0.328
	rs6567327	99.9	0.489	0.497
	rs4987774	99.9	0.278	0.325
	rs4987750	100.0	0.17	0.119
	rs17756073	99.9	0.189	0.187
	rs17070946	100.0	0.256	0.307
	rs4987726	100.0	0.114	0.111
	rs7242542	100.0	0.144	0.172
	rs4987835	99.9	0.422	0.43
	rs2850761	100.0	0.267	0.193
	rs3943258	99.9	0.456	0.422
	rs9972995	100.0	0.488	0.463
	rs17841946	100.0	0.067	0.078
	rs7231914	99.9	0.189	0.189
	rs2849377	100.0	0.091	0.097
	rs17759659	100.0	0.156	0.098
	rs4987739	100.0	0.102	0.045
	rs17841945	100.0	0.1	0.122
	rs8093973	96.9	0.178	0.172
	rs17070798	100.0	0.111	0.124
	rs7226979	100.0	0.444	0.468
	rs17685559	100.	0.078	0.038
	rs12458289	100.0	0.256	0.26
	rs956572	99.8	0.378	0.477
	rs1344229	100.0	0.189	0.202
	rs12454712	100.0	0.467	0.451
	rs1005793	100.0	0.056	0.03
	rs7236090	Failed in design	0.5	
	rs10503077	99.6	0.056	0.041
	rs949037	100.0	0.344	0.354
	rs8094315	100.0	0.333	0.382
	rs4987808	Failed in design	0.056	
	rs3810027	100.0	0.455	0.58
	rs4987716	100.0	0.056	0.075
	rs1381547	99.5	0.233	0.372
	rs7240319	Failed in design	0.144	
	rs17757541	99.8	0.089	0.159
	rs17070848	99.4	0.211	0.256
	rs12967026	Failed in design	0.456	
	rs1026825	100.0	0.278	0.345
	rs8083946	100.0	0.411	0.351
	rs7243091	100.0	0.159	0.194
	rs1381548	100.0	0.267	0.266
	rs4941185	Failed in design	0.489	
	rs4941190	100.0	0.111	0.092
	rs4987851	Failed in design	0.011	

[&]Minor Allele Frequency based on the database in NCBI. [§]Minor Allele Frequency based on our study.

Supplementary Table 2. Association between clinical characteristics and OS/PFS in 972 NSCLC patients after platinum-based chemotherapy

			OS				PFS			
Variables		N	n	n%	P	HR (95% CI)	n	n%	P	HR (95% CI)
Gender	Male	690	531	77.0			374	59.4		
	Female	282	200	70.9	0.003*	0.78 (0.66-0.92)	159	59.8	0.324	1.10 (0.91-1.32)
Smoker	Never	405	291	71.9			225	59.5		
	Ever	563	436	77.4	0.012*	1.21 (1.04-1.40)	307	59.4	0.403	1.08 (0.91-1.28)
Age	<58	502	359	71.5			282	60.4		
	≥58	467	369	79.0	0.003*	1.25 (1.08-1.44)	250	58.4	0.653	0.96 (0.81-1.14)
PS	1	879	658	74.9			472	58.0		
	2	80	62	77.5	0.080	1.26 (0.97-1.64)	53	72.6	0.000*	1.66 (1.25-2.20)
Stage	IIIa	76	56	73.7	0.045*	0.75 (0.57-0.99)	35	53.8	0.057	0.71 (0.50-1.01)
	IIIb	283	217	76.7	0.842	1.02 (0.57-0.99)	146	57.5	0.213	0.88 (0.73-1.07)
	IV	608	454	74.7	0.113	R	349	61.0	0.105	R
Treatment	Platinum-gemcitabine	234	175	74.8	0.174	0.89 (0.7501.06)	136	65.4	0.436	1.08 (0.89-1.32)
	Platinum-tubulin targeting drugs	611	471	77.1	0.220	R	323	57.2	0.421	R
	Other platinum combinations	127	85	66.9	0.180	0.85 (0.68-1.08)	74	60.2	0.225	1.17 (0.91-1.51)
Histology	Adenocarcinoma	612	457	74.7	0.093	R	346	60.4	0.890	R
	Squamous cell	213	161	75.6	0.044*	1.20 (1.01-1.44)	111	58.1	0.733	0.97 (0.78-1.20)
	Adenosquamo carcinoma	19	13	68.4	0.491	1.21 (0.70-2.11)	8	44.4	0.449	0.76 (0.38-1.54)
	Others	122	94	77.0	0.063	1.24 (0.99-1.54)	66	58.9	0.933	0.99 (0.76-1.29)

Analyzed by univariate Cox's Regression analysis. Abbreviations: PS, performance status; OS, overall survival time (taken at 60 months). PFS, progression-free survival time (taken at 18 months). HR: hazard ratio. P: *P* value for data calculated by univariate cox regression model. *P: P<0.05. R: reference.

Supplementary Table 3. The summary of association between BCL2 SNPs and OS/PFS in our study

			Overall survival time				Progression-free survival time			
SNP	Genotype	n	No.	n%	P	HR (95% CI)	No.	n%	P	HR (95% CI)
	GG	426	324	76.1	0.694	1.04 (0.89-1.21)	242	61.1	0.865	1.02 (0.85-1.21)
rs1564483	AG	441	330	74.8	0.768	R	243	60.0	0.360	R
	AA	105	77	73.3	0.499	0.95 (0.74-1.22)	48	50.5	0.190	0.81 (0.60-1.11)
Dominant	GG+AG/AA	867/105	654/77	75.4/73.3	0.576	1.07 (0.85-1.36)	485/48	60.5/50.5	0.156	1.24 (0.92-1.67)
Recessive	GG/AG+AA	426/546	324/407	76.1/74.5	0.540	1.05 (0.91-1.21)	242/291	61.1/58.2	0.545	1.05 (0.89-1.25)
	CC	374	286	76.5	0.153	1.18 (0.94-1.48)	199	58.0	0.588	0.93 (0.71-1.22)
rs2279115	AC	457	347	75.9	0.307	R	260	61.2	0.773	R
	AA	136	96	70.6	0.145	1.18 (0.94-1.50)	72	58.1	0.918	0.99 (0.76-1.28)
Dominant	AA+AC/CC	593/374	443/286	74.7/76.5	0.549	0.96 (0.82-1.11)	332/199	60.5/58.0	0.477	1.07 (0.89-1.27)
Recessive	AA/AC+CC	136/831	96/633	70.6/76.2	0.125	0.84 (0.68-1.05)	72/459	58.1/59.8	0.749	1.04 (0.81-1.34)
	GG	431	331	76.8	0.713	R	237	59.2	0.776	R
rs17070809	AG	435	325	74.7	0.879	1.02 (0.79-1.32)	240	59.9	0.812	0.97 (0.72-1.30)
	AA	100	71	71.0	0.558	1.08 (0.84-1.40)	54	59.3	0.846	1.03 (0.77-1.38)
Dominant	AA+AG/GG	535/431	396/331	74.0/76.8	0.568	1.04 (0.90-1.21)	294/237	59.8/59.2	0.494	1.06 (0.90-1.26)
Recessive	AA/AG+GG	100/866	71/656	71.0/75.8	0.703	0.95 (0.75-1.22)	54/477	59.3/59.6	0.980	1 (0.76-1.33)
	GG	246	192	78.0	0.898	1.01 (0.85-1.21)	122	56.7	0.862	0.98 (0.80-1.20)
rs6567327	AG	489	364	74.4	0.548	R	266	59.8	0.812	R
	AA	236	174	73.7	0.405	0.92 (0.75-1.13)	144	61.3	0.538	0.93 (0.73-1.18)
Dominant	AA+AG/GG	725/246	538.192	74.2/78.0	0.800	0.98 (0.83-1.16)	388/144	58.8/61.3	0.708	0.96 (0.80-1.17)
Recessive	AA/AG+GG	236/735	174/556	73.7/75.6	0.276	0.91 (0.77-1.08)	122/410	56.7/60.3	0.534	0.94 (0.77-1.15)
	AA	432	338	78.2	0.612	0.93 (0.71-1.23)	234	58.8	0.219	0.82 (0.60-1.12)
rs4987774	AG	452	332	73.5	0.756	R	250	60.0	0.200	R
	GG	87	61	70.1	0.470	0.90 (0.69-1.19)	48	60.0	0.081	0.76 (0.56-1.04)
Dominant	GG+AG/AA	539/432	393/338	72.9/78.2	0.586	1.04 (0.90-1.20)	298/234	60.0/58.8	0.200	1.12 (0.94-1.33)
Recessive	GG/AG+AA	87/884	61/670	70.1/75.8	0.521	1.09 (0.84-1.42)	48/484	60/59.4	0.121	1.27 (0.94-1.70)
	AA	751	563	75.0	0.893	R	419	60.8	0.122	R
rs4987750	AG	208	156	75.0	0.981	0.99 (0.56-1.76)	108	55.7	0.174	1.75 (0.78-3.92)
	GG	13	12	92.3	0.868	0.95 (0.53-1.71)	6	46.2	0.358	1.47 (0.65-3.35)
Dominant	GG+AG/AA	221/751	168/563	76.0/75.0	0.655	0.96 (0.81-1.14)	114/419	55.1/60.8	0.061	0.82 (0.67-1.01)
Recessive	GG/AG+AA	13/959	12/719	92.3/75.0	0.955	1.02 (0.57-1.80)	6/527	46.2/59.7	0.204	0.59 (0.27-1.33)
	AA	650	488	75.1	0.925	R	365	60.9	0.583	R
rs17756073	AG	281	212	75.4	0.759	0.94 (0.65-1.37)	148	56.9	0.961	1.01 (0.64-1.60)
	GG	40	30	75.0	0.701	0.93 (0.63-1.36)	19	52.8	0.713	0.91 (0.57-1.47)

Dominant	GG+AG/AA	321/650	242/488	75.4/75.1	0.918	0.99 (0.85-1.16)	167/365	56.4/60.9	0.329	0.91 (0.76-1.10)
Recessive	GG/AG+AA	40/931	30/700	75.0/75.2	0.736	1.07 (0.74-1.54)	19/513	52.8/59.7	0.936	1.02 (0.65-1.61)
	GG	465	347	74.6	0.218	R	251	59.1	0.848	R
rs17070946	AG	419	320	76.4	0.367	1.13 (0.87-1.48)	232	59.6	0.872	1.03 (0.76-1.39)
	AA	88	64	72.7	0.116	1.24 (0.95-1.62)	50	61.0	0.658	1.07 (0.79-1.46)
Dominant	AA+AG/GG	507/465	384/347	75.7/74.6	0.474	1.06 (0.91-1.22)	282/251	59.9/59.1	0.717	1.03 (0.87-1.22)
Recessive	AA/AG+GG	88/884	64/667	72.7/75.5	0.205	0.85 (0.66-1.10)	50/483	61/59.3	0.757	0.96 (0.71-1.28)
	GG	779	571	73.3	0.016*	R	426	59.2	0.628	R
rs4987726	AG	173	143	82.7	0.099	1.17 (0.97-1.40)	97	62.2	0.663	1.15 (0.61-2.15)
	AA	20	17	85.0	0.013*	1.84 (1.14-2.99)	10	50.0	0.483	1.26 (0.66-2.42)
Dominant	AA+AG/GG	193/779	160/571	82.9/73.3	0.030*	0.82 (0.69-0.98)	108/426	60.8/59.2	0.522	1.07 (0.87-1.33)
Recessive	AA/AG+GG	20/952	17/714	85.0/75.0	0.018*	0.56 (0.35-0.90)	10/523	50/59.7	0.625	0.86 (0.46-1.60)
	CC	661	490	74.1	0.662	R	349	57.9	0.292	R
rs7242542	AC	287	221	77.0	0.781	1.07 (0.68-1.67)	172	63.7	0.350	1.32 (0.74-2.34)
	AA	24	20	83.3	0.576	1.14 (0.72-1.80)	12	52.2	0.201	1.47 (0.82-2.63)
Dominant	AA+AC/CC	311/661	241/490	77.5/74.1	0.479	1.06 (0.91-1.23)	184/349	62.8/57.9	0.394	1.08 (0.90-1.29)
Recessive	AA/AC+CC	24/948	20/711	83.3/75.0	0.712	0.92 (0.59-1.44)	12/521	52.2/59.7	0.290	0.73 (0.41-1.30)
	AA	331	243	73.4	0.722	0.97 (0.80-1.17)	171	56.4	0.367	1.11 (0.89-1.39)
rs4987835	AG	438	329	75.1	0.208	R	250	61.6	0.409	R
	GG	202	158	78.2	0.118	0.85 (0.70-1.04)	112	59.9	0.865	0.98 (0.77-1.24)
Dominant	GG+AG/AA	640/331	487/243	76.1/73.4	0.083	1.15 (0.98-1.34)	362/171	61/56.4	0.330	1.10 (0.91-1.31)
Recessive	GG/AG+AA	202/769	158/572	78.2/74.4	0.318	1.09 (0.92-1.31)	112/421	59.9/59.4	0.634	0.95 (0.77-1.17)
	GG	636	479	75.3	0.434	R	357	60.7	0.929	R
rs2850761	AG	301	229	76.1	0.221	1.30 (0.85-1.97)	161	57.9	0.756	1.09 (0.65-1.82)
	AA	35	23	65.7	0.323	1.24 (0.81-1.91)	15	50.0	0.843	1.06 (0.62-1.79)
Dominant	AA+AG/GG	336/636	252/479	75.0/75.3	0.390	0.94 (0.80-1.09)	176/357	57.1/60.7	0.719	0.97 (0.81-1.16)
Recessive	AA/AG+GG	35/937	23/708	65.7/75.6	0.245	0.78 (0.52-1.18)	15/518	50/59.8	0.781	0.93 (0.56-1.55)
	GG	333	257	77.2	0.089	0.83 (0.67-1.03)	174	57.0	0.877	0.98 (0.76-1.27)
rs3943258	AG	460	343	74.6	0.160	R	271	63.0	0.535	R
	AA	178	130	73.0	0.124	0.88 (0.75-1.04)	87	54.4	0.358	1.09 (0.90-1.32)
Dominant	AA+AG/GG	638/333	473/257	74.1/77.2	0.066	0.87 (0.75-1.01)	358/174	60.7/57.0	0.504	1.06 (0.89-1.28)
Recessive	AA/AG+GG	178/793	130/600	73.0/75.7	0.263	0.90 (0.74-1.09)	87/445	54.4/60.5	0.529	0.93 (0.74-1.17)
	GG	271	219	80.8	0.351	0.90 (0.73-1.12)	155	60.8	0.649	0.94 (0.74-1.21)
rs9972995	AG	504	372	73.8	0.577	R	276	60.4	0.699	R
	AA	197	140	71.1	0.378	0.93 (0.79-1.10)	102	55.4	0.699	1.04 (0.85-1.27)
Dominant	AA+AG/GG	701/271	512/219	73.0/80.8	0.312	0.92 (0.79-1.08)	378/155	59/60.8	0.902	1.01 (0.84-1.22)

Recessive	AA/AG+GG	197/775	140/591	71.1/76.3	0.573	0.95 (0.79-1.14)	102/431	55.4/60.5	0.448	0.92 (0.74-1.14)
	GG	829	628	75.8	0.907	R	462	60.2	0.631	R
rs17841946	AG	139	100	71.9	0.701	1.25 (0.40-3.89)	70	55.6	0.353	2.54 (0.36-18.042)
	AA	4	3	75.0	0.736	1.22 (0.39-3.85)	1	33.33	0.372	2.46 (0.34-17.68)
Dominant	AA+AG/GG	143/829	103/628	72.0/75.8	0.770	0.97 (0.79-1.19)	71/462	55/60.2	0.680	0.95 (0.74-1.22)
Recessive	AA/AG+GG	4/968	3/728	75.0/75.2	0.705	0.80 (0.26-2.50)	1/532	33.3/59.6	0.355	0.40 (0.06-2.82)
	GG	638	479	75.1	0.399	R	346	58.6	0.899	R
rs7231914	AG	301	226	75.1	0.190	1.31 (0.88-1.96)	166	60.8	0.668	1.10 (0.70-1.73)
	AA	32	25	78.1	0.279	1.26 (0.83-1.90)	20	62.5	0.745	1.08 (0.68-1.72)
Dominant	AA+AG/GG	333/638	251/479	75.4/75.1	0.395	0.94 (0.80-1.09)	186/346	61/58.6	0.740	0.97 (0.81-1.16)
Recessive	AA/AG+GG	32/939	25/705	78.1/75.1	0.209	0.77 (0.52-1.15)	20/512	62.5/59.3	0.668	0.91 (0.58-1.43)
	GG	793	600	75.7	0.607	R	443	60.4	0.722	R
rs2849379	AG	173	127	73.4	0.587	1.31 (0.49-3.51)	86	54.8	0.929	1.05 (0.39-2.80)
	AA	6	4	66.7	0.710	1.21 (0.45-3.27)	4	66.7	0.922	0.95 (0.35-2.59)
Dominant	AA+AG/GG	179/793	131/600	73.2/75.7	0.351	0.91 (0.76-1.10)	90/443	55.3/60.4	0.422	0.91 (0.73-1.14)
Recessive	AA/AG+GG	6/966	4/727	66.7/75.3	0.607	0.77 (0.29-2.07)	4/529	66.7/59.4	0.955	0.97 (0.36-2.60)
	AA	788	593	75.3	0.666	R	435	59.9	0.963	R
rs17759659	AG	178	134	75.3	0.432	1.48 (0.56-3.97)	96	57.5	0.976	0.98 (0.24-3.93)
	GG	6	4	66.7	0.491	1.42 (0.53-3.84)	2	66.7	0.990	1.01 (0.25-4.09)
Dominant	GG+AG/AA	184/788	138/593	75.0/75.3	0.547	0.95 (0.79-1.14)	98/435	57.6/59.9	0.785	1.03 (0.83-1.28)
Recessive	GG/AG+AA	6/966	4/727	66.7/75.3	0.441	0.68 (0.25-1.82)	2/531	66.7/59.5	0.982	1.02 (0.25-4.07)
	GG	885	664	75.0	0.000*	R	481	59.2	0.393	R
rs4987739	AG	85	65	76.5	0.536	1.08 (0.84-1.40)	52	63.4	0.877	1081 (0.00-2.320E+041)
	AA	2	2	100	0.000*	25.38 (6.19-104.17)	0	0	0.873	1318 (0.00-2.830E+041)
Dominant	AA+AG/GG	87/885	67/664	77.0/75.0	0.395	0.90 (0.70-1.15)	52/481	61.9/59.2	0.203	1.20 (0.91-1.60)
Recessive	AA/AG+GG	2/970	2/729	100/75.2	0.000*	0.04 (0.01-0.16)	0/533	0		
	GG	746	558	74.8	0.923	R	420	60.2	0.424	R
rs17841945	AG	214	165	77.1	0.689	1.15 (0.57-2.32)	106	57.0	0.286	0.67 (0.32-1.41)
	AA	12	8	66.7	0.472	1.15 (0.57-2.34)	7	58.3	0.216	0.62 (0.29-1.33)
Dominant	AA+AG/GG	226/746	173/558	76.5/74.8	0.903	0.99 (0.83-1.17)	113/420	57.1/60.2	0.626	0.95 (0.77-1.17)
Recessive	AA/AG+GG	12/960	8/723	66.7/75.3	0.690	0.87 (0.43-1.74)	7/526	58.3/59.5	0.267	1.53 (0.72-3.22)
	AA	649	478	73.7	0.505	R	348	58.4	0.626	R
rs8099575	AG	260	208	80.0	0.244	0.78 (0.51-1.19)	154	63.6	0.717	1.11 (0.64-1.93)
	GG	32	23	71.9	0.298	0.80 (0.52-1.22)	13	46.4	0.521	1.20 (0.68-2.12)
Dominant	GG+AG/AA	292/649	231/478	79.1/73.7	0.615	1.04 (0.89-1.22)	167/348	61.9/58.4	0.476	1.07 (0.89-1.29)
Recessive	GG/AG+AA	32/909	23/686	71.9/75.5	0.252	1.28 (0.84-1.93)	13/502	46.4/59.9	0.651	0.88 (0.51-1.53)

	AA	746	558	74.8	0.355	R	412	59.9	0.695	R
rs17070798	AG	213	163	76.5	0.161	1.57 (0.84-2.93)	115	58.7	0.607	1.24 (0.55-2.77)
	GG	13	10	76.9	0.207	1.51 (0.80-2.86)	6	50	0.744	1.15 (0.51-2.61)
Dominant	GG+AG/AA	226/746	173/558	76.5/74.8	0.454	0.94 (0.79-1.11)	121/412	58.2/59.9	0.428	0.92 (0.75-1.13)
Recessive	GG/AG+AA	13/959	10/721	76.9/75.2	0.168	0.64 (0.35-1.20)	6/527	50/59.6	0.636	0.82 (0.37-1.84)
	AA	280	208	74.3	0.239	0.90 (0.76-1.07)	149	57.5	0.824	0.98 (0.79-1.21)
rs7226979	AG	473	368	77.8	0.074	R	259	59.3	0.430	R
	GG	219	155	70.8	0.026*	0.81 (0.67-0.97)	125	62.5	0.249	0.87 (0.69-1.10)
Dominant	GG+AG/AA	692/280	523/208	75.6/74.3	0.679	0.97 (0.82-1.14)	384/149	60.3/57.5	0.201	1.13 (0.92-1.39)
Recessive	GG/AG+AA	219/753	155/576	70.8/76.5	0.053	1.19 (1.00-1.42)	125/408	62.5/58.6	0.506	1.07 (0.88-1.31)
	GG	902	674	74.7	0.003*	R	492	59.3	0.539	R
rs17685559	AG	65	52	80.0	0.027*	1.38 (1.04-1.83)	39	62.9	0.910	0.92 (0.23-3.71)
	AA	5	5	100	0.009*	3.22 (1.33-7.77)	2	40	0.886	1.11 (0.27-4.60)
Dominant	AA+AG/GG	70/902	57/674	81.4/74.7	0.007*	0.69 (0.53-0.91)	41/492	61.2/59.3	0.271	1.20 (0.87-1.65)
Recessive	AA/AG+GG	5/967	5/726	100/75.1	0.011*	0.32 (0.13-0.77)	2/531	40/59.6	0.925	1.07 (0.27-4.29)
	CC	536	405	75.6	0.598	R	292	59.3	0.832	R
rs12458289	AC	368	275	74.7	0.599	1.08 (0.81-1.45)	202	59.2	0.919	1.02 (0.73-1.42)
	AA	68	51	75.0	0.983	1.00 (0.74-1.35)	39	61.9	0.828	0.96 (0.68-1.36)
Dominant	AA+AC/CC	436/536	326/405	74.8/75.6	0.311	0.93 (0.80-1.07)	241/292	59.7/59.3	0.570	0.95 (0.80-1.13)
Recessive	AA/AG+GG	68/904	51/680	75.0/75.2	0.745	0.95 (0.72-1.27)	39/494	61.9/59.3	0.973	1.01 (0.73-1.39)
	GG	271	203	74.9	0.637	0.95 (0.77-1.17)	143	57.4	0.857	1.02 (0.80-1.30)
rs956572	AG	476	364	76.5	0.869	R	268	60.4	0.983	R
	AA	223	163	73.1	0.960	1.00 (0.84-1.18)	120	59.7	0.902	1.01 (0.83-1.24)
Dominant	AA+AG/GG	699/271	527/203	75.4/74.9	0.822	0.98 (0.84-1.15)	388/143	60.2/57.4	0.873	1.01 (0.82-1.25)
Recessive	AA/AG+GG	223/747	163/567	73.1/75.9	0.598	0.95 (0.80-1.14)	120/411	59.7/59.3	0.893	1.06 (0.86-1.33)
	GG	616	459	74.5	0.260	R	344	59.2	0.707	R
rs1344229	AG	316	238	75.3	0.155	0.78 (0.55-1.10)	177	60.2	0.412	0.84 (0.54-1.29)
	AA	40	34	85.0	0.102	0.74 (0.52-1.06)	22	57.9	0.488	0.86 (0.55-1.33)
Dominant	AA+AG/GG	356/616	272/459	76.4/74.5	0.854	0.99 (0.85-1.15)	199/334	59.9/59.2	0.655	1.04 (0.87-1.24)
Recessive	AA/AG+GG	40/932	34/697	85.0/74.8	0.125	1.31 (0.9301.85)	22/511	57.9/59.6	0.428	1.19 (0.78-1.82)
	AA	279	220	78.9	0.124	0.86 (0.71-1.04)	162	63.	0.850	1.02 (0.81-1.29)
rs12454712	AG	507	371	73.2	0.173	R	274	58.3	0.578	R
	GG	186	140	75.3	0.819	0.98 (0.79-1.21)	97	57.4	0.377	1.12 (0.87-1.44)
Dominant	GG+AG/AA	693/279	511/220	73.7/78.9	0.272	0.92 (0.78-1.07)	371/162	58.1/63	0.303	0.91 (0.76-1.09)
Recessive	GG/AG+AA	186/786	140/591	75.3/75.2	0.255	1.11 (0.93-1.34)	97/436	57.4/60	0.623	0.95 (0.76-1.18)
	AA	915	693	75.7		R	507	59.8		R

rs1005793	AG	57	38	66.7	0.134	1.28 (0.93-1.78)	26	54.2	0.286	1.24 (0.84-1.83)
	GG	0	0				0	0		
Dominant	GG+AG/AA	57/915	38/693	66.7/75.7	0.134	0.78 (0.56-1.08)	26/507	54.2/59.8	0.286	0.81 (0.54-1.20)
Recessive	GG/AG+AA	0/972	0/732				0/533			
	GG	894	678	75.8	0.545	R	488	59.4	0.788	R
rs10503077	AG	72	47	65.3	0.469	0.60 (0.15-2.40)	43	62.3	0.494	1.98 (0.28-14.12)
	AA	4	4	100	0.378	0.53 (0.13-2.18)	1	50	0.490	2.01 (0.28-14.61)
Dominant	AA+AG/GG	74/894	49/678	66.2/75.8	0.481	0.90 (0.67-1.20)	44/488	62/59.4	0.954	0.99 (0.73-1.35)
Recessive	AA/AG+GG	2/966	2/725	100/75.1	0.461	1.69 (0.42-6.76)	1/531	50/59.7	0.493	0.503 (0.07-3.58)
	GG	406	304	74.9	0.121	0.88 (0.76-1.03)	211	55.7	0.581	0.93 (0.71-1.21)
rs949037	AG	443	335	75.6	0.005*	R	251	62.1	0.325	R
	AA	123	92	74.8	0.027*	1.20 (1.03-1.64)	71	62.8	0.186	0.83 (0.64-1.09)
Dominant	GG+AG/AA	849/123	639/92	75.3/74.8	0.004*	1.38 (1.11-1.72)	462/71	59/62.8	0.329	0.88 (0.69-1.13)
Recessive	GG/AG+AA	406/566	304/427	74.9/75.4	0.021*	1.19 (1.03-1.38)	211/322	55.7/62.3	0.165	0.88 (0.74-1.05)
	AA	366	271	74.0	0.928	0.99 (0.80-1.23)	198	58.4	0.285	1.15 (0.89-1.49)
rs8094315	AG	467	356	76.2	0.396	R	260	61.5	0.440	R
	GG	139	104	74.8	0.332	0.89 (0.71-1.12)	75	56.0	0.738	1.05 (0.80-1.37)
Dominant	GG+AG/AA	606/366	460/271	75.9/74.0	0.174	1.11 (0.96-1.29)	335/198	60.1/58.4	0.492	1.06 (0.89-1.27)
Recessive	GG/AG+AA	139/833	104/627	74.8/75.3	0.602	1.06 (0.86-1.30)	75/458	56/60.1	0.431	0.91 (0.71-1.16)
	GG	311	215	69.1	0.005*	0.79 (0.66-0.93)	86	56.2	0.999	1 (0.83-1.21)
rs3810027	CG	497	382	76.9	0.013*	R	284	61.1	0.598	R
	CC	164	134	81.7	0.104	0.85 (0.70-1.03)	163	58.6	0.370	0.89 (0.68-1.15)
Dominant	CC+CG/GG	661/311	516/215	78.1/69.1	0.016*	0.82 (0.70-0.96)	370/163	59.9/58.6	0.756	0.97 (0.81-1.17)
Recessive	CC/GC+GG	164/808	134/597	81.7/73.9	0.468	1.07 (0.89-1.29)	86/447	56.2/60.2	0.311	0.89 (0.71-1.12)
	CC	831	619	74.5	0.624	R	446	58.5	0.953	R
rs4987716	AC	134	106	79.1	0.437	0.73 (0.33-1.62)	82	64.6	0.762	0.87 (0.36-2.11)
	AA	7	6	85.7	0.369	0.69 (0.30-1.56)	5	71.4	0.782	0.88 (0.36-2.17)
Dominant	AA+AC/CC	141/831	112/619	79.4/74.5	0.689	0.96 (0.79-1.17)	87/446	64.9/58.5	0.894	1.02 (0.81-1.28)
Recessive	AA/AC+CC	7/965	6/725	85.7/75.1	0.424	1.39 (0.62-3.10)	5/528	71.4/59.4	0.764	1.14 (0.47-2.76)
	AA	391	285	72.9	0.931	1.01 (0.81-1.25)	226	61.7	0.024*	1.24 (1.03-1.50)
rs1381547	AG	430	335	77.9	0.958	R	210	61.7	0.007*	R
	GG	146	108	74.0	0.800	1.03 (0.83-1.28)	94	68.1	0.004*	1.43 (1.12-1.83)
Dominant	GG+AG/AA	576/391	443/285	76.9/72.9	0.778	0.98 (0.84-1.14)	304/226	57.8/61.7	0.178	1.13 (0.95-1.34)
Recessive	GG/AG+AA	146/821	108/620	74.0/75.5	0.861	0.98 (0.80-1.21)	94/436	68.1/57.8	0.026*	0.78 (0.62-0.97)
	CC	681	510	74.9	0.264	R	369	59.0	0.255	R
rs17757541	CG	272	207	76.1	0.546	1.19 (0.67-2.12)	157	61.6	0.374	1.40 (0.66-3)

	GG	17	12	70.6	0.318	1.35 (0.75-2.41)	7	50	0.229	1.59 (0.75-3.40)
Dominant	GG+GC/CC	289/681	219/510	75.8/74.9	0.277	1.11 (0.92-1.35)	164/369	56.7/59.0	0.576	1.05 (0.72-1.50)
Recessive	GG/GC+CC	17/681	12/510	70.6/74.9	0.540	0.84 (0.47-1.48)	4/445	57.14/68.04	0.367	0.71 (0.34-1.50)
	GG	525	382	72.8	0.621	R	279	58	0.840	R
rs17070848	AG	385	298	77.4	0.803	1.04 (0.77-1.41)	220	61.5	0.761	1.06 (0.73-1.55)
	AA	56	47	83.9	0.501	1.11 (0.82-1.51)	30	57.7	0.616	1.10 (0.75-1.62)
Dominant	AA+AG/GG	441/525	345/382	78.2/72.8	0.485	1.05 (0.91-1.22)	250/279	61/58	0.759	1.03 (0.87-1.22)
Recessive	AA/AG+GG	56/910	47/680	83.9/74.7	0.655	0.94 (0.70-1.26)	30/499	57.7/59.5	0.688	1.08 (0.75-1.56)
	AA	428	329	76.9	0.984	R	236	60.8	0.928	R
rs1026825	AG	416	304	73.1	0.982	1.00 (0.80-1.25)	230	58.5	0.755	1.04 (0.80-1.37)
	GG	128	98	76.6	0.894	0.99 (0.78-1.24)	67	58.3	0.921	1.01 (0.77-1.33)
Dominant	GG+AG/AA	544/428	402/329	73.9/76.9	0.901	0.99 (0.86-1.15)	297/236	58.5/60.8	0.710	0.96 (0.8-1.16)
Recessive	GG/AG+AA	128/844	98/633	76.6/75.0	0.935	1.01 (0.82-1.25)	67/466	58.3/59.7	0.827	0.97 (0.75-1.26)
	AA	402	301	74.9	0.637	1.06 (0.84-1.34)	232	62	0.036*	1.21 (1.01-1.45)
rs8083946	AG	459	345	75.2	0.503	R	239	57.2	0.075	R
	GG	111	85	76.6	0.303	1.14 (0.89-1.44)	62	59.6	0.851	0.97 (0.74-1.29)
Dominant	GG+AG/AA	570/402	430/301	75.4/74.9	0.282	0.92 (0.80-1.07)	301/232	57.7/62	0.023*	1.22 (1.03-1.45)
Recessive	GG/AG+AA	111/861	85/646	76.6/75.0	0.441	0.92 (0.73-1.15)	62/471	59.6/59.5	0.387	1.12 (0.86-1.47)
	GG	635	475	74.8	0.971	R	339	58.1	0.706	R
rs7243091	AG	298	226	75.8	0.825	1.04 (0.72-1.51)	173	62.7	0.531	1.15 (0.74-1.79)
	AA	39	30	76.9	0.874	1.03 (0.71-1.51)	21	56.8	0.427	1.20 (0.76-1.89)
Dominant	AA+AG/GG	337/635	256/475	76.0/74.8	0.854	0.99 (0.85-1.15)	194/339	62/58.1	0.814	1.02 (0.86-1.22)
Recessive	AA/AG+GG	39/933	30/701	76.9/75.1	0.838	0.96 (0.67-1.39)	21/512	56.8/59.6	0.482	0.84 (0.52-1.36)
	GG	521	397	76.2	0.995	R	292	59.8	0.457	R
rs1381548	AG	380	280	73.7	0.959	1.00 (0.75-1.32)	207	59.8	0.240	1.24 (0.87-1.77)
	AA	71	54	76.1	0.929	0.99 (0.74-1.32)	34	54.8	0.216	1.26 (0.88-1.81)
Dominant	AA+AG/GG	451/521	334/397	74.1/76.2	0.960	1.00 (0.86-1.15)	241/292	59.1/59.8	0.820	0.98 (0.83-1.16)
Recessive	AA/AG+GG	71/901	54/677	76.1/75.1	0.944	1.01 (0.77-1.33)	34/499	54.8/59.8	0.215	0.80 (0.57-1.14)
	AA	798	601	75.3	0.677	R	430	58.3	0.440	R
rs4941190	AG	167	124	74.3	0.380	0.70 (0.31-1.56)	99	65.1	0.924	0.95 (0.36-2.55)
	GG	7	6	85.7	0.382	0.69 (0.31-1.57)	4	57.1	0.853	1.10 (0.41-2.99)
Dominant	GG+AG/AA	174/798	130/601	74.7/75.3	0.927	1.01 (0.84-1.22)	103/430	64.8/58.3	0.205	1.05 (0.84-1.33)
Recessive	GG/AG+AA	7/965	6/725	85.7/75.1	0.378	1.44 (0.64-3.21)	4/529	57.1/59.5	0.964	1.02 (0.38-2.74)

Analyzed by univariate Cox's Regression analysis. Abbreviations: OS, overall survival time (taken at 60 months). PFS, progression-free survival time (taken at 18 months). HR: hazard ratio. P: *P* value for data calculated by univariate cox regression model. *P: P<0.05. R: reference.

Supplementary Table 4. The summary of association between Haplo/diplotypes and OS/PFS in our study

			OS				PFS			
	Genotype	n	No.	n%	P	HR (95% CI)	No.	n%	P	HR (95% CI)
Haplotype										
	AA	817	604	73.9	0.126		446	59.4	0.697	
bcl01	AG	766	586	76.5	0.042*	1.13 (1.00-1.26)	434	61.2	0.506	1.06 (0.89-1.26)
	GG	361	272	75.3	0.429	1.06 (0.92-1.23)	186	56	0.399	1.08 (0.91-1.28)
	AAA	925	692	74.8	0.501		511	60.2	0.758	
bcl02	GAG	668	498	74.6	0.808	1.01 (0.90-1.14)	361	58.3	0.330	0.65 (0.27-1.56)
	AGG	344	269	78.2	0.454	1.06 (0.92-1.22)	189	59.6	0.303	0.63 (0.26-1.52)
	OTHER	7	3	42.9	0.188	0.47 (0.15-1.45)	5	71.4	0.342	0.65 (0.27-1.58)
	AG	981	748	76.2	0.677		555	60.7	0.848	
bcl03	AA	724	531	73.3	0.677	0.98 (0.87-1.09)	384	58.4	0.743	412 (0-1.863E+18)
	GA	238	182	76.5	0.239	0.91 (0.77-1.07)	127	58	0.744	402 (0-1.816E+18)
	GG	1	1	100	0.734	1.41 (1.99-10.00)	0	0		
bcl04	GGAA	706	543	59.42	0.659		385	58.6	0.248	
	GGAG	623	452	72.6	0.542	1.04 (0.92-1.18)	345	60.1	0.348	1.21 (0.82-1.78)
	GAAA	238	181	76.1	0.968	1.00 (0.84-1.18)	120	57.1	0.105	1.38 (0.93-2.05)
	AGAA	317	246	77.6	0.649	1.04 (0.89-1.20)	189	63	0.286	1.26 (0.83-1.91)
	OTHER	60	40	66.7	0.216	0.82 (0.59-1.13)	27	52.9	0.163	1.33 (0.89-1.99)
bcl05	CG	1118	812	72.6	0.683		609	59.7	0.199	
	CC	491	389	79.2	0.269	1.07 (0.95-1.21)	261	57.2	0.069	0.16 (0.02-1.15)
	AC	334	261	78.1	0.423	1.06 (0.92-1.22)	195	61.9	0.058	0.15 (0.02-1.07)
	AG	1	0	0	0.899	0.00 (0-7.181E+043)	1	100	0.070	0.16 (0.02-1.16)
bcl06	GAGA	683	489	71.6	0.035*		377	60.3	0.160	
	AAGA	502	396	78.9	0.653	1.03 (0.90-1.18)	283	60.7	0.660	0.93 (0.68-1.27)
	GGGA	450	335	74.4	0.628	0.97 (0.84-1.11)	243	59.4	0.408	0.87 (0.64-1.20)
	GGGG	230	179	77.8	0.862	0.99 (0.83-1.17)	119	55.1	0.266	0.83 (0.60-1.15)
	OTHER	79	63	79.7	0.003*	1.49 (1.16-1.94)	44	57.9	0.079	0.73 (0.52-1.04)
bcl07	AAGG	743	563	75.8	0.413		409	59.4	0.335	
	GAAA	592	446	75.3	0.502	0.96 (0.85-1.09)	331	60.2	0.608	0.94 (0.73-1.20)
	AAGA	289	220	76.1	0.438	0.94 (0.80-1.10)	147	55.5	0.657	0.94 (0.73-1.22)
	GGGA	180	135	75.0	0.826	0.98 (0.81-1.18)	107	64.8	0.163	0.82 (0.62-1.09)
	OTHER	140	98	70.0	0.053	0.81 (0.65-1.00)	72	58.5	0.717	1.06 (0.78-1.43)
bcl08	GG	1573	1187	75.5	0.506		875	60.2	0.740	
	GA	186	140	75.3	0.516	0.94 (0.79-1.12)	97	57.4	0.460	1.08 (0.88-1.34)
	AA	185	135	73.0	0.301	0.91 (0.76-1.09)	94	55.6	0.499	1.10 (0.83-1.47)
bcl09	CAC	687	517	75.3	0.000*		392	62.3	0.114	
	CGC	524	403	76.9	0.006*	0.83 (0.73-0.95)	269	55.1	0.943	0.93 (0.13-6.63)
	AGA	502	375	74.7	0.025*	0.86 (0.75-0.98)	280	60.1	0.806	0.78 (0.11-5.57)
	CGA	227	163	71.8	0.104	0.86 (0.73-1.03)	124	59.9	0.881	0.86 (0.12-6.13)
	OTHER	4	4	100	0.000*	6.91 (2.57-18.57)	1	50	0.993	1.01 (0.14-7.22)
Diplotype										
	AGAA	310	233	75.2	0.289		190	65.5	0.350	
bcl01	AAAA	178	130	73.0	0.414	0.92 (0.74-1.13)	87	54.4	0.278	1.15 (0.89-1.49)
	AGAG	163	126	77.3	0.121	0.83 (0.65-1.05)	89	59.3	0.780	0.96 (0.71-1.29)
	AAGG	151	111	73.5	0.887	0.98 (0.77-1.26)	82	58.2	0.778	0.96 (0.71-1.29)
	OTHER	170	131	77.1	0.083	0.80 (0.62-1.03)	85	54.8	0.582	0.92 (0.68-1.24)
bcl02	AAAGAG	303	222	73.3	0.994		165	57.9	0.962	

	AAAAAA	224	164	73.2	0.951	0.99 (0.79-1.25)	121	59.9	0.813	0.97 (0.74-1.27)
	AAAAGG	172	142	82.6	0.695	0.95 (0.75-1.22)	103	65.2	0.932	1.01 (0.76-1.35)
	AGGGAG	126	96	76.2	0.940	0.99 (0.77-1.27)	66	58.4	0.691	1.06 (0.79-1.43)
	OTHER	147	107	72.8	0.960	0.99 (0.75-1.31)	76	56.5	0.873	0.97 (0.70-1.35)
bcl03	AAAG	364	270	74.2	0.814		199	59.8	0.892	
	AGAG	245	191	78.0	0.228	1.17 (0.91-1.50)	144	61.5	0.344	1.16 (0.86-1.57)
	AAAA	137	97	70.8	0.311	1.15 (0.88-1.49)	69	57	0.309	1.17 (0.86-1.61)
	AGGA	126	95	75.4	0.522	1.10 (0.82-1.49)	68	60.2	0.486	1.14 (0.79-1.63)
	OTHER	100	78	78.0	0.369	1.15 (0.85-1.55)	53	55.8	0.504	1.13 (0.79-1.62)
bcl04	GGAAGGAG	247	182	73.7	0.692		134	59	0.553	
	GGAAAGAA	117	96	82.1	0.944	0.99 (0.83-1.20)	70	63.6	0.943	1.01 (0.81-1.26)
	GGAAGGAA	116	89	76.7	0.763	1.04 (0.82-1.31)	65	57	0.854	1.03 (0.78-1.35)
	GGAGAGAA	105	77	73.3	0.799	0.97 (0.76-1.23)	66	66.7	0.674	0.94 (0.71-1.25)
	OTHER	387	287	74.2	0.184	1.19 (0.92-1.53)	198	57.2	0.129	1.24 (0.94-1.64)
bcl05	CGCG	310	215	69.4	0.035*		162	58.5	0.648	
	CGCC	294	228	77.6	0.500	0.93 (0.75-1.15)	160	58.6	0.432	1.11 (0.86-1.44)
	CGAC	203	154	75.9	0.113	1.19 (0.96-1.47)	124	64.6	0.629	1.07 (0.82-1.39)
	OTHER	165	134	81.2	0.186	1.17 (0.93-1.47)	87	56.5	0.222	1.19 (0.90-1.56)
bcl06	GAGAAAGA	194	147	75.8	0.265		117	64.3	0.151	
	GAGAGGGA	170	120	70.6	0.108	0.82 (0.64-1.04)	86	58.5	0.090	1.22(0.97-1.53)
	GGGAAAGA	120	98	81.7	0.635	1.06 (0.82-1.37)	66	60	0.512	1.09 (0.85-1.40)
	GAGAGAGA	98	64	65.3	0.233	0.84 (0.62-1.12)	55	61.8	0.656	1.07 (0.81-1.40)
	OTHER	390	302	77.4	0.368	0.91 (0.75-1.11)	209	56.8	0.021	1.42 (1.06-1.91)
bcl07	AAGGGAAA	233	186	79.8	0.155		133	62.1	0.830	
	AAGGAAGG	137	103	75.2	0.082	1.18 (0.98-1.42)	74	56.1	0.607	1.06 (0.85-1.32)
	AAGAAAGG	117	84	71.8	0.582	1.07 (0.85-1.33)	63	60.6	0.445	0.90 (0.69-1.18)
	GAAAGAAA	88	64	72.7	0.419	0.91 (0.71-1.53)	50	61	0.702	0.95 (0.72-1.25)
	OTHER	397	294	74.1	0.357	0.88 (0.67-1.15)	213	58.5	0.728	0.95 (0.70-1.29)
bcl08	GGGG	636	479	75.3	0.617		357	60.7	0.836	
	GAGG	152	117	77	0.221	1.30 (0.85-1.97)	85	59.4	0.756	1.09 (0.65-1.82)
	GGAA	149	112	75.2	0.295	1.27 (0.81-1.99)	76	56.3	0.674	1.13 (0.65-1.95)
	OTHER	35	23	65.7	0.399	1.21 (0.77-1.90)	15	50	0.960	0.99 (0.57-1.72)
bcl09	CACCGC	179	133	74.3	0.067		104	63.8	0.809	
	CACAGA	131	104	79.4	0.887	0.98 (0.76-1.27)	72	57.6	0.903	0.99 (0.79-1.23)
	CGCAGA	121	90	74.4	0.046*	1.31 (1.00-1.72)	70	62.5	0.630	0.94 (0.73-1.22)
	OTHER	541	404	74.7	0.709	0.96 (0.79-1.17)	287	57.9	0.466	1.10 (0.85-1.43)

Abbreviations: HR: hazard ratio. P: *P* value for data calculated by univariate cox regression model. *P: P<0.05. R: reference.