Research Article

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A Misleading Parameter in the Diagnosis of Chronic Hepatitis B: Persistently Normal Transaminases

Kronik Hepatit B Tanısında Yanıltıcı Bir Parametre: Sürekli Olarak Normal Transaminazlar

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ABSTRACT

Objectives: Most of the patients with hepatitis B e (HBe)-negative hepatitis B have persistently normal transaminases (PNALT) levels. Patients, who have higher fibrosis and necroinflammatory activity scores, are at high risk for hepatocellular carcinoma and cirrhosis. Therefore, it is important to distinguish between active and inactive hepatitis in this group.

Materials and Methods: Sixty-six treatment-naïve, non-cirrotic, HBe antigen (HBeAg)-negative and a PNALT and a level of a hepatitis B virus (HBV) DNA level of ≥2000 IU/mL were included in this study. Ishak's scoring system was used for histopathological evaluation. Chronic hepatitis was defined as a fibrosis score of higher than/equal to 2 and/or a histological activity index score of higher than 4.

Results: The percentage of patients diagnosed with advanced fibrosis score and high necroinflammatory activity was 65% and 48%, respectively. Accordingly, 76% of patients were considered to have chronic hepatitis. Level of the HBV DNA was the most significant value for predicting chronic hepatitis. 94.1% of patients with a HBV DNA value over 20000 IU/mL had chronic hepatitis (p<0.001).

Conclusion: As a result of this study, it has been found that the prevalence of chronic hepatitis in our country was high in HBeAg-negative patients with PNALT and a HBV DNA level higher than 2000 IU/mL. We recommend starting treatment in patients with a HBV DNA level higher than 20000 IU/mL without considering any other criteria. Close monitoring or biopsy is recommended in patients with HBV DNA values between 2000 and 20000 IU/mL.

Keywords: Hepatitis B, hepatitis B virus DNA, hepatitis B e antigen-negative chronic hepatitis, inactive hepatitis B virus carrier

ÖZ

Amaç: Hepatit B e (HBe) negatif hepatit B'li hastaların çoğu, sürekli olarak normal transaminazlara (PNALT) sahip olgulardır. Daha yüksek fibrozis ve nekroenflamatuvar aktivite skoru olan hastalar siroz ve hepatosellüler karsinoma için ciddi risk altında olduğundan dolayı bu gruptaki hastalarda aktif/inaktif hepatit ayrım yapmak önemlidir.

Gereç ve Yöntemler: HBe antijen (HBeAg)-negatif olan, sirozu olmayan, hepatit B virüs (HBV) DNA değeri 2000 IU/mL ve üzerinde olan PNALT'li naif 66 hasta çalışmaya dahil edildi. Histopatolojik değerlendirme için İshak skorlama sistemi kullanıldı. Fibrozis skoru 2 ve/veya histolojik aktivite indeksi skoru >4 olan hastalar kronik hepatit olarak kabul edildi.

Bulgular: İleri fibrozis skoru ve yüksek nekroenflamatuvar aktivitesi olan hastaların oranı sırasıyla %65 ve %48 idi. Kronik hepatit olarak kabul edilen hasta oranı %76 idi. HBV DNA seviyeleri, kronik hepatitin öngörme de en önemli değerdi. HBV DNA seviyeleri 20000 IU/m'nin üzerinde olan hastaların %94,1'inde kronik hepatit vardı (p<0,001).

Sonuç: Ülkemizde HBV DNA değerinin 2000 IU/mL üzerinde olduğu HBeAg-negatif PNALT hastalarında kronik hepatit oranı yüksektir. Bu hastalarda HBV DNA'nın 20000 IU/mL'nin üzerinde olması halinde başka kriterlere bakılmaksızın tedaviye başlanmasını öneririz. HBV DNA seviyeleri 2000 ve 20000 IU/mL arasında olan hastalarda yakından izleme veya biyopsi uygun gözükmektedir.

Anahtar Kelimeler: Hepatit B, hepatit B virüs DNA, hepatit B e antijen-negatif kronik hepatit, inaktif hepatit B virüs taşıyıcı

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Introduction

It is estimated that more than 2 billion people, all over the world, have been infected with hepatitis B virus (HBV). On the other hand, there are more than 240 million HBV carriers as well (1). Majority of chronic hepatitis cases (more than half of these cases) are estimated to be hepatitis B e antigen (HBeAg)-negative worldwide (2). In studies conducted in Europe, increased rates of hepatitis B surface antigen (HBsAg)-negative hepatitis have been shown and this ratio has been reported to be 70%-90% in recent years (3,4). Turkey is a country with intermediate endemicty for hepatitis B (2%-8%) and the prevalence of HBeAg-negative hepatitis is 40-85%

Chronic hepatitis B (CHB) can be classically described as presence of positive serum HBsAg for longer than 6 months (5,6). As a dynamic process, CHB infection course can be investigated into five phases. These phases can be defined as follows (7):

i. First phase: HBeAg-positive chronic infection,
ii. Second phase: HBeAg-positive chronic hepatitis,
iii. Third phase: HBeAg-negative chronic infection,
iv. Forth phase: HBeAg-negative chronic hepatitis, and
v. Fifth phase: HBsAg-negative phase.

HBeAg-negative chronic infection is the latent phase that infection enters into non-replicative phase associated with termination of immune response. In this phase, antibody against HBeAg occurs and HBsAg positivity continues, but HBV DNA as indicative of active viral replication is negative or too low (<2000 IU/mL). Formerly, in this period called "inactive HBV carrier" state. HBeAg-negative chronic hepatitis may develop in this phase, therefore, if these patients have not been followed for a long duration, they should not be considered inactive HBV carriers (8). This distinction is important because inactive HBV carriers show a good course while risk of progression to fibrosis, hepatic cirrhosis, and hepatocellular carcinoma (HCC) is more than in patients diagnosed with active disease (9). HBeAg-negative chronic hepatitis is different from inactive carrier state by HBV DNA levels above 2000 IU/mL, continuously or intermittently elevated alanine aminotransferase (ALT) levels, and/or at least moderate fibrosis or liver necroinflammation (10). Approximately in 1-3 of every 100 patients, inactive HBV carrier state progresses to HBeAg-negative chronic hepatitis (11). Guidelines of major professional liver organizations in the world agreed that there is no need to treat or biopsy inactive HBV carrier patients (HBV DNA<2000 IU/mL and ALT levels within the normal range) (7,12,13). These guidelines recommend periodical close monitoring with serum ALT and some parameters including HBV DNA for inactive carrier patients. If ALT and/or HBV DNA levels increase, either direct treatment or treatment according to biopsy results is recommended in these patients. Also, in a small number of patients with a HBV DNA level over 2000 IU/mL, persistently normal ALT (PNALT) is observed and guidelines do not give any clear recommendation for these patients. There are few studies on these patients in the literature and different results are reported from different regions. In our country, there are very few studies in this group of patients. In this context, it was aimed in this study to reveal the prevalence of HBeAg-negative chronic hepatitis in our country and investigate some parameters which indicate HBeAg-negative chronic hepatitis.

Materials and Methods

Patient Enrollment

This was a single-center cross-sectional study. Consecutive HbeAg-negative and HbsAg-positive treatment-naïve patients with a HBV DNA level of >2000 IU/mL, who were admitted to our unit between March 2010 and April 2013, were included in the study. Patients with malignancy, any autoimmune or comorbid disorder and sings of chronic liver disease or cirrhosis were excluded. Additionally, those with hepatitis C and hepatitis D, as well as human immunodeficiency virus-positive patients were also excluded. Clinical and demographic characteristics were noted and body mass index (BMI) was calculated in all patients.

Serological, Biochemical and Hepatitis B Virus DNA Assay

Blood samples of the patients were taken in the morning after a 12-hour overnight fast. Routine examinations were studied in the laboratory of the departments of clinical biochemistry and clinical microbiology. The normal range for ALT values for women was 10-35 U/L and for men, 10-45 U/L. HBsAg, anti-HBs and anti-HCV were studied using an Eti-Max 3000 device with micro-ELISA method. HBeAg, anti-HBe, HAV immunoglobulin (Ig) M and IgG, and anti-HCV were studied on a Liaison device with macro-ELISA method. The level of HBV DNA was studied on a TaqMan 48 analyzer (CTM 48; Roche Molecular Systems, Inc.) using the polymerase chain reaction method and the results were were reported in IU/mL. HBV DNA values were calculated by taking the average of the last two measurements. We investigated a cut-off value to determine the chronic hepatitis using the significant parameters. We have identified 20.000 IU/mL as the cut off value for HBV DNA because HBV DNA is used in many researches (14,15,16,17,18,19,20) and guidelines (7,12,13) to standardize rather than receiver operating characteristics (ROC). For the same reason, the cut off value for ALT was determined as 19 U/L for women and 30 U/L for men (13,14,20,21). We allocated two patient groups with regard to ALT levels: low-normal ALT (LNALT) (for women <19 U/L, for men <30 U/L) and high-normal ALT (HNALT) (for women 19-35, U/L for men 30-45 U/L).

Liver Biopsy and Histopathological Evaluation

Liver biopsies were performed in our clinic by a single physician after an overnight fast by a 16-gauge Hepafix needle using the ultrasound-guided technique. Biopsy samples containing at least 10 portal areas were included in the study and evaluated by an independent pathologist. The pathologist had no information about the patients. Ishak scoring system [fibrosis stage (range, 0-6) and histology activity index (HAI) (range, 0-18)] were used as the classification system (23). Patients with a fibrosis score of ≥2 and /or HAI score of >4 were considered to have HBeAg-negative chronic hepatitis.

This study was approved by the Local Ethics Committee (Şişli Hamidiye Etfal Training and Research Hospital, approval number:12.01.2010, 1119). Written informed consent received.

Statistical Analysis

Statistical analyses were carried out with the use the SPSS program version 21 (Chicago, IL, USA). The variables were examined using analytical techniques (the Shapiro-Wilk test/the Kolmogorov-

Smirnov test) and visual inspection (probability plots, histograms) to find out distribution of the samples. Standard deviations and means were used to carry out descriptive analysis. Ordinal and continuous variables that do not have normal distributions were compared using the Mann-Whitney U test. Student's t-test was used to evaluate differences between the two study subgroups in normally distributed continuous variables. According to the availability of data, the Pearson and Spearman correlation coefficients were used to test correlations among the study variables. A p value of less than 0.05 was considered statistically significant.

Results

Sixty-six patients were enrolled in this study. The mean age of the participants was 40.7±10.5 years. 39 (59.1%) patients were male, 27 (40.9%) were female. The mean ALT level was 31.1±10.1 U/L. The lowest HBV-DNA level was 2.010 IU/mL, the highest was 853.000 IU/mL and the mean HBV DNA value was 101.780±185.426 IU/mL. The number of patients with a HBV DNA value between 2.000 and 20.000 IU/mL was 32 (48%). The characteristics of the patients are shown in Table 1.

The fibrosis score was 2 or over in 65% of the patients (43/66) and the mean score was 1.83±0.83. Only 1 patient had a fibrosis score of 5. In patients with a fibrosis score of 2 or higher, the mean HBV DNA, ALT and aspartate aminotransferase (AST) levels were 141.442±124.089 IU/mL, 32.9±11.6 U/L and 27.9±18.3 U/L, respectively. In patients with a fibrosis score of <2, the mean HBV DNA, AST and ALT levels were 27.630±56.856 IU/mL, 23.1±14.6 U/L and 27.6±12.5U/L, respectively. There was a statistically significant difference in these parameters between the two groups (p<0.001, p=0.037 and p=0.006, respectively). HBV DNA was over the level of 20.000 IU/mL in 30 (69.8%) patients with a fibrosis score of ≥2 and, 27 of these (62.8%) were male.

The mean HAI score was 5.06±2.27 (range: 2-11). HAI score was found to be above 4 in 32 patients (48.5%). The mean HBV DNA, ALT, AST levels in patients with a HAI >4 (192.677±76.645 IU/mL, 35.3±23.1 U/L, 28.8±14.2 U/L, respectively) were considerably higher than in patients with a HAI score of ≤4 (16.231±11.230 IU/mL, 27.03±17.1 U/L, 23.8±16.9 U/L, respectively) (p<0.001, p<0.001, p=0.002, respectively). The HBV DNA level was above 20.000 IU/mL in 26 patients (81.3%), all of whom were male.

Chronic hepatitis was found in 50 HBeAg-negative patients (76%). HBV DNA, ALT and AST values in patients with chronic hepatitis were higher than in those without chronic hepatitis (p<0.001, p=0.03, and p=0.01 respectively). Platelets were found to be significantly lower in chronic hepatitis group. On the other hand, there was no statistically significant difference in other parameters (Table 1).

We evaluated the correlations of other parameters with fibrosis and HAI scores because presence of chronic hepatitis in patients with a HBV DNA level of higher than 2.000 IU/mL was analyzed

Table 1. Characteristics of all patients and those in chronic hepatitis group and non-chronic hepatitis group

	Total (n=66)	Non-chronic hepatitis (n=16)	Chronic hepatitis (n=50)	p
Age (years)	40.7±10.5	38.7±8.1	41.3±11.1	0.472
Disease age (years)	7.5±4.5	6.1±4.7	7.9±4.4	0.07
BMI (kg/m^2)	25.0±3.9	23.8±3.2	25.3±4.0	0.15
Male	39 (59.1%)	8 (50%)	31(62%)	0.43
Fibrosis stage ≥2	43 (65.2%)	0 (0%)	43(86%)	**<0.001**
HAI >4	32 (48.5%)	0 (0%)	32 (64%)	**<0.001**
HBV DNA (10^3 IU/mL)	101.8±185.4	10.8±7.7	130.9±204.9	**<0.001**
ALT (U/L)	31.1±10.1	26.4±9.0	32.60±10.1	**0.03**
AST (U/L)	26.3±6.8	22.7±4.4	27.4±7.1	**0.01**
GGT (U/L)	25.8±15.1	28.5±17.0	24.9±14.6	0.42
ALP (U/L)	73.5±23.4	70.0±16.2	74.6±25.4	0.88
TG (mg/dL)	114.6±56.5	128.0±79.3	110.4±47.2	0.77
TCHOL (mg/dL)	178.2±32.4	175.9±36.9	179.0±31.2	0.74
Alb/Glob ratio	1.6±0.3	1.6±0.3	1.6±0.3	0.96
TSH (mU/L)	2.2±1.4	2.8±2.2	2.0±1.0	0.23
AFP (IU/mL)	4.0±3.5	3.1±2.7	4.3±3.6	0.07
Plt (10^9/L)	213.1±49.4	239.7±59.5	204.1±43.0	**0.03**
MPV (fL)	10.3±0.7	10.3±0.4	10.3±0.8	0.91
Sedimentation (mm/hr)	6.9±5.6	4.7±2.9	7.7±6.1	0.09

Values were given as mean ± standard deviation and categorical variables were given as numbers and percentages in parenthesis. HAI: Histology activity index, ALT: Alanine aminotransaferase, AST: Aspartate aminotransferase, GGT: γ-glutamyl transferase, ALP: Alkaline phosphatase, TG: Triglyceride, TCHOL: Total cholesterol, Alb/Glob ratio: Albumin/globulin ratio, TSH: Thyroidstimulating hormone, AFP: Alpha fetoprotein, Plt: Platelet, MPV: Mean platelet volume, fL: Femtolitre, BMI: Body mass index, HBV: Hepatitis B virus

Table 2. Simple correlation coefficients (r) between histological assessments and clinical and laboratory variables

	Fibrosis		HAI	
	Correlation coefficient	p	Correlation coefficient	p
Age	0.017	0.892	0.119	0.341
Disease age	**0.274**	**0.026**	0.069	0.581
BMI	0.144	0.247	0.139	0.267
Fibrosis	-	-	0.384	**0.001**
HAI	**0.384**	**0.001**	-	-
HBV DNA	**0.535**	**<0.001**	**0.646**	**<0.001**
ALT	**0.319**	**0.009**	**0.398**	**0.001**
AST	**0.414**	**0.001**	**0.427**	**<0.001**
GGT	-0.004	0.975	0.018	0.888
ALP	0.127	0.310	0.110	0.380
TG	-0.035	0.778	0.036	0.776
TCHOL	0.001	0.996	-0.019	0.883
Alb/Glob ratio	-0.060	0.631	0.036	0.776
TSH	-0.045	0.718	**-0.374**	**0.002**
AFP	0.125	0.317	**0.313**	**0.011**
Plt	-0.233	0.060	**-0.382**	**0.002**
MPV	0.108	0.388	0.054	0.668
Sedimentation	0.237	0.055	**0.268**	**0.030**

HAI: Histology activity index, ALT: Alanine aminotransaferase, AST: Aspartate aminotransferase, GGT: γ-glutamyl transferase, ALP: Alkaline phosphatase, TG: Triglyceride, TCHOL: Total cholesterol, Alb/Glob ratio: Albumin/globulin ratio, TSH: Thyroid stimulating hormone, AFP: Alpha fetoprotein, Plt: Platelet, MPV: Mean platelet volume, BMI: Body mass index, HBV: Hepatitis B virus

by HAI and Ishak scoring system. Parameters of HBV DNA, ALT ve AST correlated with fibrosis and HAI scores (p<0.001, p=0.001, p<0.001, respectively). To correlation other parameters with of fibrosis and HAI were either not meaningful or significant (Table 2). The fibrosis score was ≥2 and HAI was >4 in 88% of patients (30/34) and 76% (26/34) of patients with a HBV DNA level of higher than 20.000 IU/mL, respectively. At the same time, a fibrosis score of ≥2 and a HAI score of >4 were present in 40% of patients (13/32) and 19% (6/32) with a HBV DNA value between 2.000 and 20.000 IU/mL (p<0.001). Chronic hepatitis was detected in 94.1% (32/34) of patients with a HBV DNA level of higher than 20.000 IU/mL and in 56.2% (18/32) of patients with a HBV DNA level between 2.000 and 20.000 IU/mL (Figure 1). The specificity and sensitivity of HBV DNA 20.000 IU/mL in the detection of chronic hepatitis were found to be 64% and 87.5%, respectively.

Thirty-three (71.7%) patients had a fibrosis score of ≥2 and 26 patients (56.5%) had a HAI score of >4 in the HNALT group. Ten patients (50%) had a fibrosis score of ≥2 and 5 patients (25%) had a HAI score of >4 in the LNALT group (Figure 2). According to ROC analyses, when the serum ALT cut-off level was 19 U/L for women and 30 U/L for men, sensitivity and specifity in the detection of chronic hepatitis were found to be 75.5% and 47.1%, respectively.

We compared those under and above 40 years of age in order to analyze the relationship between age and chronic hepatitis. Twenty-three of the 31 patients (74.2%) had chronic hepatitis in the group aged below 40 years, while 28 (80%) of 35 patients had chronic

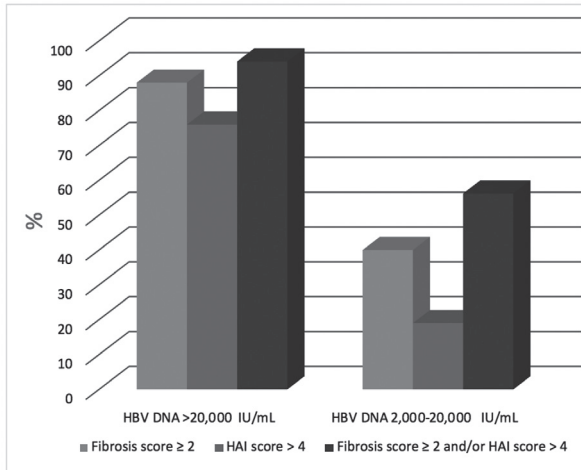

Figure 1. Relationship between HBV DNA levels and rates of chronic hepatitis
HBV: Hepatitis B virüs, HAI: Histology activity index

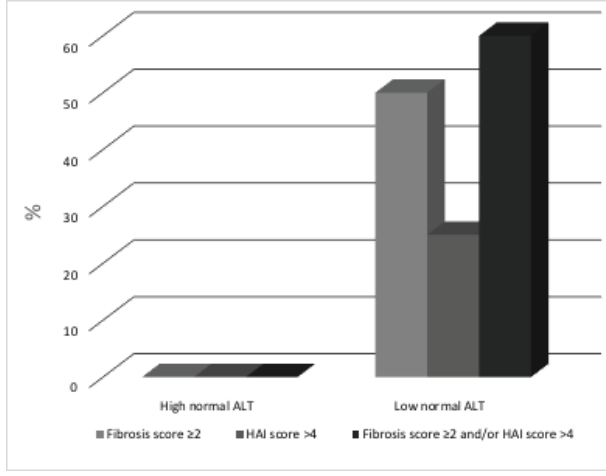

Figure 2. Relationship between serum alanine aminotransaferase levels and rates of chronic hepatitis
ALT: Alanine aminotransaferase, HAI: Histology activity index

hepatitis in the group aged above 40. There was no statistically significant correlation between age and the rate of chronic hepatitis (p>0.05). In addition, there was no statistically significant difference in the rate of chronic hepatitis between females and males [19/27 (70%) vs. 31/39 (79%), respectively p>0.05].

Discussion

It is important to predict chronic hepatitis in patients with HBeAg-negative chronic infection phase (formerly, this period called "inactive HBV carrier" state), because of the fact that while chronic hepatitis patients have a considerably high risk of complications such as HCC and cirrhosis, inactive carriers show a normal course. Liver biopsy is the method which is considered the gold standard test for this distinction (22). We showed in this study that chronic hepatitis rate is considerably higher in HBeAg-negative patients with a HBV DNA level of higher than or equal to the level of 2000 IU/mL and PNALT.

In studies carried out accross Europe**,** the incidence of chronic hepatitis ranges from 0.5% to 4% (13,14,18). Contrary to these

studies, in two studies from Asia, minimal necroinflammation levels (HAI score <4/18 Knodell or Desmet classification system) were detected to be 81% (77/95) and 40% (23/58) (16,17). In a study from United States including192 patients, it was observed that 37% of 59 patients with PNALT had significant fibrosis or inflammation (17). In studies conducted in European countries, fibrosis grade and HAI scores were significantly lower than in studies carried out in other regions.

In our study, the rate of chronic hepatitis was found to be similar to data from Asia. This rate is higher than that in the European populations and it may be due to exclusion of patients with HBV DNA lower than 2000 IU/mL and use of an upper limit of 45 U/L for ALT instead of 40 U/L. In addition, differences in age and genotypes at the time of HBV infection diagnosis between Europe and Asia may have contributed to this result. In the study of Dagtekin et al. (23) from our country, it was reported that need for treatment was determined in 56% of patients according to the biopsy results of 46 patients who had normal ALT, HBeAg-negative and HBV DNA values between 113 and 110.000.000 IU/mL. This result is in agreement with our findings

In our results, patients with a HBV DNA level of higher than 20.000 IU/mL had a higher HAI score, fibrosis level and rate of chronic hepatitis than in those with a HBV DNA value between 2000 and 20.000 IU/mL. In their study including 203 HBeAg-negative patients, Sanai et al. (24) reported that hepatic fibrosis ≥F2 was found in 52.9% (18/34) of patients with a HBV DNA of ≥20.000 IU/mL and PNALT and 18.9% (14/74) of patients with HBV DNA <20.000 IU/mL and PNALT. In a study conducted in Pakistan, the rates of patients with a fibrosis score of ≥2 and a HAI score of >4 were found to be 19% (8/42) and %35.7 (15/42), respectively (25). In a study by Kumar et al. (16), 29 patients with HBV DNA over 20.000 IU/mL were evaluated. Approximately 60% of patients had least moderate levels of necroinflammatory activity but this rate was found to be 15% in patients with HBV DNA between 2.000 and 20.000 IU/mL. In a study by Charatcharoenwitthaya et al. (20) carried out on 142 HBeAg-negative PNALT patients who had a HBV DNA of 2.000-19.999, 20.000-199.999 and ≥200.000 IU/mL, histological indication for treatment (at least grade A2 or stage F2 by METAVIR scoring) was present in 15%, 31%, and 36%, respectively. In the light of this information, it can be stated that level of HBV DNA is the most important parameter. HBV DNA level is an important indicator of disease activity and viral replication. In the literature, increased viral load has been shown to be an important risk factor for HCC and cirrhosis (26,27). We also propose that in the presence of a HBV DNA level over 20.000 IU/mL in HBeAg-negative patients with PNALT, biopsy is required, regardless of any other value. In this study, ALT was measured at least every 3 months and at least 3 times for with a minimum follow-up period of 1 year.

Some studies recommend close follow-up of ALT in patients with HBV DNA values higher than 20.000 IU/mL (14,20). Many studies reported cases of patients with HBV-DNA levels higher than or equal to 20.000 IU/mL and PNALT (15,16,20,23,24). Even though ALT levels correlate with liver cell necrosis and fibrosis, we assume that ALT cannot always correlate with chronic HBV infection like hepatitis C. Geographical origin, race, BMI, gender, abnormal lipid and carbohydrate metabolism, and alcohol use can affect the levels of ALT. Maybe it is important to set an upper limit for ALT. Recent studies (19,20) and guidelines (7,12,13) showed that the normal upper limit of ALT should be lowered to 19 U/L for women and to 30 U/L for men, but in most of studies including HBeAg-negative patients with PNALT, conventional values (basal normal range values) were frequently used. In a study using a conventional ALT value of 40 U/L (20), if the ALT level was determined as 19 U/L for women and 30 U/L for men, there would be no significant differences between groups of LNALT and HNALT according to histological indication for treatment (18% vs. 28%, p=0.2). In another study that separated the two groups according to upper or lower ALT level of 23 U/L, no considerable differences were found between groups of HNALT and LNALT for fibrosis and HAI score (p=0.86 and p=0.091, respectively) (28). In our study, HBV DNA level, fibrosis and HAI scores were significantly higher in HNALT group than in LNALT group (p<0.001, p=0.031, p=0.005, respectively). We assume this is important because a slightly increased ALT but still within the normal ranges, is associated with increased risk of death from liver disease, as was shown in a study (29). However, this relationship is not as strong as with HBV DNA.

In this study, it was found that there was no difference in HAI score and fibrosis level between genders. In a study from Iran including 132 HBeAg-negative CHB patients with PNALT genotype D, hepatitis, fibrosis and histological activity scores were higher in men than women (28). Fattovich et al. (11) have reported that advanced age, male gender and cirrhosis at entry and absence of sustained remission predicted liver-related death. However, we assume that there is no considerable association between age over 40 years and HAI fibrosis score.

Study Limitation

Our study has several limitations. Monitoring of patients could not be continued after biopsy due to the study design. Additionally, number of patients could have been higher. Also patients with a HBV DNA level of lower than 2000 IU/mL were excluded because of restriction of treatment according to the regulations of the social security institution.

Conclusion

In patients with HBeAg-negative chronic infection phase HBV DNA is the most significant value for determining chronic hepatitis. Age, gender, BMI, alkaline phosphatase, and other parameters, such as platelets, alpha fetoprotein were found not to be useful in chronic hepatitis distinction. We recommend starting treatment regardless of any other criteria if HBV DNA level is higher than 20.000 IU/mL and close monitoring or biopsy in patients with HBV DNA values within the limits of 2.000 and 20.000 IU/mL.

Ethics

Ethics Committee Approval: This study was approved by the Local Ethics Committee (Şişli Hamidiye Etfal Training and Research Hospital, approval number:12.01.2010, 1119).

Informed Consent: Written informed consent received.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practise: O.Ö., A.R.K., E.A., M.B., C.A., B.Y.Ö., Concept: O.Ö., S.Y., E.A., C.A., Desing: O.Ö., S.Y., A.R.K, E.A., C.A., B.Y.Ö., Data Collection or Processing: O.Ö., A.R.K,

E.A.,M.B., C.A., Analysis: O.Ö., S.Y., B.Y.Ö., Literature Search: O.Ö., S.Y., A.R.K., E.A., M.B., Writing: O.Ö., S.Y., E.A.

Conflict of Interest: All authors declare to have no conflict of interest.

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