DOI: 10.4274/vhd.galenos.2021.2021-7-1
Viral Hepatitis Journal 2022;28(1):1-6

Is Liver Biopsy Necessary in Patients with Chronic Hepatitis B with Normal Alanine Aminotransferase Level?

Alanin Aminotransferaz Düzeyi Normal Olan Kronik Hepatit B'li Hastalarda Karaciğer Biyopsisi Gerekli midir?

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ABSTRACT

Objectives: If not treated early, morbidity and mortality will remain high in hepatitis B virus infection. In this study, it was aimed to analyze the liver biopsy results of patients with chronic hepatitis B with normal alanine aminotransferase (ALT) levels.

Materials and Methods: The study was conducted retrospectively. The patients who were admitted in the infectious diseases and clinical microbiology outpatient clinic, had liver biopsy and received treatment between 01.09.2019 and 01.12.2019, were included.

Results: A total of 169 patients were included in the study. Of the individuals, 95 (56.2%) were female, with a mean age of 42.4±11.15 years. The rates of having an histological activity index (HAI) score of 6/18 and above and a fibrosis stage of 2/6 or more (90%, 100%, respectively) in patients with ALT level above upper limit of normal (ULN) were higher than in patients with ALT level belowULN (63.6% and 79.1%, respectively) (p=0.001 and p=0.002, respectively). When 129 patients with ALT level below ULN were evaluated in subgroup analyses. HAI score was 6 or higher in 59 (58.4%) of the hepatitis B e antigen (HBeAg) negative patients, and fibrosis stage was 2 or higher in 76 (75.2%) patients. In patients with ALT below ULN and HBeAg positivity, the rates of HAI score of 6 and above and fibrosis stage of 2 and above were found to be statistically significantly higher than in HBeAg negative patients.

Conclusion: Liver fibrosis and necroinflammation may develop in patients with normal ALT levels. In making the biopsy decision, ALT level should be considered together with other factors that may affect liver damage.

Keywords: Liver biopsy, normal ALT level, necroinflammation and fibrosis, HBeAg negativity

ÖZ

Amaç: Hepatit B virüsü enfeksiyonu erkenden tedavi edilmediği takdirde yüksek morbidite ve mortaliteye sahip olmaya devam etmektedir. Çalışmada alanin aminotranferaz (ALT) düzeyi normal seyreden kronik hepatit B'li hastaların karaciğer biyopsi sonuçlarının incelenmesi ve kendi klinik deneyimlerimizin paylaşılması amaçlandı.

Gereç ve Yöntemler: Bu retrospektif tanımlayıcı çalışmaya 01.09.2019-01.12.2019 tarihleri arasında enfeksiyon hastalıkları ve klinik mikrobiyoloji polikliniğince takip edilmiş, karaciğer biyopsisi yapılmış olan ve antiviral tedavi alan hastalar alındı.

Bulgular: Toplam 169 hasta çalışmaya dahil edildi. Bireylerin 95'i (%56,2) kadın idi ve ortalama yaş 42,4±11,15 yıldı. ALT değeri normalin üst sınırı (NÜS) ve üzerinde olan hastalarda histolojik aktivite indeksi (HAİ) skorunun 6 ve üzerinde, fibrozis evresinin ise 2 ve üzerinde saptanma oranları (sırasıyla; %90, %100), NÜS'nin altında olan hastalara göre (sırasıyla; %63,6, %79,1) daha yüksek olup fark istatistiksel açıdan anlamlıydı (sırasıyla; p=0,001, p=0,002). Alt grup analizlerinde ALT değeri NÜS'nin altında olan 129 hasta değerlendirildiğinde; hepatit B e antijeni (HBeAg) negatif olan hastaların 59'unda (%58,4) HAİ skoru 6 ve üzerinde, 76'sında da (%75,2) fibrozis evresi 2 ve üzerinde bulundu. ALT değeri NÜS'nin altında ve HBeAg pozitif olan hastalarda, negatif olanlara göre HAİ skoru 6 ve üzerinde olma oranı ve fibrozis evresi 2 ve üzerinde olma oranı istatistiksel açıdan anlamlı olarak daha yüksek bulundu (sırasıyla; p=0,021, p=0,043).

Sonuç: Bu çalışma ile ALT düzeyi normal hastalarda da karaciğerde fibrozis ve nekroenflamasyon gelişebileceği görülmüştür. Biyopsi kararının verilmesinde ALT düzeyi, karaciğer hasarını etkileyebilen diğer faktörlerle birlikte göz önünde bulundurulmalıdır.

Anahtar Kelimeler: Karaciğer biyopsisi, normal ALT düzeyi, nekroinflemasyon ve fibrozis, HBeAg negatifliği

Cite this article as: Yıldız İE, Bahçeci İ, Ilgar T, Beyazal M, Kostakoğlu U, Ertürk A. Is Liver Biopsy Necessary in Patients with Chronic Hepatitis B with Normal Alanine Aminotransferase Level?. Viral Hepatitis Journal 2022;28(1):1-6

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Introduction

Hepatitis B virus (HBV) infection; it is an important public health problem that progresses to cirrhosis, hepatocellular carcinoma (HCC) and liver failure, has high morbidity and mortality, affects the country's economy and continues to affect globally (1,2).

It is reported that more than 2 billion people worldwide are infected with HBV, approximately 240-257 million individuals progress to chronic HBV infection or chronic hepatitis, and approximately one million people is expected to die annually. HBV is the most common cause of chronic hepatitis and death due to liver failure in Turkey. If HBV-infected individuals are not diagnosed and treated early, they usually present with various complications in the future. In the report published by the World Health Organization in 2020, it is stated that HBV-related deaths prevent infections such as malaria, tuberculosis and human immunodeficiency virus (HIV), which are among the top ten causes of death in recent years (1,2,3,4,5,6).

In chronic hepatitis B patients, it is very important to start treatment before disease-related morbidity and mortality develops (4,5,6). Early treatment contributes to the reduction of social contagion as well as increasing the quality of life of the individual. Countries have their own consensus on initiating treatment and in Turkey, the treatment decision is made according to the liver biopsy results of the patients (4,7). In the evaluation of liver damage, the biopsy decision is applied in line with the recommendations of the international and national guidelines, but there is no clear consensus in the guidelines on this issue. There is no standard for reference ranges of liver enzymes in our country and there may be changes on a laboratory basis (4,7,8). In our study, it was aimed to examine the liver biopsy results of chronic hepatitis B patients with normal alanine aminotransferase (ALT) levels, to evaluate our results using different ALT upper limits of normal determined by our own laboratory and internationally, and to share our own clinical experiences.

Materials and Methods

The study was conducted as a retrospective study. This study was approved by the Recep Tayyip Erdoğan University Non-Interventional Clinical Research Ethics Committee (approval number: 2019/129, date: 17.07.2019). Patients over the age of 18, who were diagnosed with chronic hepatitis B infection and who were over 18 years of age, who had a liver biopsy and received treatment at the Recep Tayyip Erdoğan University Faculty of Medicine and Training and Research Hospital, Infectious Diseases and Clinical Microbiology Outpatient Clinic between 01.09.2019 and 01.12.2019 were included in the study. Patients with malignancy, pregnancy, metabolic or immunological disease, concomitant viral liver disease, immunosuppressive therapy and chemotherapy, and those with missing data were excluded from the study.

Demographic data and laboratory data of the patients were reviewed retrospectively from patient files and hospital electronic records, modified histological activity index (HAI) scores and fibrosis stage defined by Ishak scoring system (7). ALT values measured at the time of liver biopsy of the patients were recorded. Hepatitis serology was evaluated by hepatitis B surface antigen, anti-HBs, hepatitis B e antigen (HBeAg), anti-HBe "ELISA" method. HBV-DNA levels were studied by polymerase chain reaction. All these values were recorded in the prepared study form. The upper limit of ALT (ULN) was accepted as 55 U/L, which was the upper limit value studied by the microbiology laboratory of our hospital between 01.09.2019 and 01.12.2019. However, in the study of Kwo et al. (8), an evaluation was made according to the actual healthy ALT levels that were stated to be in the population, and the upper limit values for ALT of 25 U/L for women and 33 U/L for men were taken as ULN-2 in our study.

Statistical Analysis

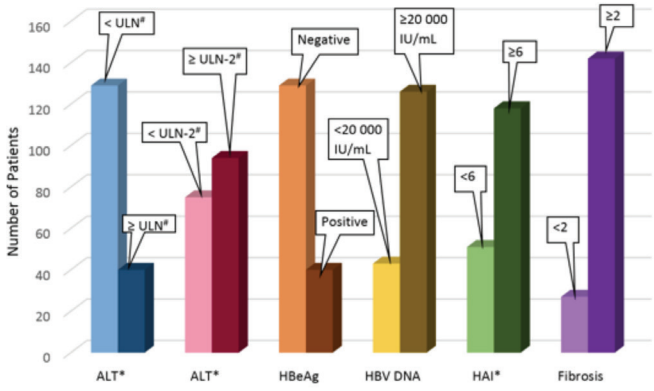
Statistical analysis of the study was performed with the IBM SPSS version 23.0 (Armonk, NY: IBM Corp) program. The conformity of the variables to the normal distribution was examined using analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Descriptive analyzes were given using the mean for normally distributed data and the median for non-normally distributed data. Cross tables were used for statistical evaluation, independent groups t-test was used for variables with normal distribution, and Kruskal-Wallis test was used for those not normally distributed. The cross-tables were compared to see if there was a difference between the groups, using chi-square and Fisher's exact tests when the values observed in the cells did not meet the chi-square test assumptions. P-value below 0.05 were considered as statistically significant.

Results

The data of 241 patients with a diagnosis of chronic hepatitis B who received antiviral therapy were evaluated. Seventy-two of the patients were excluded from the study due to missing data, co-infection with chronic hepatitis C or HIV, a total of 169 patients were included in the study. Ninety-five (56.2%) of the patients were female. Their mean age was 42.4±11.15 (18-73) years. Hundred and three of the individuals (60.9%) were aged 40 years and over. Considering the laboratory values determined when liver biopsy of the patients was performed; the median ALT value was 30 (7-1007) U/L. ALT value was found to be ULN or higher in 40 patients (23.7%), and ULN-2 and higher in 94 patients (55.6%). HBeAg was positive in 129 (76.3%) of the patients. Median HBV-DNA values were found to be 176,063 (2,263-17.3x10^9) IU/mL. The HBV-DNA value of 126 (74.6%) patients was found to be over 20,000 IU/mL (Graphic 1).

Liver biopsy results of the patients presented, the median HAI score was 6 (2-16), and the median fibrosis score was 2 (0-6). HAI score was 6 or higher in 118 patients (69.8%) and fibrosis stage 2 or higher in 142 patients (84%) (Graphic 1).

There was no statistically significant difference in the mean age of the patients between patients with a HAI score of less than 6, patients with a score of 6 and above, and patients with fibrosis stage 2 and patients with a HAI score of 2 and above (p=0.440, p=0.435, respectively) (Table 1). In terms of HAI score and fibrosis stage values; no statistically significant difference was found between patients aged 40 and over and those under (p=0.316, p=0.274), and between women and men (p=0.072, p=0.106, respectively) (Table 2).



Graphic 1. Distribution of patients according to laboratory values and liver histopathology

*ALT: Alanine aminotransferase, HAI: Histological activity index, #: ULN: The upper limit of normal was accepted as 55 U/L, which was taken as the upper limit by our laboratory. ULN-2: Upper limit of normal-2; 25 U/L for women and 33 U/L for men

HAI score was 6 or higher in 35 (87.5%) of 40 patients who were positive for HBeAg at the time of liver biopsy, and 83 (64.3%) of 123 negative patients. However, fibrosis stage 2 and above was found in 38 (95%) of the HBeAg positive patients and 104 (80.6%) of the negative patients. The rates of HBeAg positive patients with a HAI score of 6 and above and a fibrosis stage of 2 and above were found to be statistically significantly higher than in HBeAg negative patients (p=0.005, p=0.030, respectively (Table 2).

The median ALT values of the patients; in patients with HAI score of 6 and above [40 U/L minimum (min)-maximum (max): 11-1007 U/L], compared to patients with less than 6 (21 U/L, min-max: 7-153 U/L), and in patients with fibrosis stage 2 and above (36 U/L, min-max: 7-1,007 U/L), compared to patients with fibrosis stage 2 (20 U/L, min-max: 11-52 U/L) statistically were found to be significantly higher in terms of terms (p=0.000, p=0.000, respectively) (Table 1). The rates of HAI score of 6 and above and fibrosis stage of 2 and above in patients with ALT value of ULN and above (90%, 100%, respectively), compared to patients with ALT below ULN (63.6% and 79.1%, respectively) were statistically significant. were found to be significantly higher (p=0.001, p=0.002, respectively). The rates of having an HAI score of 6 and above and fibrosis stage of 2 and above were found to be statistically significantly higher in patients with ALT of ULN-2 and above, compared to patients with a lower ALT (p=0.000, p=0.001, respectively) (Table 2).

Median HBV-DNA values; in patients with a HAI score of 6 and above (507,408.5 IU/mL), compared to patients with a HAI score of less than 6 (12,170 IU/mL), and in patients with a fibrosis score of 2 or above (335,020.5 IU/mL), compared to patients with a HAI score of less than 6 (11,936 IU) /mL) was found to be statistically significantly higher (p<0.001, p<0.001, respectively) (Table 1). In patients with HBV-DNA level of 20,000 IU/mL and above, the rates of detection of HAI score of 6 and above, and fibrosis stage of 2 and above (79.4%, 89.7%, respectively); it was found to be statistically significantly more common than patients with <20,000 IU/mL (41.9% and 67.4%, respectively) (p<0.001, p=0.001, respectively) (Table 2).

When 129 patients with ALT values below ULN were evaluated in subgroup analyses; HAI score was 6 or higher in 59 (58.4%) HBeAg negative patients, and fibrosis stage 2 or higher in 76 (75.2%) patients. HAI score was 6 and above in 23 (82.1%) of HBeAg positive patients, and fibrosis stage 2 and above in 26 (92.6%) patients. In patients with ALT below ULN and positive for HBeAg, the rate of HAI score of 6 and above and fibrosis stage 2 and above were found to be statistically significantly higher than in HBeAg negative patients (p=0.021, p=0.043, respectively). When patients with an ALT value below ULN-2 were evaluated, no statistically significant difference was found between HBeAg negative and positive patients in terms of HAI score of 6 and above and fibrosis stage 2 and above (p=0.069, p=0.102, respectively), (Table 3).

In patients with ALT below ULN, 18 (42.9%) patients with HBV-DNA levels below 20,000 IU/mL had HAI score of 6 and above, and 28 (66.7%) had fibrosis stage 2 and above. Of the patients with HBV-DNA level of 20,000 IU/mL and above, 64 (73.6%) had a HAI score of 6 and above, and fibrosis stage 2 and above in 74 (85.1%). In patients with ALT below ULN and HBV-DNA level of 20,000 IU/mL and above, the rate of HAI score of 6 and above and fibrosis stage 2 and above were found to be statistically significantly higher than those with a lower ALT level (p=0.001 and p= 0.016, respectively). When patients with ALT values below ULN-2 are evaluated, the rate of HAI score of 6 and above in patients with HBV-DNA level of 20,000 IU/mL and above (73.7%) compared to the rate of patients with HBV-DNA level below (37.8%) was found to be statistically significantly higher (p=0.002). However, no statistically significant difference was found between patients

Table 1. Distribution of patients' age, alanine aminotransferase and HBV-DNA values according to liver histopathology results

	Age (years) [mean ± standard deviation]#	p	ALT* (U/L) [median (min-max)]#	p	HBV-DNA (IU/mL) [median (min-max)]#	p
HAI* score						
<6 (n=51)	43.4±11.02	0.440	21 (7-153)	<0.001	12,170 (2,263-13,076x10^9)	<0.001
6 (n=118)	41.9±11.22		40 (11-1007)		507,408.5 (2,737-17,3x10^9)	
Fibrosis stage						
<2 (n=27)	43.9±12.12	0.435	20 (11-52)	<0.001	11,936 (2,263-2,299x10^9)	<0.001
≥2 (n=142)	42.1±10.97		36 (7-1007)		335,020.5 (2,737-17,3x10^9)	

*ALT: Alanine aminotransferase, HAI: Histological activity index, HBV: Hepatitis B virus, #: The mean ± standard deviation values were given for the data conforming to the normal distribution, and the median (minimum-maximum) values were given for the data that did not

with HBV-DNA level of 20,000 IU/mL and above and those with below in terms of the rate of fibrosis stage 2 and above (p=0.123) (Table 3).

Discussion

HBV infection is a global public health problem and has attracted attention with its increasing morbidity and mortality rates in recent years. There is no clear consensus on which patient group should be biopsied for initiation of treatment in HBV-infected individuals, and there is no common recommendation in the guidelines regarding biopsy, especially in patients with negative HBeAg and normal ALT levels (2,3,4,5). Countries have experience in line with their own guides. As a result of our research, which is one of the first studies conducted in our country on this subject, significant fibrosis and necroinflammation in the liver were found in patients with high ALT levels as well as patients with normal ALT levels. It seems ALT alone is not sufficient and should be evaluated together

Table 2. Distribution of liver histopathology results of the patients

	HAI* score (n, %)		p	Fibrosis stage (n, %)		p
	<6	≥6		<2	2	
Age (years)						
<40	17 (25.8)	49 (74.2)	0.316	8 (12.1)	58 (87.9)	0.274
≥40	34 (33.0)	69 (67.0)		19 (18.4)	84 (81.6)	
Gender						
Female	34 (35.8)	61 (64.2)	0.072	19 (20.0)	76 (80.0)	0.106
Male	17 (23.0)	57 (77.0)		8 (10.8)	66 (89.2)	
HBeAg						
Negative	46 (35.7)	83 (64.3)	0.005	25 (19.4)	104 (80.6)	0.030
Positive	5 (12.5)	35 (87.5)		2 (5.0)	38 (95.0)	
ALT*						
<ULN#	47 (36.4)	82 (63.6)	0.001	27 (20.9)	102 (79.1)	0.002
≥ULN#	4 (10.0)	36 (90.0)		0 (0)	40 (100)	
AST						
<ULN-2#	33 (44)	42 (56)	<0.001	20 (26.7)	55 (73.3)	0.001
≥ULN-2#	18 (19.1)	76 (80.9)		7 (7.4)	87 (92.6)	
HBV-DNA (IU/mL)						
<20,000	25 (58.1)	18 (41.9)	<0.001	14 (32.6)	29 (67.4)	0.001
≥20,000	26 (20.6)	100 (79.4)		13 (10.3)	113 (89.7)	

*ALT: Alanine aminotransferase, HAI: Histological activity index, HBV: Hepatitis B virus, #ULN: The upper limit of normal was accepted as 55 U/L, which was taken as the upper limit of normal by our laboratory. ULN-2: Upper limit of normal-2; 25 U/L for women and 33 U/L for men

Table 3. Distribution of liver histopathology results of patients with ALT levels below the upper limit of normal

	HAI* score (n, %)		p	Fibrosis stage (n, %)		p
	<6	≥6		<2	≥2	
ALT < ULN#*						
HBeAg						
Negative	42 (41.6)	59 (58.4)	0.021	25 (24.8)	76 (75.2)	0.043
Positive	5 (17.9)	23 (82.1)		2 (7.1)	26 (92.9)	
HBV-DNA (IU/mL)						
<20,000	24 (57.1)	18 (42.9)	0.001	14 (33.3)	28 (66.7)	0.016
≥20,000	23 (26.4)	64 (73.6)		13 (14.9)	74 (85.1)	
ALT <ULN -2#*						
HBeAg						
Negative	32 (48.5)	34 (51.5)	0.069	20 (30.3)	46 (69.7)	0.102
Positive	1 (11.1)	8 (88.9)		0 (0)	9 (100)	
HBV-DNA (IU/mL)						
<20,000	23 (62.2)	14 (37.8)	0.002	13 (35.1)	24 (64.9)	0.123
≥20,000	10 (26.3)	28 (73.7)		7 (18.4)	31 (81.6)	

*ALT: Alanine aminotransferase, HAI: Histological activity index, HBV: Hepatitis B virus, #ULN: The upper limit of normal was accepted as 55 U/L, which was taken as the upper limit by our laboratory. ULN-2: Upper limit of normal-2; 25 U/L for women and 33 U/L for men

with other factors that may affect liver damage when deciding on liver biopsy to initiate treatment.

Considering the studies in the literature examining the relationship between ALT level and liver histopathology; in the study of Lai et al. (9), 37% of the patients whose ALT levels were consistently normal were found to have significant fibrosis or inflammation (10). In the study of Park et al. (11), significant fibrosis was reported in 61.9% of patients whose ALT level was 2 times or less than ULN. In our study, although the ALT level was below ULN or ULN-2, the percentage of patients with HAI score of 6 and above (63.6% and 56%, respectively) and the percentage of patients with fibrosis stage 2 and above (79.1% and 73.3%, respectively) were detected high. In patients with ALT levels below ULN or UL-2, the rates of high HAI score or fibrosis stage were generally higher than mentioned in the literature. It has been mentioned in studies that ALT may be insufficient to show liver damage, may be affected by various factors such as herbal medicine use in the course of the disease, and may be seen as lower than its true value and may be misleading. In addition, it has been reported that fibrosis and necroinflammation in the liver are affected by many factors such as age, gender, serum HBV-DNA level (11,12,13,14,15,16,17). In addition, factors such as family history, age at onset of the disease, smoking-alcohol use may also cause liver damage. In our study, the detection of significant fibrosis and necroinflammation in the liver in patients with normal ALT levels compared to previous studies may be related to these additional factors affecting liver damage.

It has been observed that there are different recommendations in the guidelines regarding liver biopsy indications in patients with HBeAg negative and ALT levels within normal limits. APASL 2016 guideline recommended liver biopsy to determine fibrosis status if patients are over 35 years old. However, biopsy is not recommended for these patients in the current AASLD and EASL guidelines (3,4,5,6). In the literature, different results have been found in studies on this subject. In the study of Liao et al. (12), the rates of detecting significant fibrosis in the liver in patients with normal ALT levels were reported as 49.4% in HBeAg positive patients and 30.9% in HBeAg negative patients. In our study, the HAI score was 6 or higher in 83 (64.3%) of 129 patients who were HBeAg negative. In 104 (80.6%) fibrosis stage 2 and above were detected. However, in our study, it was found that although HBeAg was negative in patients with normal ALT levels, significant necroinflammation (58.4% in those below ULN, 51.5% in those below ULN-2) and fibrosis (75.5% for those below ULN, 69.7% for those below UL-2) could be seen at high rates. In our study, the percentage of HBeAg-negative patients with elevated HAI score or fibrosis stage was found to be higher than in the literature. This situation may be related to epidemiological factors. In a systematic review, it was reported that histologically significant liver damage is rare in patients with HBV-DNA level below 20,000 IU/mL, HBeAg negative, and ALT level normal, and that liver biopsy is not required and patients should be followed up (13). In the study of Abdo et al. (14), the rate of detection of necroinflammation 2 and above was 10.2%, and the rate of detection of fibrosis stage 2 and above was 13.6% in patients whose HBV-DNA level was below 20,000 IU/mL and ALT level was normal. In our study, in patients with ALT levels within normal limits and HBV-DNA levels below 20,000 IU/mL, significant necroinflammation (42.9% in patients below ULN, 37.8% in patients below ULN-2) and fibrosis (66.7% of patients with ULN below and 64.9% of those with ULN-2) were observed. In our study, in patients with normal ALT levels, significant necroinflammation and fibrosis were detected at higher rates compared to the literature, although HBeAg negative or HBV-DNA was below 20,000 IU/mL. In these patients, there may be regional differences and factors such as age of the disease, presence of hepatitis in the family, alcohol-smoking, drug use, which may affect liver damage but not evaluated in our study.

Initiation of treatment without delay in hepatitis B infection; is very important in terms of preventing the progression of the disease, increasing the life span and quality, and reducing the development of extrahepatic complications, cirrhosis and HCC (18,19,20). It has been reported that antiviral treatment inhibits HBV replication, reduces necroinflammatory activity, limits the progression of fibrosis, and reduces the risk of HCC. It is stated that decompensated liver cirrhosis and HCC develop in 25-40% of chronic hepatitis B patients who do not receive appropriate treatment, and more than 1 million of these patients die each year. Today, it has been stated that the most effective method to prevent the clinical progression of HBV infection is treating patients with antiviral therapy (4,5,6,7,14). Although it differs according to the countries, it has been observed that there are some obligations before starting the treatment. In Turkey, liver biopsy is required to initiate treatment. Antiviral treatment could be started in patients with HAI score of 6 and above or fibrosis stage 2 and above (7). In addition, it has been determined that there are differences of opinion and difficulties in the decision of biopsy in the literature and the real world. While some clinicians argue that patients with normal liver enzymes should be followed without biopsy, others seem to believe that they should be evaluated for treatment by performing a biopsy. It is thought that sharing the results of studies on this subject may contribute to the formation of a common consensus.

Study Limitations

These outputs will be shared with VHSD and TKAD and can be used as references in a possible national guideline update. Although it is known that various factors such as having a family history of chronic hepatitis or cirrhosis, duration of the disease, alcohol-cigarette use, etc. may have an effect in determining liver damage, the fact that these factors were not evaluated due to the retrospective nature of our study was considered as an important limitation of our study. In addition, another limitation of our study is that the ULN value of ALT of our hospital at the time of the study were 55 for both men and women. However, our data were also evaluated according to the actual healthy ALT levels that should be present in the population as stated in the study of Kwo et al. (8). The ALT values recommended for our country in the study of Degertekin et al. (21) are quite close to the values in the study of Kwo et al. (8).

Conclusion

In our study, it was found that patients with ALT levels within normal limits could have significant fibrosis or necroinflammation in the liver, even though they were HBeAg negative or HBV-DNA level

was below 20,000 IU/mL. It has been observed that only laboratory values can be misleading in the decision to perform liver biopsy and start treatment. In this context, ALT elevation alone should not be taken as a reference in making the biopsy decision for the initiation of treatment. It should be considered that patients should be evaluated as a whole with additional factors that may affect liver damage. However, it is thought that a standardization should be made in the evaluation of the ALT normal range in Turkey and further studies are needed on this subject. Considering reference values separately for men and women and using the common reference values can contribute more to data of our country.

Ethics

Ethics Committee Approval: This study was approved by the Recep Tayyip Erdoğan University Non-Interventional Clinical Research Ethics Committee (approval number: 2019/129, date: 17.07.2019).

Informed Consent: Informed consent of patients couldn't obtained due to retrospective design of study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İ.E.Y., İ.B., T.I., M.B., U.K., A.E., Concept: İ.E.Y., İ.B., T.I., M.B., U.K., A.E., Data Collection or Processing: İ.E.Y., T.I., Analysis or Interpretation: İ.E.Y., T.I., Literature Search: İ.E.Y., T.I., Writing: İ.E.Y., T.I.

Conflict of Interest: The authors of this article declare that they have no conflict of interest.

Financial Disclosure: The authors declare that this study has not received any financial support.

References

1. Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH; American Association for the Study of Liver Diseases. AASLD guidelines for treatment of chronic hepatitis B. Hepatology. 2016;63:261-283.
2. Chen DS, Locarnini S, Wait S, Bae SH, Chen PJ, Fung JY, Kim HS, Lu SN, Sung J, Tanaka J, Wakita T, Ward J, Wallace J; CEVHAP North Asia Workshop on Viral Hepatitis. Report from a Viral Hepatitis Policy Forum on implementing the WHO Framework for Global Action on viral hepatitis in North Asia. J Hepatol. 2013;59:1073-1080.
3. Shiha G, Ibrahim A, Helmy A, Sarin SK, Omata M, Kumar A, Bernstien D, Maruyama H, Saraswat V, Chawla Y, Hamid S, Abbas Z, Bedossa P, Sakhuja P, Elmahatab M, Lim SG, Lesmana L, Sollano J, Jia JD, Abbas B, Omar A, Sharma B, Payawal D, Abdallah A, Serwah A, Hamed A, Elsayed A, AbdelMaqsod A, Hassanein T, Ihab A, GHaziuan H, Zein N, Kumar M. Asian-Pacific Association for the Study of the Liver (APASL) consensus guidelines on invasive and non-invasive assessment of hepatic fibrosis: a 2016 update. Hepatol Int. 2017;11:1-30.
4. Turkish Liver Research Association and Viral Hepatitis Combating Association. Turkey Viral Hepatitis Diagnosis and Treatment Guidelines. 2017. https://www.vhsd.org/tr/article/desc/48317/tu-rkiye-viral-hepatitler-tani-ve-tedavi-kilavuzu-2-7.html
5. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, Brown RS Jr, Bzowej NH, Wong JB. Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance. Clin Liver Dis (Hoboken). 2018;12:33-34.
6. European Association for the Study of the Liver. European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67:370-398.
7. Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F, Denk H, Desmet V, Korb G, MacSween RN, et al. Histological grading and staging of chronic hepatitis. J Hepatol. 1995;22:696-699.
8. Kwo PY, Cohen SM, Lim JK. ACG Clinical Guideline: Evaluation of Abnormal Liver Chemistries. Am J Gastroenterol. 2017;112:18-35.
9. Lai M, Hyatt BJ, Nasser I, Curry M, Afdhal NH. The clinical significance of persistently normal ALT in chronic hepatitis B infection. J Hepatol. 2007;47:760-767.
10. Papatheodoridis GV, Manolakopoulos S, Liaw YF, Lok A. Follow-up and indications for liver biopsy in HBeAg-negative chronic hepatitis B virus infection with persistently normal ALT: a systematic review. J Hepatol. 2012;57:196-202.
11. Park JY, Park YN, Kim DY, Paik YH, Lee KS, Moon BS, Han KH, Chon CY, Ahn SH. High prevalence of significant histology in asymptomatic chronic hepatitis B patients with genotype C and high serum HBV DNA levels. J Viral Hepat. 2008;15:615-621.
12. Liao B, Wang Z, Lin S, Xu Y, Yi J, Xu M, Huang Z, Zhou Y, Zhang F, Hou J. Significant fibrosis is not rare in Chinese chronic hepatitis B patients with persistent normal ALT. PLoS One. 2013;8:e78672.
13. Moreno-Cubero E, Arco RTSD, Peña-Asensio J, Villalobos ES, Míquel J, Larrubia JR. Is it possible to stop nucleos(t)ide analogue treatment in chronic hepatitis B patients? World J Gastroenterol. 2018;24:1825-1838.
14. Abdo AA, Bzeizi KI, Babatin MA, AlSohaibani F, AlMana H, Alsaad KO, AlGhamdi H, Al-Hamoudi W, AlSwat K, AlFaleh FZ, Myers RP, Sanai FM. Predictors of significant fibrosis in chronic hepatitis B patients with low viremia. J Clin Gastroenterol. 2014;48:e50-e56.
15. Chen EQ, Huang FJ, He LL, Bai L, Wang LC, Zhou TY, Lei XZ, Liu C, Tang H. Histological changes in chinese chronic hepatitis B patients with ALT lower than two times upper limits of normal. Dig Dis Sci. 2010;55:432-437.
16. Keeffe EB, Dieterich DT, Han SH, Jacobson IM, Martin P, Schiff ER, Tobias H, Wright TL. A treatment algorithm for the management of chronic hepatitis B virüs infection in the United States: an update. Clin Gastroenterol Hepatol. 2006;4:936-962.
17. Kumar M, Sarin SK, Hissar S, Pande C, Sakhuja P, Sharma BC, Chauhan R, Bose S. Virologic and Histological Features of Chronic Hepatitis B Virus-Infected Asymptomatic Patients with Persistently Normal ALT. Gastroenterology. 2008;134:1376-1384.
18. Tsang PS, Trinh H, Garcia RT, Phan JT, Ha NB, Nguyen H, Nguyen K, Keeffe EB, Nguyen MH. Significant prevalence of histologic disease in patients with chronic hepatitis B and mildly elevated serum alanine amino transferase levels. Clin Gastroenterol Hepatol. 2008;6:569-574.
19. Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, Huang GT, Iloeje UH; REVEAL-HBV Study Group. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA. 2006;295:65-73.
20. Iloeje UH, Yang HI, Su J, Jen CL, You SL, Chen CJ; Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-In HBV (the REVEAL-HBV) Study Group. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. Gastroenterology. 2006;130:678-686.
21. Degertekin B, Tozun N, Demir F, Soylemez G, Yapali S, Bozkurt U, Gurtay E, Seymenoglu TH, Mutlu D, Toraman M. Determination of the upper limits of normal serum alanine aminotransferase (ALT) level in healthy Turkish population. Hepatology Forum. 2020;2:44-47.