Assessment of HLADP gene rs3128917 and rs9380343 polymorphisms in chronic HBV infection

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ABSTRACT

Background/Aims: *About 400 million people worldwide have been exposed to Hepatitis B (HBV) infection. A range of 10%-15% of chronic HBV carriers may present with various liver diseases including cirrhosis and hepatic cancer. The chronicity or clearance of HBV infection is dependent on viral and genetic variables. Genome-wide association studies (GWAS) have reported that the variants of human leukocyte antigen (HLA), rs3128917 and rs9380343, are significantly related to persistent HBV infection. HLA molecules are responsible for introducing various antigens into the immune system. These variants might affect antigen presentation by influencing HLA mRNA expression, therefore, antigen presentation may not be performed properly.*
This study aims to assess the relationship of HLA gene variants to chronic HBV infection.

Materials and Methods: *HLA variants were explored in 238 chronic HBV patients and in 238 individuals with spontaneous clearance of HBV using PCR-RFLP assay.*

Results: *The allele and genotype of rs9380343 polymorphism were associated with persistent HBV infection risk (allele: p=0.038, genotype: p=0.029), but rs3128917 polymorphism was not significant. Additionally, rs9380343 polymorphism was also related to increased risk of HBV infection in males (p<0.05).*

Conclusion: *The current study is the first report demonstrating the HLA rs9380343 polymorphism as a genetic risk factor for chronicity of HBV infection. Further independent studies are required to confirm the current findings using a larger sample size in different populations.*

Keywords: *HLA polymorphism, rs3128917, rs9380343, HBV infection*

INTRODUCTION

Hepatitis B (HBV) infection is a considerable health challenge worldwide. It causes persistent hepatitis, cirrhosis, and cancer of the liver (1). Advancement from acute infection to chronic hepatitis B infection (CHB) takes place in about 90% of persons by the vertical transmission route from mother to infant, but only 15% people contract it in adulthood (2). The HBV vaccine is a vital tool for developing immunity against the disease, yet approximately 400 million individuals worldwide continue to suffer from CHB infection, and over half a million persons die per year (3,4). Notwithstanding the accomplishment of HBV inoculation in reducing the HBV carrier rate in recent years, the proportion of healthy individuals who do not respond to the HBV vaccine is 10% (5). A cross-country study conducted in Turkey from the west to the east has reported the increasing prevalence of HBV infection in this region (6).

The natural clearance of CHB or HBV depends on many complex factors such as host and HBV variants, age and sex of the host, co-infection by other viruses, and environmental exposures (7). Many studies have shown that variations in the host genes such as TNF-α and IFN-gamma, estrogen receptor alpha, mannose-binding protein, vitamin D receptor, IL-28B polymorphisms and human leukocyte antigen (HLA) affect the body's immune response to the HBV infection (8-13). HLA class II genes encode surface glycoproteins on the surface of antigen-presenting cells, and these glycoproteins have a vital role in the presentation of antigens to CD4+ T-helper lymphocytes (14). HLA genes consist of many polymorphic domains which are related to the immune response for many different antigens. *HLA-DP*, an HLA class II molecule, plays an important role in T-cell recognition and peptide binding (15,16). The first genome-wide association study (GWAS) detected 11 variants in the class II *HLA-DP* genes at chromosome 6p21, which have reported as being related to the occurrence of HBV infection (16). The *rs3128917 G* and *rs9380343 T* alleles of these variants within the *HLA-DPB1* gene are significantly associated with increased

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risk of HBV infection (1,16). *HLA-DPB1* variants impress mRNA expression and mRNA stability via alteration in the fastening sites of transcription factors (17,18), therefore, the introduction of the antigens to CD4 + cells may be impaired due to these polymorphic sites (19).

This research aimed to assess the relationship between the HLA gene (*rs3128917 G/T*, *rs9380343 C/T*) variants and the risk of CHB in a Turkish population. HLA gene variants were explored in 238 CHB carriers and in 238 individuals with spontaneous clearance of HBV using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay.

MATERIALS AND METHODS

Study design

This study was approved by the Ethics Committee of Çukurova University in Turkey. The subjects in the case and control groups were enrolled for study at Balcalı Hospital from May 2013 to July 2016. Written informed consent was obtained from all subjects before they participated. This study was performed according to the Helsinki Declaration adopted at the World Medical Association convention in Edinburgh in 1964. A total of 238 subjects that were either serologically positive for anti-HBc and HBsAg or contained HBV DNA for ≥ 6 months were registered as the patient group. In these current patients, the phases of chronic HBV infection are as follows; immune tolerance: 5, HBeAg-positive immune active: 22, HBeAg-negative immune active: 99, and inactive carriers: 112.

According to the Ishak score, the degree of fibrosis of patients who underwent biopsy was as follows; F0-1: 40, F2: 23, F3: 61, F4: 3. The patients having co-infection with HIV, HCV, HDV were excluded from this study. Simultaneously, 238 individuals with spontaneous clearance of HBV were included in the control group. HBV spontaneous clearance was described by patients testing positive for Anti-HBc and Anti-HBsAg and negative for the presence of HBsAg. Biochemical parameters of all participants and the amount of HBV DNA for HBV patients were measured for statistical analysis. The blood and serum samples of all subjects were frozen at -20°C until analysis.

The detection of rs3128917 and rs9380343 variants

The detection of *rs3128917* and *rs9380343* variants was done by PCR-RFLP analysis. Genomic DNA of participants was isolated according to former guidelines (20). To identify the *rs3128917* and *rs9380343* variants, a 218 base pair (bp) DNA fragment and a 155 bp fragment were amplified by two sets of primers: 5′-GCC CAG GAA ATA AAG GTG GT-3′ (forward), 5′-GGA GCC AGT CAT TGA GGG TA -3′ (reverse) and 5′- TTC CCC GCA ATC CTA TAC TG -3′ (forward), 5′- TGT GAT CCT GTA CGA CCT CCT -3′ (reverse), respectively.

The PCR amplification was carried out as previously defined (20). Briefly, PCR cycling conditions were used: 5 minutes at 95 °C, followed by 36 cycles at 94 °C, 60 °C and 58 °C for 60 seconds (for both *rs9380343* and *rs3128917*) and 72 °C for 60 seconds, with a last extension at 72 °C for 10 minutes. Later the PCR products were digested for over 12 hours with restriction enzymes: 5 units HinfI (for *rs3128917*) and 5 units HaeIII (for *rs9380343*) at 37 °C. Subsequently, the digested products were electrophoresed and monitored by UV. For rs3128917, the products 158-bp and 60-bp were scored as GG; 218-bp, 158-bp, and 60-bp as TG; and 218-bp as TT. For *rs9380343*, the digested products 134-bp and 21-bp were scored as CC; 155-bp, 134-bp, and 21-bp as TC; and 155-bp as TT.

Statistical analysis

The effective sample size for use in the case-control study and for obtaining 80% power was calculated by Quanto ver. 1.1 software (http://hydra.usc.edu/gxe) using minor allele frequency data from HapMap (http://hapmap.ncbi.nlm.nih.gov/). Data analysis was performed using the computer software IBM Statistical Package for Social Sciences ver. 20 (SPSS) (SPSS, Inc., Chicago, IL, USA) for Windows. Continuous variables were presented as the mean (standard deviation, SD) or median (between the minimum and maximum) for non-normal distributions and categorical variables were presented as frequencies (in %). Comparisons between the distributions of demographical characteristics among the patients with chronic HBV infection and the control subjects were evaluated using the Student's t-test or Mann-Whitney U test for continuous variables whenever appropriate depending on their Gaussian distribution. The chi-square test was used to evaluate categorical variables.

The observed genotype frequencies were compared with expected values calculated using the Hardy-Weinberg equilibrium theory. Significant variables after univariate regression analysis were entered into a stepwise logistic regression analysis to identify the risk factor of chronic HBV infection. Statistical analysis of genotypes, haplotype estimation, and linkage disequilibrium (LD) was analyzed using the website for SNP Statistics (https://www.

snpstats.net/start.htm?q=snpstats/start.htm). Logistic regression analysis was used to analyze the association of genotypes in inheritance models (co-dominant, dominant, recessive, over-dominant) in the case and control groups. Results were expressed as odds ratios (OR) with 95% confidence interval (CI). All tests were two-sided and *p*-value <0.05 was considered significant.

RESULTS

The baseline findings of the HBV and control groups are indicated in Table 1. The individuals in this study were Caucasian. The majority of the individuals were male the in case group and female in the control group. As expected, the characteristics and biochemical parameters between cases and controls were statistically different (Table 1).

The allelic and genotypic distributions of the rs3128917 and the rs9380343 variants

The total allelic distribution of HLA gene *rs3128917* polymorphisms were 84.9% and 15.1% for T and G, respectively. Alongside this, the total allele distributions for *rs9380343* polymorphism were 95% and 5% for C and T, respectively. There were substantial differences between both groups for the allelic and genotypic distributions of the *rs9380343* variant (p=0.038 and p=0.029, respectively), yet *rs3128917* polymorphism did not display any differences (Table 2).

Further, once both groups were classified by gender, there were significant differences seen in terms of the allele and genotype frequencies of *rs9380343* in males (p<0.05) (Table 3). It was found that the frequency of *rs9380343* TT genotype in this study was very rare. Only the TT genotype was found among females in the control group. In addition, the positivity of HBe antigen was not associated with *rs3128917* and *rs9380343* variants (p=0.53 and p=0.13, data not shown in Table 2). Additionally, the patients' and controls' distributions were calculated using the Hardy-Weinberg equilibrium (p>0.05).

The relationship between HLA genotypes and the CHB infection risk

To determine the effect of genotypes of *rs3128917* and *rs9380343* on the risk of CHB infection, logistic regression analysis was used (Table 2). The *rs3128917* variant was not related with CHB infection risk in any of the genetic models. For the *rs9380343* variant, the persons having TC genotype showed an increased CHB risk by a factor of 2.23 as compared to persons with CC genotype (p=0.017). Similarly, the persons carrying the T allele showed the greatest risk of CHB infection when compared with the persons having C allele in dominant and over-dominant models (p=0.022 and p=0.014) (Table 2). Further, male patients having *rs9380343* T variant or TC genotype were at significant risk of CHB infection (p=0.006 and p=0.008) (Table 3).

Haplotype analysis of rs3128917 and rs9380343 variants

LD was weak between *rs3128917* and *rs9380343* variants (D'=0.45). The haplotypes of these variants were not associated with CHB risk. Although the GT haplotype showed some chronic HBV infection risk, it was not significant (OR=2.36, 95%CI: 0.92-6.09, *p*=0.076) (Table 4).

DISCUSSION

The current study is the first of its kind to investigate the effect of HLA gene variants (*rs3128917* G/T and *rs9380343* C/T) on the CHB infection risk using a control group comprising individuals with spontaneous clearance of HBV in a Turkish population.

Table 1. Distribution of selected characteristics in cases and controls.

Variable	Cases (%) (chronic HBV carriers) n =238	Controls (%) (HBV natural clearance) n=238	p
Age*	50 (17-90)	53 (21-84)	0.002[a]
Sex: male (%)	155 (65.1)	117 (49.2)	0.001[b]
Drinkers (%)	13 (5-.6)	12 (5.2)	0.86[b]
BMI (kg/m2)**	27.33 ± 4.36	27.61± 3.75	0.44[c]
ALT (U/L)*	24 (12-1024)	22 (8-183)	0.03[a]
AST(U/L)*	24 (15-590)	23 (16-155)	0.008[a]
GGT(U/L)*	17 (5-480)	20 (8-344)	0.02[a]
PLT(uL)*	215 (30-482)	249 (35-590)	0.001[a]
HCT(uL)**	41.06 ± 5.64	39.97 ± 4.86	0.013[c]
Albumin (g/dL)**	4.11 ± 0.57	4.19 ± 0.53	0.17[c]
Total Bilirubin(mg/dL)*	0.70 (0.01-4.5)	0.60 (0.01-1.6)	0.002[a]
PTZ**	12.85 ± 1.86	12.15 ± 1.26	0.002[c]
INR**	1.09 ± 0.16	1.00 ± 0.16	0.33[c]
HBeAg (-)/HBeAg (+), (%)	211 (88.7)/27 (11.3)	-	-
HBV DNA, log (IU/mL)**	6.99 ±7.56	-	-

[a]p-values were calculated by Mann-Whitney *test*. [b]p-values were calculated by the *chi-square test*. [c]p-values were calculated by *student* t-test. *Data were shown as median (min-max). **Data were shown as mean±SD. Drinker was described as alcohol consumption of >40g/week.

Table 2. Distribution of selected characteristics in cases and controls.

	Cases (%) (chronic HBV carriers) n =238	Controls (%) (HBV natural clearance) n=238	p	OR (95% CI)
For rs3128917,				
Allele frequency, %				
T/G	85.3/14.7	84.5/15.5	0.72[a]	0.93 (0.66-1.34)
Co-dominant model				
TT	174 (73.1)	167 (70.2)	0.38[a]	1.00 (Reference)
TG	58 (24.4)	68 (28.6)	0.39[b]	0.83 (0.55-1.26)
GG	6 (2.5)	3 (1.3)	0.38[b]	1.89 (0.46-7.88)
Dominant model				
TT	174 (73.1)	167 (70.2)		1.00 (Reference)
TG+GG	64 (26.9)	71 (29.8)	0.52[b]	0.88 (0.58-1.32)
Recessive model				
TT+TG	232 (97.5)	235 (98.7)		1.00 (Reference)
GG	6 (2.5)	3 (1.3)	0.33[b]	1.99 (0.48-8.26)
Over-dominant model				
TT+GG	180 (75.6)	170 (71.4)		1.00 (Reference)
TG				
	58 (24.4)	68 (28.6)	0.34[b]	0.82 (0.54-1.24)
For rs9380343,				
Allele frequency, %				
C/T	93.5/6.5	96.4/3.6	0.038[a]	1.88 (1.03-3.46)
Co-dominant model				
CC	207 (87)	222 (93.3)	0.029[a]	1.00 (Reference)
TC	31 (13)	15 (6.3)	0.017[b]	2.23 (1.15-4.31)
TT	0 (0)	1 (0.4)	-	-
Dominant model				
CC	207 (87)	222 (93.3)		1.00 (Reference)
TC+TT	31 (13)	16 (6.7)	0.022[b]	2.08 (1.10-3.94)
Recessive model				
CC+TC	238 (100)	237 (99.6)		1.00 (Reference)
TT	0 (0)	1 (0.4)	-	-
Over-dominant model				
CC+TT	207 (87)	223 (93.7)		1.00 (Reference)
TC				
	31 (13)	15 (6.3)	0.014[b]	2.21 (1.15-4.24)

[a]p-values were calculated by chi-square test. [b]Data were calculated by logistic regression analysis. Adjusted for age, sex, and alcohol consumption.

Recently, a few GWAS studies reported that *HLA-DP* gene variants, *rs3128917*, and *rs9380343*, were significantly related to CHB infection and HBV spontaneous clearance in Japanese and Thai populations (1,16). Moreover, Wong et al. showed that the *rs3128917* T allele was associated with an increased chance of HBV sponta-

Table 3. Allele and genotype frequencies of *HLA* polymorphisms according to sex and their association with the risk of chronic HBV infection.

rs3128917	Allele/Genotype	Cases, n (%)	Controls, n (%)	p	OR (95% CI)
Male		155 (65.1)	117 (49.2)		
	T	262 (84.5)	199 (85)	--	1.00 (Reference)
	G	48 (15.5)	35 (15)	0.89[a]	1.03 (0.64-1.66)
	TT	112 (72.4)	83 (70.9)	0.35[a]	1.00 (Reference)
	TG	38 (24.4)	33 (28.2)	0.61[b]	0.86 (0.50-1.50)
	GG	5 (3.2)	1 (0.9)	0.23[b]	3.81 (0.44-33.2)
Female		83 (34.9)	121 (50.8)		
	T	144 (86.7)	203 (83.9)	--	1.00 (Reference)
	G	22 (13.3)	39 (16.1)	0.46[a]	0.81 (0.46-1.42)
	TT	62 (74.7)	84 (69.4)	0.74[a]	1.00 (Reference)
	TG	20 (24.1)	35 (28.9)	0.45[b]	0.78 (0.41-1.49)
	GG	1 (1.2)	2 (1.7)	0.77[b]	0.69 (0.06-8.05)
rs9380343					
Male		155 (65.1)	117 (49.2)		
	C	287 (92.6)	229 (97.9)	-	1.00 (Reference)
	T	23 (7.4)	5 (2.1)	0.006[a]	3.67 (1.37-9.80)
	CC	132 (85.2)	112 (95.7)	-	1.00 (Reference)
	TC	23 (14.8)	5 (4.3)	0.008[b]	3.86 (1.41-10.55)
	TT	-	-	-	-
Female		83 (34.9)	121 (50.8)		
	C	158 (95.2)	230 (95)	-	1.00 (Reference)
	T	8 (4.8)	12 (5)	0.95[a]	0.97 (0.39-2.43)
	CC	75 (90.4)	110 (90.9)	0.67[a]	1.00 (Reference)
	TC	8 (9.6)	10 (8.3)	0.69[b]	1.22 (0.45-3.28)
	TT	0 (0)	1 (0.8)	-	-

[a]p-values were calculated by the chi-square test. [b]Data were calculated by logistic regression analysis. Adjusted for age and alcohol consumption.

Table 4. Frequency distribution of haplotypes of *HLA* gene *rs3128917* and *rs9380343* polymorphisms in cases and controls.

Haplotypes HLA rs3128917	Frequency			
G/T and rs9277535 C/T	Cases	Controls	OR (95%CI)	p
TC	0.8247	0.8257	1.00 (Reference)	--
GC	0.1103	0.1382	0.78 (0.51-1.18)	0.24
GT	0.0366	0.0171	2.36 (0.92-6.09)	0.076
TT	0.0284	0.019	1.38 (0.53-3.58)	0.50

Global haplotype association p-value: 0.12

neous clearance in a Chinese population (3). However, Seto et al. reported that *rs3128917* polymorphism had no association with HBV sero-clearance in Chinese population (19). Furthermore, Posuwan et al. proclaimed that *rs3128917* polymorphism was not associated with HBV carrier status in Thai population (4). Although *HLA-DP* gene polymorphisms of *rs3128917* and *rs9380343* have been investigated in relation to HBV infection in Asian populations, these polymorphisms have not been explored in Caucasian populations as yet. Hence, these variants were chosen due to their critical role in CHB infection risk.

Table 5. The comparison of studies concern with HLA gene *rs3128917* and *rs9380343* polymorphisms.

Studies, (reference no.)	Patients	Controls	Population	*rs3128917/rs9380343*	p
Kamatani et al. (ref. 16)	786 CHB	2201 healthy	Japanese	G/T allele	*Sig/Sig[a1/a2]
	1300 CHB	2100 healthy	Japanese/Thai	G/T allele	*Sig/Sig[b1/b2]
Guo et al. (ref. 1)	521 CHB	571 HBV natural clearance, 248 healthy	Han Chinese	G/T allele	*Sig/Sig[c1/c2]
Wong et al. (ref. 3)	500 CHB	259 HBV natural clearance, 245 healthy	Chinese	rs3128917	Sig/NS[d1/d2]
Seto et al. (ref. 19)	203 CHB with sero-clearance	203 CHB without sero-clearance	Chinese	rs3128917	NSe
Posuwan et al. (ref. 4)	219 CHB	113 resolved HBV, 123 healthy	Thai	rs3128917	NS/NS[f1/f2]
The current study	238 CHB	238 HBV natural clearance	Turkish	G/T allele	*NS/Sig[g1/g2]

Sig: signifigant, NS: nonsignificant, *p-values for *rs3128917* and *rs9380343*, respectively; [a1/a2]p=<0.0001/<0.0001; [b1/b2]p=<0.0001/<0.0001; [c1/c2]p= $3.2x10^{-11}$/$2.4x10^{-11}$ for *rs3128917*; [c1/c2]p=$7.8x10^{-8}$/$1.5x10^{-7}$ for *rs9380343*; and [d1/d2]p=0.00017/0.054; ep=0.349; [f1/f2]p=0.372/0.673 for *rs3128917*; [g1/g2]p=0.72/0.038

In the present study, the minor allele distributions of HLA variants in the control group with HBV natural clearance were found to be 15.5% and 3.6% for *rs3128917* G and *rs9380343* T alleles, respectively. Considering the previous findings, the frequencies of *rs3128917* G allele among the populations were distributed as 37.2% in Han Chinese, 44.6% in Southern Chinese, 47.8% in Thai, respectively (1,3,4). For the *rs9380343* T allele frequency, there is only one report by Guo et al., which states that the gene frequency is 29.6% in the Han Chinese population (1). Furthermore, a European HapMap Cohort study reported that *rs3128917* G and *rs9380343* T allele distributions were seen in 25% and 6% for CEU in a healthy population.

The minor allele frequencies reported in this study were much lower than those reported in Asian populations. On the contrary, the results of the current study are almost in agreement with the results of the European HapMap Cohort. Moreover, in this study, neither allele frequencies nor genotype frequencies of *rs3128917* polymorphism are associated with HBV infection. Further, there are only two studies that are in line with the results of the current study for *rs3128917* (4,19). Conversely, in the other studies, while the *rs3128917* G allele was strongly related to the susceptibility of the persistent HBV infection (1,16), the *rs3128917* T allele was found to be associated with an increased chance of HBV clearance (3). In addition, the *rs9380343* T minor allele significantly increased the CHB infection risk in the present study (OR =1.88; 95% CI=1.03-3.45, p=0.038). The patients carrying T allele had a 2.09- and 2.24-fold persistent HBV risk higher than non-carriers in dominant and over-dominant models, respectively (p=0.022 and p=0.014). Two GWAS studies have reported observations similar to the current study (1,16). Both the studies reported that the *rs9380343* T allele is strongly associated with CHB infection risk. Additionally, O'Brien et al. reported that both *rs3128917* and *rs9380343* polymorphisms were not associated with HLA-DP mRNA expression in the normal human liver (12). In our haplotype analysis, although the GT haplotype (for *rs3128917* G and *rs9380343* T) increased the chronic HBV risk by a factor of 2.36, it was not significant (p=0.076). There have been no studies conducted as yet to compare the results of the current study in the Caucasian population.

The current study analyzed the relationship of both variants with CHB infection by gender. The male patients with the *rs9380343* T allele and the *rs9380343* TC genotype had a 3.67- and a 3.86-fold persistent HBV risk as compared to the persons with C allele or CC genotype, respectively (p=0.006 and p=0.008). Additionally, the *rs3128917* variant was not significant in males. Furthermore, the results of the present study showed that both *rs3128917* and *rs9380343* variants were not associated with CHB infection in females in the control group. Unfortunately, there are no studies as yet on the relationship of these polymorphisms with CHB infection in terms of gender. Hence, the results of the current study could not be compared. Briefly, the results of the studies concerned with these polymorphisms are given in table 5.

The antigen-binding sites of HLA-DP glycoproteins are highly polymorphic regions, which is why these molecules bind a wide variety of antigenic structures and present to the CD4+T-lymphocytes (2). Recently, some studies have described an association between the *rs3128917*

and the *rs9380343* gene variants and chronic CHB infection in Asian populations (1,3,16). Even though both of these polymorphisms do not cause specific changes to the *HLA-DPB1* gene, they may affect the function of HLA-DP molecules in the post-transcription process in indirect ways such as the alteration in microRNA binding site and microRNA-mRNA interaction (21,22). Therefore, it can be concluded that the clinical outcome of HBV infection might be affected by these polymorphisms in the *HLA-DPB1* gene.

There were some limitations in the current study. First of all, this study did not evaluate all HBV patients and all subjects with HBV spontaneous clearance in the Turkish population because it was implemented around the city of Adana. Secondly, it should be noted that the extremely rare occurrence of the TT genotype frequency in this study limited the statistical analysis by gender, which is why more extensive studies with a larger sample size of with both genders are required. Lastly, this research was limited to the Turkish population owing to differences in allele distribution among different ethnic groups.

In conclusion, the current study is the first of its kind demonstrating the association between HBV infection and the HLA gene variants in the Caucasian population. The results of this study show that the variant of the *HLA-DPB1* gene, *rs9380343* exhibits polymorphism that influences the CHB infection risk. However, *rs3128917* polymorphism is not associated with CHB infection.

The worldwide mortality of CHB infection is approximately half a million each year. Moreover, the high HBV-related morbidity and mortality rates lead to economic burden. Therefore, it is necessary to investigate host genetic factors in detail to understand the molecular pathogenesis of hepatitis B infection. In the light of these studies, it may be possible to develop personalized treatment methods for CHB infection and HBV-related diseases.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Medical Experiment on Human Subjects, Çukurova University School of Medicine.

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

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