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Original Article

Association between genetic variations in tumor necrosis factor receptor genes and survival of patients with T-cell lymphoma

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Abstract

The prognosis of T-cell lymphoma (TCL) has been shown to be associated with the clinical characteristics of patients. However, there is little knowledge of whether genetic variations also affect the prognosis of TCL. This study investigated the associations between single nucleotide polymorphisms (SNPs) in tumor necrosis factor receptor superfamily (*TNFRSF*) genes and the survival of patients with TCL. A total of 38 tag SNPs in 18 *TNFRSF* genes were genotyped using Sequenom platform in 150 patients with TCL. Kaplan-Meier survival estimates were plotted and significance was assessed using log-rank tests. Cox proportional hazard models were used to analyze each of these 38 SNPs with adjustment for covariates that might influence patient survival, including sex and international prognostic Index score. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated. Among the 38 SNPs tested, 3 were significantly associated with the survival of patients with TCL. These SNPs were located at LTβR (rs3759333C>T) and *TNFRSF17* (rs2017662C>T and rs2071336C>T). The 5-year survival rates were significantly different among patients carrying different genotypes and the HRs for death between the different genotypes ranged from 0.45 to 2.46. These findings suggest that the SNPs in *TNFRSF* genes might be important determinants for the survival of TCL patients.

Key words Tumor necrosis factor receptor, SNP, T-cell lymphoma, survival

T-cell lymphoma (TCL) originates from mature T cells and natural killer cells and is a rare malignant lymphatic and hematopoietic tumor that accounts for 12% of all lymphomas[1]. In China, TCL accounts for 34% of non-Hodgkin's lymphomas (NHLs), and the incidence of TCL is increasing[2-4]. The prognosis of TCL is inferior to that of B-cell lymphoma. Currently, the international prognostic index (IPI) is widely used to predict the prognosis of TCL. IPI is determined by multiple factors, including patient age, performance status, serum lactic dehydrogenase level, tumor stage, extranodal and bone marrow involvement. However, IPI is not applicable for predicting the prognosis of all patients, suggesting that other factors may also play roles in patient prognosis. A substantial amount of recent investigations indicated that genetic variations exert significant effects on the prognosis of cancer patients. However, the exact genetic variations remain to be identified.

Tumor necrosis factor (TNF) refers to a group of cytokines secreted by lymphocytes and macrophages. TNF has multiple functions, such as inflammatory response, immune regulation, and antitumor effects. The biological functions of TNF are mediated by TNF receptor superfamily (TNFSF), which possesses similar structures and functions. Previous studies revealed that single nucleotide polymorphisms (SNPs) in the *TNF*-α promoter are associated with increased risk of NHL[5,6], indicating that they might also affect the progress of TCL. Nevertheless, TCL pathogenesis is complex, and few studies focusing on the association between genetic factors and prognosis have been performed. Currently, no studies have been conducted to analyze the relationship between *TNFRSF* genetic variations and the

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survival of TCL patients. In this study, we investigated the associations between multiple SNPs in 18 *TNFRSF* genes and the survival of patients with TCL.

Subjects and Methods

Patients

A total of 150 TCL patients diagnosed at the Cancer Institute & Hospital, Chinese Academy of Medical Sciences between January 1992 and April 2009 were enrolled in this study. The subjects had T-lymphoblastoma or leukemia, anaplastic large cell lymphoma, mycosis fungoides, adult T-cell leukemia or TCL, and peripheral TCL. All patients underwent CHOP regimen (cyclophosphamide, adriamycin, vincristine, and prednisone) or CHOP-based chemotherapy. All patients were Han ethnicity. Patients' clinical information, including age, sex, tumor classification and stage, and IPI were obtained from medical records. Overall survival was measured from the date of diagnosis to the date of last follow-up or death. Whether and when a patient died were obtained from inpatient and outpatient records, patients' families, or local Public Security Census Register Office through follow-up telephone calls. This study was approved by the Institutional Review Board of Chinese Academy of Medical Sciences Cancer Institute. Informed consent was signed by all patients.

SNP selection and genotype analysis

Genomic DNA was extracted from patient peripheral blood samples or paraffin-embedded lymphoma biopsy samples. Blood DNA kit (catalog number: DP319-02) was provided by Tiangen Biochemical Technology Co., Ltd. (Beijing, China). The Wizard MagneSil genomic DNA purification system (catalog number: MD1490) was provided by Promega Company. The procedure was performed strictly according to the manufacturer's instructions.

SNPs within the *TNFRSF* genes[7] and their 2-kb upstream and downstream with the minor allele frequency (MAF) $\geqslant$0.05 were selected according to the HapMap database of Chinese population (NCBI Build 36). All SNPs on the same chromosome were compared pairwise to measure the linkage disequilibrium, and r^2 > 0.8 was used to determine the tag SNPs. The tag SNPs located in gene regulatory and/or coding regions were genotyped and relevant association analysis was performed. By using these criteria, 38 SNPs in 18 *TNFRSF* genes were chosen and genotyped using the Sequenom platform by CapitalBio Co. (Beijing, China).

Statistical analysis

SAS 9.0 software was used for statistical analyses. Cox regression under a log-additive genetic model was performed for genotypes with adjustment for covariates, including sex and IPI score, that might influence patients' survival. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated. Kaplan-Meier survival estimates were plotted and *P* values were assessed using log-rank tests. The survival package in R was used to perform the analyses of TCL-related death. All statistical analyses were two- side tests. *P* values < 0.05 were considered significant.

Results

Patient characteristics

The clinical characteristics of the patients are presented in Table 1. Among the 150 patients, 99 were males and 51 were females. Thirty-one patients had precursor TCL and 119 had mature TCL. The numbers of stage I, II, III, and IV patients were 37, 49, 19, and 45, respectively. A total of 149 patients had IPI scores: 38 scored 0; 51 scored 1; 40 scored 2; 16 scored 3; and 4 scored 4. By February 2011, 69 patients (46.0%) died of TCL: 16 had precursor TCL (median survival: 22 months; 5-year survival rate: 18%), and the other 53 had mature TCL (median survival: 48 months; 5-year survival rate: 47.8%).

Effect of SNPs in the *TNFRSF* genes on patient survival

In total, 38 tag SNPs in 18 *TNFRSF* genes were genotyped (Table 2). The results of association analysis between these 38 SNPs and the survival of TCL patients are presented in Table 3. Three SNPs (rs3759333C>T at *LTβR*, rs2017662C>T at *TNFRSF17*, and rs2071336C>T at *TNFRSF17*) were associated with the TCL patient survival (Table 4).

The 5-year survival rates of patients carrying the rs3759333CC, TC, and TT genotypes were 51.7%, 43.0%, and 25.2%, respectively. The HR of death for patients carrying the TT genotype was 2.46 compared to patients with the CC genotype (95% CI: 1.22–4.97; *P* = 0.012). The 5-year survival rates of patients carrying the rs2017662CC, TC, and TT genotypes were 34.3%, 56.7%, and 66.7%, respectively. The HR of death for patients carrying the TT or TC genotype was 0.53 compared to those carrying the CC allele (95% CI: 0.29–0.97; *P* = 0.039). The 5-year survival rates of patients carrying the rs2071336CC and TC genotypes were 38.9% and 63.2%, respectively. The HR of death for patients

Table 1. Distribution of basic clinical characteristics of the patients with T-cell lymphoma

Characteristic	Patients [cases (%)]	Deaths [cases (%)]	Median survival (months)
Total	150	69	
Age (years)			
⩽60	135 (90.0)	61 (88.4)	46.0
>60	15 (10.0)	8 (11.6)	96.0
Gender			
Male	99 (66.0)	44 (63.8)	47.0
Female	51 (34.0)	25 (36.2)	45.0
Subtype[a]			
Precursor T-cell neoplasm	31 (20.7)	16 (23.2)	22.0
Mature T-cell neoplasm	119 (79.3)	53 (76.8)	48.0
Stage			
I	37 (24.7)	12 (17.4)	34.6[b]
II	49 (32.7)	21 (30.5)	48.0
III	19 (12.6)	9 (13.0)	96.0
IV	45 (30.0)	27 (39.1)	24.0
IPI score			
0	38 (25.3)	8 (11.6)	41.4[b]
1	51 (34.0)	29 (42.0)	24.0
2	40 (26.7)	18 (26.1)	48.0
3	16 (10.7)	11 (15.9)	12.0
4	4 (2.7)	3 (4.4)	21.0
5	0 (NC)	0 (NC)	NC
Unknown	1 (0.7)	0 (NC)	NC

IPI, international prognostic index; NC, not calculated. [a]Precursor T-cell neoplasm includes precursor T-lymphoblastic lymphoma/leukemia; mature T-cell neoplasm includes peripheral T-cell lymphoma, anaplastic large-cell lymphoma, mycosis fungoides, and adult T-cell leukemia/lymphoma. [b]Mean survival time is provided because median survival time is not reached.

carrying the TT or TC genotype was 0.45 compared to those carrying the CC allele (95% CI: 0.21–1.00; P = 0.049). Figure 1 shows Kaplan-Meier survival curves of all patients.

Discussion

In this study, we investigated the association bewteen SNPs in *TNFRSF* genes and prognosis of TCL. The binding of TNF to TNFR can induce two opposite signaling pathways: one activates cell death process through the combination of TNFR I and FAS-associated death domain (FADD), leading to cell apoptosis; the other activates nuclear factor-kappa B (NF-κB) and c-Jun N-terminal kinase (JNK) through the combination of TNFR and TNFR-associated factors (TRAF), promoting cell survival and proliferation. Hence, the complex biological effects induced by the binding of TNF to TNFR play significant roles in cell fate. It has been shown that TNFR family members are involved in the development and progression of malignant tumors and play an important role in cell apoptosis and inflammatory reactions [8,9]. Previous studies have reported that SNPs in the *TNF* and *TNFRSF* genes are associated with susceptibility to human cancers, including NHL [10-12]. Wang *et al.* [6] systematically examined the relationship between 500 tag SNPs in *TNF* and *TNFRSF* genes and susceptibility to NHL and noted that the SNP in 6p21.3 region was related with patient survival.

This study systematically analyzed the association between tag SNPs in 18 *TNFRSF* genes and the survival of patients with TCL. Our results indicated that three SNPs in the *LTβR* and *TNFRSF17* genes were associated with the survival of TCL patients. *LTβR* plays an essential role in the genesis of secondary lymph tissues and T cells and can activate the NF-κB pathway and induce cellular physiologic changes [13-16]. *TNFRSF17*, mainly expressed in mature B cells, plays a vital role in B-cell development and immune response [17]. *TNFRSF17* can directly combine with cytokine BAFF

Table 2. Tagging SNPs genotyped within selected candidate genes of the tumor necrosis factor receptors and corresponding ligands

Gene	SNP	Location
TNFRSF1A	rs4149570	Upstream
	rs2234649	Upstream
	rs767455	Exon
LTβR	rs3759333	Upstream
	rs2364480	Exon
	rs12354	Downstream
TNFRSF7	rs2286598	Upstream
	rs2286597	Upstream
	rs11569361	Upstream
TNFRSF8	None	
TNFRSF1B	rs945439	Exon
	rs1061622	Exon
	rs1061624	3′ UTR
	rs3397	3′ UTR
	rs1061628	3′ UTR
	rs1061631	3′ UTR
TNFRSF9	rs519546	Upstream
	rs161826	3′ UTR
TNFRSF12A	rs13209	3′ UTR
TNFRSF13B	rs11078355	Exon
TNFRSF13C	rs7290134	3′ UTR
TNFRSF14	rs3762440	Upstream
	rs2234167	Exon
TNFRSF17	rs12926535	Upstream
	rs2017662	Exon
	rs2071336	Exon
	rs1126889	3′ UTR
CD40	rs752118	Upstream
	rs1883832	3′ UTR
TRADD	None	
TNFRSF10B	rs1047266	Exon
	rs1047275	3′ UTR
TNFRSF10C	rs12549481	Upstream
TNFRSF10D	rs6651394	Upstream
	rs1133782	Exon
	rs7957	3′ UTR
TNFRSF10A	rs13278062	Upstream
TNFRSF25	None	
FAS	rs1468063	3′ UTR
FASL	rs763110	Upstream
FADD	None	
CFLAR	rs1594	Exon

SNP, single nucleotide polymorphism; UTR, untranslated region.

(also known as B-cell activating factor) to activate the NF-κB and MAPK/JNK pathways. Moreover, *TNFRSF17* can combine with TRAF family members to induce cell apoptosis and proliferation [18]. Other studies have also shown that *TNFRSF17* can promote cell apoptosis by T-cell dependent activation of memory B cells[19].

rs3759333 located at *LTβR* might affect the binding of transcriptional factors to DNA, influencing *LTβR* transcription, thereby resulting in the differentiation of unconventional T cells expressing the γδT-cell receptor.

Table 3. Genetic variations in tumor necrosis factor receptor and corresponding ligand genes and association with survival of the patients with T-cell lymphoma[a]

Gene	SNP	Common homozygote			Heterozygote					Rare homozygote					Dominant model		Recessive model	
		Genotype	Patients	Deaths	Genotype	Patients	Deaths	HR(95% CI)[b]	*P*	Genotype	Patients	Deaths	HR(95% CI)[b]	*P*	HR(95% CI)[b]	*P*	HR(95% CI)[b]	*P*
TNFRSF1A	rs4149570	TT	39	16	GT	58	27	1.35 (0.71–2.57)	0.353	GG	37	18	1.21 (0.58–2.52)	0.620	1.28 (0.71–2.32)	0.409	1.04 (0.59–1.85)	0.885
	rs2234649	AA	107	47	CA	18	8	0.89 (0.41–1.90)	0.760	CC	9	4	1.05 (0.37–2.95)	0.933	0.95 (0.50–1.82)	0.877	1.10 (0.39–3.07)	0.859
	rs767455	TT	99	45	CT	43	18	0.71 (0.40–1.25)	0.236	CC	3	2	0.98 (0.21–4.47)	0.978	0.72 (0.42–1.25)	0.247	1.18 (0.28–5.00)	0.826
LTβR	rs3759333	CC	52	18	TC	56	27	1.40 (0.76–2.59)	0.284	TT	27	16	2.46 (1.22–4.97)	0.012	1.67 (0.95–2.93)	0.072	1.78 (1.00–3.17)	0.051
	rs2364480	AA	107	46	CA	24	14	1.18 (0.64–2.19)	0.596	CC	14	7	0.97 (0.43–2.19)	0.947	1.09 (0.64–1.86)	0.744	0.95 (0.43–2.10)	0.894
	rs12354	GG	104	46	TG	23	14	1.22 (0.66–2.56)	0.535	TT	9	2	0.39 (0.09–1.62)	0.194	0.96 (0.53–1.73)	0.893	0.38 (0.09–1.56)	0.177
TNFRSF7	rs2286598	CC	36	17	GC	72	34	1.30 (0.72–2.36)	0.379	GG	28	9	0.63 (0.26–1.50)	0.292	1.07 (0.61–1.90)	0.809	0.56 (0.27–1.20)	0.137
	rs2286597	CC	108	48	TC	38	18	1.02 (0.58–1.78)	0.953	TT	1	0	NC	NC	1.00 (0.57–1.74)	0.988	NC	NC
	rs11569361	GG	63	29	AG	49	24	1.32 (0.77–2.27)	0.320	AA	12	2	0.28 (0.07–1.18)	0.083	1.04 (0.61–1.76)	0.895	0.26 (0.06–1.09)	0.066
TNFRSF1B	rs945439	TT	83	34	CT	36	17	1.39 (0.77–2.52)	0.277	CC	16	11	1.73 (0.81–3.66)	0.154	1.61 (0.96–2.68)	0.072	1.75 (0.86–3.56)	0.123
	rs1061622	TT	86	35	GT	42	19	1.25 (0.71–2.22)	0.437	GG	18	12	1.73 (0.86–3.48)	0.123	1.45 (0.89–2.38)	0.139	1.67 (0.86–3.22)	0.128
	rs1061624	GG	37	16	AG	76	37	1.74 (0.93–3.27)	0.083	AA	29	12	1.35 (0.60–3.03)	0.463	1.67 (0.92–3.04)	0.094	1.01 (0.53–1.90)	0.984
	rs3397	CC	57	21	TC	54	29	1.66 (0.91–3.03)	0.096	TT	18	8	1.37 (0.59–3.14)	0.463	1.72 (0.98–3.02)	0.062	1.12 (0.53–2.37)	0.771
	rs1061628	CC	77	33	TC	43	21	1.22 (0.70–2.13)	0.478	TT	19	9	1.09 (0.51–2.32)	0.828	1.18 (0.72–1.95)	0.507	1.01 (0.49–2.07)	0.977
	rs1061631	GG	127	57	AG	22	12	1.70 (0.89–3.26)	0.110	AA	0	0	NC	NC	1.70 (0.89–3.26)	0.110	NC	NC
TNFRSF9	rs519546	CC	62	31	AC	56	23	0.77 (0.44–1.34)	0.358	AA	23	11	0.92 (0.43–1.95)	0.819	0.82 (0.49–1.35)	0.434	1.13 (0.58–2.22)	0.722
	rs161826	GG	35	17	AG	47	23	0.93 (0.49–1.76)	0.818	AA	23	9	0.66 (0.25–1.74)	0.403	0.90 (0.49–1.67)	0.737	0.73 (0.33–1.62)	0.441
TNFRSF12A	rs13209	AA	102	45	GA	25	12	0.90 (0.48–1.72)	0.756	GG	8	4	0.77 (0.23–2.56)	0.672	0.88 (0.49–1.60)	0.676	0.75 (0.23–2.47)	0.640
TNFRSF13B	rs11078355	GG	102	45	AG	39	20	1.11 (0.65–1.90)	0.705	AA	8	4	0.97 (0.34–2.82)	0.961	1.11 (0.67–1.85)	0.678	1.03 (0.37–2.89)	0.951
TNFRSF13C	rs7290134	AA	97	46	GA	37	15	0.89 (0.49–1.60)	0.687	GG	8	2	0.57 (0.13–2.47)	0.453	0.82 (0.47–1.44)	0.491	0.53 (0.13–2.26)	0.391
TNFRSF14	rs3762440	CC	88	41	TC	38	17	1.04 (0.59–1.83)	0.903	TT	14	7	0.82 (0.33–2.04)	0.672	1.00 (0.59–1.67)	0.984	0.85 (0.35–2.04)	0.711
	rs2234167	GG	124	57	AG	23	11	1.06 (0.55–2.05)	0.867	AA	0	0	NC	NC	1.06 (0.55–2.05)	0.867	NC	NC
TNFRSF17	rs12926535	GG	95	48	AG	39	13	0.63 (0.34–1.18)	0.153	AA	5	1	0.33 (0.04–2.46)	0.280	0.60 (0.32–1.10)	0.097	0.40 (0.06–2.95)	0.370
	rs2017662	CC	94	51	TC	41	13	0.56 (0.30–1.05)	0.070	TT	5	1	0.33 (0.04–2.41)	0.271	0.53 (0.29–0.97)	0.039	0.37 (0.05–2.72)	0.331
	rs2071336	CC	114	56	TC	24	7	0.49 (0.22–1.09)	0.081	TT	3	0	NC	NC	0.45 (0.21–1.00)	0.049	NC	NC
	rs1126889	GG	47	26	CG	55	22	0.62 (0.35–1.09)	0.096	CC	22	10	0.75 (0.35–1.60)	0.452	0.64 (0.38–1.09)	0.103	0.89 (0.44–1.79)	0.744
CD40	rs752118	CC	66	32	TC	59	27	1.02 (0.60–1.72)	0.948	TT	19	7	0.60 (0.25–1.44)	0.248	0.88 (0.54–1.45)	0.614	0.58 (0.25–1.35)	0.207
	rs1883832	CC	54	24	TC	54	28	1.09 (0.62–1.94)	0.765	TT	24	10	0.93 (0.42–2.06)	0.862	1.11 (0.65–1.91)	0.697	0.85 (0.43–1.71)	0.652
TNFRSF10B	rs1047266	CC	66	31	TC	54	24	0.80 (0.46–1.41)	0.446	TT	17	8	0.98 (0.42–2.28)	0.968	0.87 (0.52–1.46)	0.589	1.16 (0.54–2.47)	0.703
	rs1047275	CC	53	25	GC	56	26	0.94 (0.53–1.66)	0.826	GG	25	11	0.68 (0.31–1.49)	0.338	0.90 (0.53–1.53)	0.691	0.76 (0.38–1.52)	0.436
TNFRSF10C	rs12549481	AA	84	34	GA	45	20	1.14 (0.64–2.04)	0.652	GG	15	9	1.99 (0.94–4.22)	0.073	1.30 (0.78–2.18)	0.311	1.85 (0.90–3.79)	0.093
TNFRSF10D	rs6651394	CC	40	24	TC	64	22	0.64 (0.35–1.17)	0.150	TT	29	14	0.75 (0.38–1.47)	0.395	0.66 (0.39–1.12)	0.123	1.01 (0.54–1.88)	0.976
	rs1133782	CC	111	50	TC	17	8	1.17 (0.55–2.49)	0.679	TT	2	0	NC	NC	1.08 (0.51–2.30)	0.842	NC	NC
	rs7957	TT	46	21	CT	70	29	0.86 (0.48–1.53)	0.606	CC	29	15	0.93 (0.47–1.83)	0.837	0.86 (0.51–1.47)	0.591	1.14 (0.64–2.06)	0.656
TNFRSF10A	rs13278062	GG	74	39	TG	49	16	0.61 (0.34–1.10)	0.100	TT	16	9	1.02 (0.49–2.14)	0.953	0.73 (0.44–1.21)	0.219	1.24 (0.61–2.52)	0.562
FAS	rs1468063	GG	30	13	AG	49	24	1.11 (0.52–2.39)	0.784	AA	5	2	0.80 (0.15–4.37)	0.800	1.04 (0.50–2.16)	0.922	0.96 (0.23–4.11)	0.950
FASL	rs763110	CC	64	32	TC	33	14	1.27 (0.26–6.28)	0.769	TT	7	2	1.80 (0.42–7.73)	0.429	1.73 (0.41–7.27)	0.458	1.52 (0.82–2.80)	0.182
CFLAR	rs1594	TT	51	22	CT	50	20	0.77 (0.41–1.43)	0.404	CC	9	6	1.66 (0.60–4.59)	0.329	0.87 (0.48–1.57)	0.636	1.77 (0.72–4.33)	0.213

[a]The total number of individuals may not be the same because of genotyping failure. [b]Adjusted for sex, subtype, and IPI score.

Table 4. Cox regression of overall survival of three genetic variations in tumor necrosis factor receptor genes for T-cell lymphoma patients

Gene	SNP	Location	Genotype	Patients (n = 150)[a]	Death (n = 69)[a]	Median survival (months)	Adjusted HR (95% CI)[b]	P	Log-rank P
LTβR	rs3759333	Upstream	CC	52	18	81.0	1.00		
			TC	56	27	28.0	1.40 (0.76 2.59)	0.284	0.102
			TT	27	16	20.0	2.46 (1.22 4.97)	0.012	0.007
TNFRSF17	rs2017662	Exon	CC	94	51	25.0	1.00		
			TC	41	13	25.4[c]	0.56 (0.30 1.05)	0.070	0.039
			TT	5	1	24.0[c]	0.33 (0.04 2.41)	0.271	0.270
			TC + TT	46	14	25.7[c]	0.53 (0.29 0.97)	0.039	0.023
	rs2071336	Exon	CC	114	56	45.0	1.00		
			TC	24	7	26.3[c]	0.49 (0.22 1.09)	0.081	0.075
			TT	3	0	NC	NC	NC	NC
			TC + TT	27	7	26.8[c]	0.45 (0.21 1.00)	0.049	0.038

[a]The total number of individuals may not be the same because of genotyping failure. [b]Adjusted for sex, subtype, and IPI score. [c]Mean survival time is provided because median survival time is not reached.

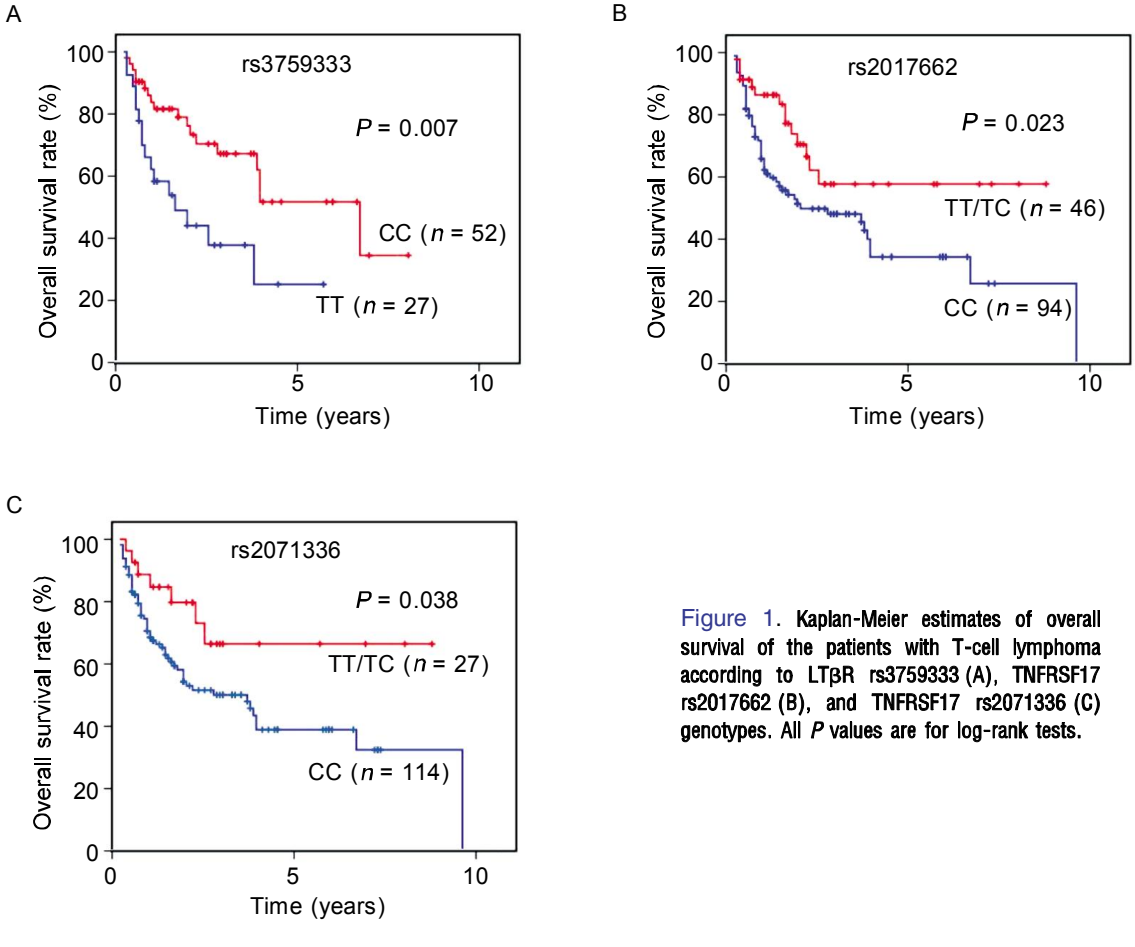

Figure 1. Kaplan-Meier estimates of overall survival of the patients with T-cell lymphoma according to LTβR rs3759333 (A), TNFRSF17 rs2017662 (B), and TNFRSF17 rs2071336 (C) genotypes. All P values are for log-rank tests.

Such unconventional T cells play a vital role in regulating host immune responses, including resisting viral infection and cancer cell invasion[13]. Both rs2017662 and rs2071336 located in the coding region of *TNFRSF17* are synonymous mutations. Synonymous mutation may also affect gene function via a variety of mechanisms. For example, synonymous mutation may create microRNA-binding sites to facilitate mRNA degradation and influence the efficiency of protein translation, eventually affecting the expression of gene products. However, more studies need to be done to elucidate the exact biological mechanism underlying the relationship between genetic variations and the survival of TCL patients.

In summary, we found 3 SNPs in 18 *TNFRSF* genes associated with the survival of patients with TCL. Our results might have potential application in clinical care of TCL patients. However, further studies with large sample size are needed to confirm our results.

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