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Major Article

Association between TGFβ1 polymorphisms and chronic hepatitis B infection in an Iranian population

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Abstract

Introduction: Transforming growth factor-beta 1 (TGFβ1) is a potent suppressive cytokine that contributes to chronic hepatitis B (CHB) infection. Disparities in TGFβ1 production among individuals have been attributed to TGFβ1 genetic polymorphisms. We examined whether three putative polymorphisms in TGFβ1[-509 C/T (rs1800469), +869 C/T (rs1800470), and +11929 C/T (rs1800472)]are associated with CHB infection in a South-Eastern Iranian population. **Methods:** In total, 341 subjects were recruited, including 178 patients with CHB and 163 healthy individuals as controls. Genotyping of the three TGFβ1 SNPs was performed by tetra amplification refractory mutation system-PCR. **Results:** TheTGFβ1 +869 TT vs.CC genotype in codominant (OR=0.445, p=0.012) and TT vs. TC+CC in the recessive (OR=0.439, p=0.003) model as well as the variant allele T vs. C(OR=0.714, p=0.038) were associated with lower CHB infection risk. However, the +11929 C/T polymorphism was associated with increased CHB risk, and the CT vs. CC genotype (OR=2.77, P=0.001) and T variant allele (OR=2.53, P=0.002) were risk factors for CHB. Furthermore, TTT (+869/-509/+11929) and CCC haplotypes were risk and protective factors for CHB, respectively. We found no significant association between viral DNA load and TGFβ1 genotype or hepatic enzyme levels (p >0.05). **Conclusions:** Results indicated that the TGFβ1+869TT genotype and T allele were protective factors, whereas the +11929 CT genotype and T allele were risk factors for CHB infection.

Keywords: Chronic hepatitis B infection. Gene polymorphism. TGFβ1.

INTRODUCTION

Hepatitis B virus (HBV) is the most frequent cause of acute and chronic liver disease worldwide. HBV infects more than 350 million people globally, especially in developing countries of Asia and Africa. Over 90% of adult onset infections are resolved within 6 months, with or without clinical symptoms. However, 5-10% of cases develop into persistent infections, which are defined as chronic hepatitis B (CHB);these can present as more severe forms such as liver cirrhosis and hepatocellular carcinoma. The risk of HBV persistence is related to two main factors: host immunological[1], and genetic[2].

Many studies have suggested that cytokines are critical for the development of a proper immune response against HBV, to eradicate the viral infection, and control hepatitis B-associated complications including cirrhosis of the liver and hepatocellular carcinoma (HCC). Transforming growth factor-beta 1 (TGFβ1) is a potent suppressive cytokine involved in the cellular immune response, and is also important for various physiological processes in the liver, as it promotes apoptosis and inhibits hepatocyte proliferation in addition to its crucial role in hepatic fibrogenesis[3]. This molecule is produced by a number of cell types, including monocytes, macrophages, endothelial cells, and vascular smooth muscle cells and is also released from a variety of liver cells, including hepatocytes and hepatic stellate cells (HSC) in addition to platelets and infiltrating mononuclear cells[4]. Compared to healthy subjects, CHB patients have been shown to express higher levels of serum TGFβ1, resulting in dysregulation of the host immune response[5,6]. As a multifunctional cytokine, TGFβ1 hinders the propagation, differentiation, and activation of immune cells, and plays key roles in the regulation of viral replication and host responses to pathogens[7].

Growing evidence suggests that genetic variations in immune-related genes such as TGFβ1 are associated with CHB risk or progression[4,8,9]. Host genetic background, particularly single nucleotide polymorphisms (SNPs), have been shown to be a crucial factor for associated clinical heterogeneity[10]. TGFβ is encoded by three different genes, namely TGFβ1, TGFβ2, and TGFβ3. Human TGFβ1 is located on chromosome 19q13.1 and

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variation among individuals in terms of TGFβ1 production is considered to be genetically controlled[8].

Three putative polymorphisms of TGFβ1include a C/T transition at the -509 position of the promoter region, a+869 T/C transition in codon 10 of exon 1, and the +11929C/T polymorphism in exon 5. Recent studies have shown that the T allele of the -509C/T (rs1800469) variation is associated with high production of TGFβ1and a lower risk of CHB[11,12]. Additionally, the exon 1 SNP +869C/T (rs1800470)located at position 29 involves an amino acid change of proline to leucine at position 10 of the signal peptide ofTGFβ1[13]. Another SNP, +11929C/T (rs1800472) in exon 5, results in the amino acid replacement of Thr263Ile, and is related to the activation of TGFβ1[14].

TGFβ1 polymorphisms have been evaluated in a number of infectious diseases, including *Mycobacterium tuberculosis* (TB) infection[15], brucellosis[7,16], hepatitis C virus (HCV) infection[6,17], and CHB[5,18,19]; however, results have been inconsistent. Considering solid evidence implicating TGFβ1 polymorphisms in infectious diseases, the current study was designed to investigate the potential relationships between three genetic polymorphisms inTGFβ1, including -509 C/T, +869C/T, and +11929C/T, and the risk of CHB in a South-East Iranian population. To the best of our knowledge, this is the first study examining TGFβ1 variations and CHB in this population.

METHODS

Study population

The current case-control study included 178 CHB patients (114 men and 64 women; age range 15-68 years and mean ± SD = 34.02 ± 10.1) and 163 healthy individuals as the control group (108 men and 55 women; age range 17-58 years and mean ± SD =33.84 ±23.2). Patients with CHB infection were recruited from blood transfusion organization outpatient clinics in Zahedan, during 2013-2015, and their ethnicity was Fars or Balouch. The research was executed at the Infectious Diseases and Tropical Medicine Research Center, Zahedan University of Medical Sciences, and the study was approved by the ethics committee of Zahedan University of Medical Sciences, Zahedan; all patients gave informed consent before taking part in the study.

Viral assessment and HBV DNA quantification

Chronic hepatitis B was determined as positivity for HBsAg for a minimum of 6 months. All patients were positive for hepatitis B surface antigen (HBsAg) and HBV-DNA and negative for HCV antibodies. The main exclusion criteria included human immunodeficiency virus or HCV co-infection, or any evidence of clinically relevant liver disease such as apparent auto-immune hepatitis-primary biliary cirrhosis, HCC, former history of alcohol abuse, or previous liver transplantation. HBsAg and HCV antibodies were tested using a commercial kit (Enzygnost, Germany). HBV-DNA in HBV-positive patients was extracted and tested by polymerase chain reaction (PCR) (Cinagen, Iran) and quantified by quantitative PCR (qPCR) (ABI 7800, Applied Biosystems, Foster City, CA). Patients were stratified into two groups according to their viral DNA loads[20]. Group 1 included patients with low serum HBV DNA levels (<2,000IU/mL; n = 63) and group 2 included patients with high titers of HBV DNA (≥2,000IU/mL; n = 34).

The control group included healthy blood donors from the same geographic area and with the same ethnicity, who were anti-HBs- and anti-HBc-positive (resolved HBV) with no history of previous liver disease. There was no difference between groups regarding gender or ethnicity.

DNA isolation and genotyping of TGFβ1SNPs (-509 C/T, +869C/T, and +11929C/T)

Blood samples were collected by withdrawing5mL of venous blood into sterile EDTA-containing tubes. DNA was extracted by the salting-out method, as described previously[21,22]. The isolated DNA was examined by electrophoresis using a 1% agarose gel, quantified spectrophotometrically, and stored at −20 °C until further use.

The threeTGFβ1polymorphisms, -509 C/T, +869C/T, and +11929C/T, were genotyped by the tetra-primer amplification refractory mutation system-polymerase chain reaction (T-ARMS-PCR) method, as described previously[23]. T-ARMS-PCR utilizes four primers including two external primers (control band) and two inner primers (allele specific primers). This method simultaneously amplifies both alleles in one single PCR tube. The cycling conditions for T-ARMS-PCR were an initial denaturation at 95°C for 5 min followed by 30 cycles of 30s at 95°C, annealing for 30s at 60°C for -509 C/T, 30s at 65°C for +869C/T, and 30s at 63°C for +11929C/T, and a final cycle of 72°C for 10 min.

PCR products were separated by standard electrophoresis on a 2% agarose gel containing ethidium bromide. The primer sequences and products sizes are shown in **Table 1**.

Statistical analysis

All statistical analyses were performed using SPSS software for Windows, version 18.0 (SPSS Inc, Chicago IL, USA). The association between genotypes and CHB was calculated by estimating the odds ratio (OR) and 95% confidence intervals (95% CI) based on logistic regression analyses. P-values below 0.05 were considered statistically significant. The Hardy-Weinberg equilibrium (HWE), differences in the distribution of the haplotype, and diplotype distributions between the two groups were assessed by the $\chi 2$ test. Linkage disequilibrium and frequencies of haplotypes and diplotypes in the controls and patients were calculated using SNPStats software[24].

RESULTS

Genotype frequencies of TGFβ1-509 C/T, +869C/T, and +11929C/T polymorphisms

ThreeTGFβ1 polymorphisms were successfully genotyped in CHB patients and control subjects. No SNPs had genotype frequencies that deviated significantly from the HWE in the studied control groups ($p>0.05$), except for the -509 C/T variation ($p=0.01$).The genotype and allele frequencies of thethreeTGFβ1gene polymorphisms in the studied groups are shown in **Table 2**.

TABLE 1

Primers used for genotyping of TGFβ1 gene polymorphisms and amplicon sizes.

SNPs	Name[1]	Primer sequence	Amplicons size (bp)
TGFβ1 SNPs			
-509 C/T	FO	AGTAAATGTATGGGGTCGCAGGGTGTTG	295
	RO	AAAGAGGACCAGGCGGAGAAGGCTTAAT	
	FI (T allele)	GGTGTCTGCCTCCTGACCCTTCCATACT	207
	RI (C allele)	GAGGAGGGGGCAACAGGACACCTTAG	141
+869 C/T	FO	CAGCTTTCCCTCGAGGCCCTCCTACCTT	255
	RO	TTCCGCTTCACCAGCTCCATGTCGATAG	
	FI (T allele)	CTCCGGGCTGCGGCTGCTTCT	123
	RI (C allele)	AGTAGCCACAGCAGCGGTAGCAGCATCG	180
+11,929 C/T	FO	AGAGTGTGTGTGTATGTCCCCTATCCCC	313
	RO	AGACAGATGCTCAGCCCAAGCACAG	
	FI (T allele)	GCCTTTCCTGCTTCTCATGGCAAC	143
	RI (C allele)	CTGGGCCCTCTCCAGCGTGA	213

TGFβ1: transforming growth factor-beta 1; **SNP:** single nucleotide polymorphisms; **bp:** base-pair; **FO:** forward outer; **RO:** reverse outer; **FI:** forward inner; **RI:** reverse inner; Nucleotide specificity is shown in parentheses.

TABLE 2

Genotype and allele frequencies of TGFβ1 SNPs between chronic hepatitis B virus (HBV)-infected patients and controls.

Genetic models	Allele/ genotype	HBV patients n(%)	Controls n(%)	*OR (95% CI)	*P-value
TGFβ1 +869 C/T					
alleles	C	228 (58.0)	201 (51.0)	Ref.	-
	T	164 (42.0)	195 (49.0)	0.714 (0.559–0.982)	0.038
codominant	CC	55 (28.0)	49 (25.0)	Ref.	-
	CT	118 (60.0)	103 (52.0)	1.021 (0.640–1.628)	0.932
	TT	23 (12.0)	46 (23.0)	0.445 (0.237–0.838)	0.012
dominant	CC	55 (28.0)	49 (25.0)	Ref.	-
	TC + TT	141 (72.0)	149 (75.0)	0.831 (0.538–1.320)	0.494
recessive	TC+CC	173 (88.0)	152 (77.0)	Ref.	-
	TT	23 (12.0)	46 (23.0)	0.439 (0.254–0.758)	0.003
GFβT1-509 C/T					
alleles	C	234 (66.0)	196 (63.0)	Ref.	-
	T	122 (34.0)	112 (37.0)	0.912 (0.663–1.255)	0.625
codominant	CC	78 (44.0)	71 (46.0)	Ref.	-
	CT	78 (44.0)	54 (35.0)	1.315 (0.819–2.110)	0.257
	TT	22 (12.0)	29 (19.0)	0.691 (0.364–1.310)	0.256
dominant	CC	78 (44.0)	71 (46.0)	Ref.	-
	TC + TT	100 (56.0)	83 (54.0)	1.096 (0.711–1.162)	0.741
recessive	TC+CC	156 (88.0)	125 (81.0)	Ref.	-
	TT	22 (12.0)	29 (19.0)	1.645 (0.901–3.004)	0.127
TGFβ1+11929 C/T					
alleles	C	299 (89.0)	310 (95.0)	Ref.	-
	T	39 (11.0)	16 (5.0)	2.527 (1.382–4.613)	0.002
codominant	CC	130 (77.0)	147 (90.0)	Ref.	-
	CT	39 (23.0)	16 (10.0)	2.765 (1.471–5.164)	0.001
	TT	0	0	-	-

TGFβ1: transforming growth factor-beta 1; **SNP:** single nucleotide polymorphisms; **HBV:** hepatitis B virus; **OR:** odds ratio; **CI:** confidence interval; .*Adjusted for age and sex. OR.

TheTGFβ1+869 C/T polymorphism was associated with a decreased rate of CHB infection. The mutant homozygote genotype (TT vs. CC) was present at a significantly lower frequently in CHB patients than in controls (12% vs. 23%), and this was associated with reduced risk of CHB infection (OR=0.445, 95%CI=0.237–0.838, p=0.012). Likewise, at the allelic level, for TGFβ1+869, the variant allele T was less prevalent in CHB patients than in controls (42 vs. 49) and was a protective factor against CHB development (OR=0.714, 95%CI=0.559–0.982, p=0.038).

The TGFβ1+11929 C/T polymorphism was associated with increased susceptibility to CHB infection. The heterozygote genotype (CT vs. CC) was present significantly more frequently in CHB patients than in controls (23% vs. 10%), and it was a risk factor for CHB infection (OR=2.765, 95%CI=1.471-5.164, p=0.001). In addition, at the allelic level, for TGFβ1+11929,the variant allele T was more prevalent in CHB patients than in controls (11 vs. 5) and was found to be a risk factor forCHB development (OR=2,527, 95%CI=1,382-4,613, p=0.002) in our population.

With respect to other TGFβ1 SNPs, for -509 C/T, the genotypes and allele distributions did not significantly differ between patients and neither was associated with CHB risk (p>0.05).

Linkage disequilibrium and haplotype association analysis of TGFβ1polymorphisms

Linkage disequilibrium (LD) was computed by calculating Lewontin's Delta' coefficient and the correlation coefficient, r^2,[25]. Pairwise LD between the TGFβ1SNPs -509 C/T, +869C/T, and +11929C/T was calculated for cases and controls. Analysis of the TGFβ1 SNPs demonstrated a moderate LD for the TGFβ1 SNP pair, -509 C/T and +869 C/T (D' = 0.689 r^2=0.315), but no LD was observed between other TGFβ1 SNP pairs, namely -509 C/T and +11929 (D' = 0.076, r^2=0.001)or +869 C/T and +11929 C/T (D' = 0.021, r^2=0.001). **Table 3** shows haplotype association analyses for TGFβ1 polymorphisms in CHB patients and controls. The TTT and CCC haplotypes (+869/-509/+11929; p=0.003) were distributed differently in CHB patients compared to that in controls. The TTT haplotype was associated with an increased risk of CHB (OR=4.253, 95%CI=1.487-12.16, p=0.003), whereas the CCC haplotype was associated with a reduced risk of CHB (OR=0.655, 95%CI=0.448-0.957, p=0.028).Owing to the small number of subjects, the haplotype findings should be interpreted with caution. Meanwhile, we performed pairwise diplotype analysis among the three TGFβ1 SNPs but the results were not statistically significant (data not shown).

Table 4 demonstrates the stratification of hepatitis B patients, based on their viral DNA load, as well as the relationship between patient sex, age, and mean level of liver enzymes and TGFβ1 genotypes. We observed that TGFβ1 genotypes were distributed equally in two groups with high and low HBV DNA levels, and the difference was not statistically significant (P>0.05). However, HBV DNA levels were associated with mean patient age (P=0.001), but not with gender or liver enzyme levels (p>0.05).

Furthermore, we compared the relationships between the levels of hepatic enzymes (ALT, AST, and ALP) and different TGFβ1 genotypes (p>0.05) among the CHB patients. ANOVA analysis (Tukey test) of the genotypes indicated that there was no significant association between *TGFβ1*genotypes and the quantity of hepatic enzymes (P>0.05) (data not shown).

TABLE 3

Haplotype association analyses for TGFβ1 -509 C/T, +869C/T, and +11929C/T polymorphisms between chronic hepatitis B patients and controls.

Haplotype*	Case/Freq (%)	Control/Freq (%)	OR (95% CI)	P-value
TGFβ1 SNPs+869/-509/+11929				
TTC	122 (12.0)	108 (0.43)	0.994 (0.706–1.400)	0.973
CCC	68 (0.2)	81 (0.3)	0.655 (0.448–0.957)	**0.028**
CCT	11 (0.03)	5 (0.02)	1.774 (0.617–5.104)	0.281
CTC	42 (0.15)	40 (0.16)	0.908 (0.567–1.455)	0.689
CTT	4 (0.01)	4 (0.14)	0.844 (0.187–3.813)	0.825
TCC	19 (0.06)	9 (0.03)	2.024 (0.890–4.605)	0.087
TCT	0.1 (0.0)	1 (0.01)	-	-
TTT	20 (1.0)	4 (0.02)	4.253 (1.487–12.16)	**0.003**

TGFβ1: transforming growth factor-beta 1; **SNP:** single nucleotide polymorphisms; **OR:** odds ratio; **CI:** confidence interval.*Haplotype analysis for frequencies below 0.01 was not performed. Bold numbers depict p < 0.05.

TABLE 4

Stratification of hepatitis B patients based on viral DNA load, and relationships between patient sex, age, and mean level of liver enzymes and TGFβ1 genotypes.

Parameter	Patients with low HBV DNA levels (<2,000MU/mL)	Patients with high HBV DNA levels (>2,000MU/mL)	P-value
Sex (male/female)	20/15	46/18	0.137
Age (years)	31	41.5	0.001
ALT (IU/L)	29.7	27.4	0.441
AST (IU/L)	36.1	30.9	0.325
ALP (IU/L)	193.3	159.1	0.326
TGFβ1 +869 C/T			
CC (%)	20 (32.0)	30 (31.0)	Ref.
CT (%)	36 (58.0)	55 (57.0)	0.995
TT (%)	6 (10.0)	11 (12.0)	0.781
TGFβ1 -509 T/C			
CC (%)	28 (45.0)	14(40.0)	Ref.
CT (%)	28 (45.0)	14(40.0)	0.998
TT (%)	6 (10.0)	7(20.0)	0.315
TGFβ1 +11929C/T			
CC (%)	44 (73.0)	26 (74.0)	Ref.
CT (%)	16 (27.0)	9 (26.0)	0.994

DNA: deoxyribonucleic acid; **TGFβ1:** transforming growth factor-beta 1; **HBV:** hepatitis B virus; **ALT:** alanine aminotransferase; **AST:** aspartate transaminase; **ALP:** alkaline phosphatase; **MU/mL:** mili units/millilitre; **IU:/L:** international Units/liter.

DISCUSSION

Growing evidence has suggested defective cellular and humoral immune functions in patients with CHB infection; this could be directly related to the chronicity of the disease[26]. In general, patients with CHB infection have a weak, relatively unfocused intra-hepatic and systemic immune response to HBV antigens[27]. Animal studies have shown an increase in the levels of TGFβ1 and TNF-α during hepatic fibrogenesis, and this contributes to fibrin matrix formation and liver fibrosis[28,29].

Our results showed that TGFβ1 +869 C/T and +11929 C/T polymorphisms were associated with lower and higher risk of CHB infection, respectively. The TGFβ1 +869 homozygote genotype (TT) might confer protection against CHB in the tested population. The carriers of the TT genotype had a comparatively (0.4-fold) lower risk of CHB than subjects with CC or CC+CT genotypes. Likewise, the TGFβ1 +869 T variant was associated with a reduced risk of CHB (OR=0.7). Concerning TGFβ1 +11929 C/T, we found that the CT genotype as well as the T allele were related to an increased risk of CHB. In addition, subjects harboring either the CT genotype or the T allele had a relatively (2.8- or 2.5-fold, respectively) increased risk of CHB in our population. Furthermore, the TTT (+869/-509/+11929) haplotype carriers had a 4.2-fold higher risk of CHB. However, the CCC (+869/-509/+11929) haplotype was shown to potentially confer protection against CHB in our population (OR=0.6).

Our data regarding the TGFβ1 +869 C/T polymorphism were similar to those of several studies on inflammatory and infectious diseases such as chronic periodontitis[23], Crohn's disease[30], childhood asthma[31], multiple sclerosis (MS)[32], and TB[33]. Schrijver et al. reported that TGFB1 T+869C variation is associated with MS susceptibility, especially in males, and with a more destructive disease course[32]. However, the study by Ribeiro et al[34] on CHB and the report of Mak et al[35] on TB showed no relation between TGFβ1 gene polymorphisms and disease risk. Our findings regarding TGFβ1-509 C/T support the results of Hosseini Razavi et al. who found no association between the TGFβ1-509C/T polymorphism and CHB in an Iranian population. Compared to their study, our study is a population-based study performed on individuals from a South-Eastern Iranian population; however, their study was a hospital-based study performed using samples obtained from the Taleghani Hospital in Tehran, the capital city of Iran, and these samples were from individuals of a different ethnicity compared to that of our subjects[5]. Although both studies examined the effect of the TGFβ1-509C/T polymorphism on CHB, we also examined two

other gene polymorphisms (+869 C/T and +11929 C/T),where were not included in the study of Hosseini Razavi et al[5].

The 11929C/T SNP (Thr263Ile; rs1800472), located in exon 5, is close to the latency-associated peptide cleavage site, required to activate the protein. Hence, this SNP might affect the activation process of TGFβ1[13]. In support of this report, we previously found that the risk of CHB is higher among those with the high producer allele T (Ile) than in those with the C (Thr) allele[12]. The +11929C/T SNP has been the basis of a number of studies; however, it was not shown to be associated with the risk of chronic periodontitis[23] or childhood asthma[31].

TGFβ1 is located on chromosome 19q13 and consists of 23,020 base pairs, including six introns and seven exons. TGFβ1exhibits bi-allelic polymorphisms at position -509C/T in the promoter region and two bi-allelic polymorphisms in exon 1 (+869C/T) and exon 5 (+11929C/T)[21].The TGFβ1 +869 C/T substitution (rs1800470) results in a proline (CCG) to leucine (CTG) change at codon 10 (Pro10Leu) of the protein. This genetic alteration occurs in the signal peptide, which is involved in export of the pre-pro-protein across the endoplasmic reticulum membrane. The +869 Leu allele (T) has been shown to elevate the secretion of this cytokine in breast cancer[36], lung fibrosis[37], and schizophrenia[38].In contrast, some studies have reported that the Pro allele (C) of +869 C/T is related to higher serum levels, compared to those associated with the Lue (T) allele, in HCC patients[12]. A transfection study using HeLa cells also indicated that the allele (C) encoding Pro 10 is associated with increased rates of TGFβ1 secretion[39]. In agreement with the latter studies, our findings showed that the risk of CHB was lower among those with the lower producer genotype TT (Leu/Leu), when compared to that in individuals with the CC genotype[12]. Dual roles of TGF-β in immune system regulation can explain the conflicting results; different studies have shown that TGF-β can have either positive or negative effects on hepatitis B infection.

TGFβ has dual roles in the regulation of the immune system. It induces the differentiation of Th17 cells, the main source of IL-17A,which is essential for both the initiation and maintenance of appropriate immune responses against microbes; in addition, it is involved in the development of cirrhosis of the liver and HCC[7,40,41,42]. In contrast, it can increase the number and activation of T regulatory lymphocytes and the recruitment of these cells to the infected liver; this leads to prolonged hepatitis B infection. Prolonged infection with the chronic, asymptomatic, and occult forms of hepatitis B contributes to HCC and cirrhosis of the liver[43]. The mechanisms responsible for the prolonged hepatitis B infection, HCC, and cirrhosis of the liver are not entirely understood.

Our study was a population-based study of South-Eastern Iranians. Similarly, Hosseini Razavi et al[5] examined the association between TGFβ1 +915G/C and -509C/T gene polymorphisms and CHB patients from Tehran, Iran. They observed no statically significant differences in terms of genotype distribution and allele frequency for both polymorphisms between healthy controls and patients with CHB. In another study (hospital-based) on HCV patients, Romani et al[44] found no significant differences in terms of the allelic frequency distribution of SNPs at -509 C/T, +869 C/T, or +915 G/C between HCV patients and healthy controls. In contrast, the hospital-based study of Talaat et al[4] on 65 Egyptian hepatitis B patients and 50 healthy controls indicated that the T29C CC genotype might act as a host genetic factor of HBV susceptibility in Egyptians.

In conclusion, our findings suggest that theTGFβ1 +869 C/T and +11929 C/T polymorphisms are associated with a lower and higher risk of CHB infection, respectively, in a South-East Iranian population. Moreover, the TTT or CCC (+869/-509/+11929) haplotype carriers were at a higher or reduced risk of CHB, respectively. The main limitation of this study were that serum TGF-β1 levels were not measured was and data regarding population risk factors for HBV infection and identification of the actual population were missed. However, the advantage of our study was the large number of subjects and the fact that it was a population-based study. Further studies using larger sample size on different ethnicities are suggested to confirm out findings regarding the implication of theTGFβ1variants in CHB infection risk.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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