Research Article

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Relationship Between Basic Laboratory Results and Fibrosis in Chronic Hepatitis B Patients

Kronik Hepatit B Hastalarında Temel Laboratuvar Sonuçları ile Fibrozis Arasındaki İlişki

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ABSTRACT

Objectives: Liver biopsy (LB) is an important cornerstone in decision to start treatment for chronic hepatitis B (HB). Viral load and liver function tests are performed to determine the most appropriate time. In this study, factors affecting liver fibrosis in hepatitis B e antigen (HBeAg) negative chronic hepatitis B patients were investigated.

Materials and Methods: LB and the other laboratory results such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), and hepatitis B virus (HBV)-DNA were collected from patient files, retrospectively. According to study protocol, necroinflammatory scores ≤4 and fibrosis scores ≤1 were accepted as normal liver (NL), and the high value in one of these scores was accepted as chronic hepatitis (CH).

Results: A total of 234 patient's LBs included in the study. A total of 74 (31.6%) patients' LB was evaluated as NL. In univariate analysis, age, gender, ALT, AST, GGT, AFP and HBV-DNA >100.000 IU/mL, and in multivariate analysis, age, AST level >29 U/L, and AFP level >2.5 ng/mL were the independent risk factors for CH.

Conclusion: According to our results, age, AST and AFP predict CH. Doctors who follow up chronic hepatitis B patients should be carefully evaluate these parameters when giving LB decision.

Keywords: Chronic hepatitis B, Liver biopsy, Fibrosis

ÖZ

Amaç: Kronik hepatit B tedavisine başlama kararını vermede karaciğer biyopsisi önemli bir mihenk taşıdır. Uygun zamanı belirlemek için viral yük ve karaciğer fonksiyon testleri ile takip yapılmaktadır. Bu çalışmada hepatit B e antigen (HBeAg) negatif kronik hepatit B hastalarında karaciğer fibrozisini etkileyen faktörler araştırıldı.

Gereç ve Yöntemler: Karaciğer biyopsisi ve alanin aminotransferaz (ALT), aspartat aminotransferaz (AST), gama-glutamil transpeptidaz (GGT) ve hepatit B virüs (HBV)-DNA gibi laboratuvar testleri geriye dönük olarak hasta dosyalarından toplandı. Çalışma protokolüne göre nekroenflamatuvar skor ≤4 ve fibrozis skoru ≤1 tespit edilenler normal karaciğer (NK), bu skorlardan birindeki yüksek değer kronik hepatit (KH) olarak kabul edildi.

Bulgular: Çalışmaya toplam 234 hastanın karaciğer biyopsisi dahil edildi. Toplam 74 (%31,6) hastanın biyopsi sonucu NK olarak kabul edildi. Tek değişkenli analizlerde yaş, cinsiyet, ALT, AST, GGT, AFP ve HBV-DNA >100,000 IU/mL düzeyi NK ve KH arasında istatistiksel olarak farklıydı. Çok değişkenli analizlerde ise yaş, AST >29 U/L ve AFP >2,5 ng/mL düzeyi KH için bağımsız risk faktörüydü.

Sonuç: Sonuçlarımıza göre, yaş, AST ve AFP, KH'yi öngörmektedir. Kronik hepatit B hastalarını izleyen doktorlar, karaciğer biyopsisi kararı alırken bu parametreleri dikkatli bir şekilde değerlendirmelidir.

Anahtar Kelimeler: Kronik hepatit B, karaciğer Biyopsisi, Fibrozis

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Introduction

Hepatitis B virus (HBV) infect the liver and can lead to a broad spectrum of disease, ranging from an inactive carriage to cirrhosis and hepatocellular carcinoma (HCC) (1). The overall hepatitis B surface antigen (hBsAg) seropositivity in Turkey was 4% (2.3% in the western and 7.3% in the eastern regains (2).

Chronic hepatitis B (CHB) may present either as hepatitis B e antigen (HBeAg)-positive or HBeAg-negative. HBeAg-negative form of the disease has been increasing. In Turkey, HBeAg-negative form is the most prevalant form (90%) (3). European Association for the Study of the Liver guidelines recommended antiviral therapy for HBeAg-negative CHB patients if their liver biopsy showing at least moderate necroinflammation and/or at least moderate fibrosis when their alanine aminotransferase (ALT) level higher than the upper limit of normal (ULN) and HBV-DNA levels above 2.000 IU/mL. Patients with HBV-DNA >20.000 IU/mL and ALT >2 x ULN can start treatment even without a liver biopsy (1). However, approximately one third of patients who have persistently normal ALT levels have moderate inflammation and/or advanced fibrosis, particularly patients older than 35 years old (4,5). So, the sufficiency of monitoring HBeAg-negative patients with ALT is controversial. Liver biopsy is often recommended for determining the degree of necroinflammation and fibrosis since hepatic histology can asist the decision to start treatment (6). In this study, we aimed to investigate factors that affect the degree of necroinflammation and fibrosis in liver biopsiy, in HBeAg-negative CHB patients.

Matherials and Methods

This study was conducted in a tertiary care hospital. Liver biopsy results between 2009 and 2013 were collected from patient files retrospectively. Demographic characteristics and laboratory parameters which were made with in one year before liver biopsy were obtained from the patients' files, too.

Inclusion criteria for patients;

- Being HBsAg-positive for at least six months,
- Being HBeAg-negative and anti-HBe positive,
- Being older than 18 years,
- Antiviral and interferon therapy naive patients.

Exclusion Criteria for Patients

- Coinfection with hepatitis C virus, hepatitis D virus or human immunodeficiency virus,
- A co-existing disease (Wilson disease, hemochromatosis, autoimmune disease, HCC or other malignant diseases
- A history of using systemic corticosteroid, antineoplastic or immunomodulator drugs.

The Biopsy Decision

The indications for liver biopsy are based mainly on the combination of three criteria; serum HBV-DNA levels, serum ALT levels and age. ULN of ALT was accepted as 35 U/L.

- Liver biopsy was performed in all patients with ALT above 2 times ULN and serum HBV-DNA above 20.000 IU/mL.
- In patients who have serum HBV-DNA above 2.000IU/mL but normal ALT levels, liver biopsy was performed when the second HBV-DNA determination was found above 2.000IU/mL again during 3-6 months period and the patients' age was above 35 years.

Biopsy procedure: Percutaneous liver biopsy was performed with tru-cut biopsy method. Disposable 16-18 G semi-automatic tru-cut biopsy needles (Geotek Healthcare products, Turkey; Matek Medical Inc, Turkey) was used in the biopsies. Obtained specimens were sent to pathology laboratory in formalin. Grading and staging of histological activity index was scored with the modified Ishac score system (7).

Necroinflammatory scores ≤4 and fibrosis scores ≤1 were accepted as normal or minimally affected liver (NL) (8). The high value in one of these scores was accepted as CH.

The study protocol was approved by the Ethics Committee of Sakarya University Faculty of Medicine (approval number: 2013/71522473.050.01.04/37). This study was carried out in accordance with the principles of the Helsinki Declaration).

Statistical Analysis

Kolmogorov-Smirnov test was used to evaluate whether the distribution of variables were normal. Therefore, two independent Sample t-test was used to compare the normal distributed continuous variables between groups. The normal distributed continuous variables were presented as the mean ± standard deviation. Mann-Whitney U test was used to compare the non-normal distributed continuous variables between groups. The non-normal distributed continuous variables were presented as the median and interquartile range (quartile 1 to 3). Categorical variables were compared by Pearson's or Yates corrected chi-square tests. Categorical variables were presented as a count and percentage.

Receiver operating characteristic (ROC) curve analysis was performed to establish the most accurate diagnostic method (biomarker) to discriminate between CH and normal patients. ROC curves were constructed for ALT, aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), and alpha-fetoprotein (AFP) to test the various biomarkers in predicting CH (Figure 1). The areas under the ROC curves (AUC) were calculated and the specificity, sensitivity, positive-predictive value, negative-predictive value, accuracy, for the ALT, AST, GGT and AFP of the most appropriate cut-off point were calculated for predicting CH. A multivariate logistic regression model was implemented to determine ALT, AST, GGT and AFP and other covariates associated with CH. A p-values <0.05 were considered significant. Analyses were performed using commercial software (IBM SPSS Statistics 20, SPSS inc., an IBM Co., Somers, NY; MedCalc 12.7, MedCalc Software bvba, Ostend, Belgium).

Results

In total, 268 liver biopsies were performed during the study period. Among these patients, 234 (87.3%) of them were HBeAg negative (140 males, 94 females). So, further evaluation was done with these patients according to our inclusion criteria. Mean age of HBeAg negative patients was 41.5±11.3 years. Mean ALT value was 56.9 U/L and 116 (49.6%) of them have ALT in the normal range. Of the patients, 142 (60.7%) had HBV-DNA >20.000IU/mL. Baseline demographic and other characteristics of patients are shown in Table 1.

Table 1. Baseline characteristics of hepatitis B e antigen-negative patients

n	234
Age	41.50±11.3
HBV-DNA IU/mL	33682 (7756.5-939050.5)
Log (HBV-DNA) IU/mL	4.53 (3.89-5.97)
Alanine aminotransferase U/L	56.9±69
Aspartate aminotransferase U/L	39.8±34
Gamma-glutamyltransferase U/L	25.5±19.6
Alpha-fetoprotein ng/mL	4.5±7.5
Median of histology activity index (range)	5 (1-16)
Median of fibrosis (range)	2 (0-5)

Data were shown as mean±standard deviation and median (Interquartile range)
HBV: Hepatitis B virus

Patients' total necroinflammatory score median was 5 (range: 1-16) and the fibrosis component was 2 (range: 0-5). Of the total, 31 (13.2%) patients had no fibrosis, 162 (69.2%) had portal fibrotic expansion (stages 1 and 2), 38 (16.2%) had bridging fibrosis (stages 3 and 4), and 3 (1.3%) had cirrhosis (stage 5). Among 31 patients who had no fibrosis, 28 patients had also ≤4 necroinflammatory scores, 12 patients had <20.000 IU/mL HBV-DNA, and 20 patients had normal ALT levels.

A total of 74 (31.6 %) patients' liver biopsy was evaluated as in normal or minimally affected liver. In univariate analysis, all baseline characteristics except mean HBV-DNA value were statistically different between NL and CH (Table 2). When patients analyzed by grouping with HBV-DNA level, meaningful statistical difference was observed between NL and CH if the cut off value was accepted as 100.000 IU/mL (p=0.04) or 1.000.000 IU/mL (p=0.005). Statistical difference was not found when the cut off value of HBV-DNA was accepted as <20.000 IU/mL (p=0.65) (Table 2).

Table 2. Demographic characteristics and laboratory findings of normal or minimally affected liver and chronic hepatitis groups

Characteristics		Normal or minimally affected Liver group (n=74)	Chronic hepatitis group (n=160)	p
Gender (male)		37 (50.0)	103 (64.4)	0.037
Age (years)		37±11.4	43.5±10.8	<0.001
HBV-DNA IU/mL		$25.9x10^3$ ($7.7x10^3$-$134.6x10^3$)	$45.8x10^3$ ($7,7x10^3$-$1696,2x10^3$)	0.161
ALT U/L		27.5 (20-39.5)	45 (23-83)	<0.001
AST U/L		24 (22-33)	34 (24-49)	<0.001
GGT U/L		17 (12-23)	23 (15-32)	<0.001
AFP ng/mL		2.5 (1.7-3.4)	3.2 (2.35-4,8)	0.002
HAI		3 (2-4)	6 (5-8)	<0.001
HAI (>4)		0	122 (76.3)	<0.001
Fibrozis		1 (0-1)	2 (2-3)	<0.001
Fibrozis (>1)		0	123 (76.9)	<0.001
HBV-DNA Level	**>20.000**	44 (59.4)	100 (42.7)	0.65
	>100.000 IU/mL	20 (27)	65 (40.6)	0.04
	>1.000.000 IU/mL	9 (12.2)	46 (28.8)	0.005

Data were shown as mean±standard deviation, median (Interquartile range) and n (%)
HBV: Hepatitis B virus, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: Gamma-glutamyl transpeptidase, AFP: Alpha fetoprotein, HAİ: Histological activity index

Table 3. Results of receiver operating characteristic analysis for various biomarkers in predicting chronic hepatitis compared to normal or minimally affected liver

	HBV-DNA	ALT	AST	GGT	AFP
AUC	0.557	0.658	0.694	0.649	0.646
CI 95% of AUC	0.491-0.622	0.594-0.719	0.631-0.753	0.582-0.712	0.570-0.717
p	0.141	**<0.001**	**<0.001**	**<0.001**	**0.002**
Cut-off point	$>789.3x10^3$	>45	>29	>25	>2.5
Sensitivity	32.5	49.38	63.52	42.38	71.90
Specificity	87.84	83.78	67.57	82.86	50.98
PPV	85.2	86.8	80.8	84.2	77.7
NPV	37.6	43.4	46.3	40.0	43.3

HBV: Hepatitis B virus, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: Gamma-glutamyl transpeptidase, AFP: Alpha-fetoprotein, AUC: Area Under the ROC Curve, CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value

Table 4. A multivariate logistic regression model of biomarkers and other covariates associated with chronic hepatitis

Independent variables	β	SE of β	p	OR	95% CI for OR
ALT U/L	0.001	0.015	0.971	1.001	0.971-1.031
AST U/L	0.072	0.034	**0.034**	1.074	1.005-1.148
GGT U/L	0.004	0.016	0.785	1.004	0.974-1.036
AFP ng/mL	0.167	0.083	**0.045**	1.182	1.004-1.392
Age (years)	0.056	0.020	**0.005**	1.058	1.017-1.099
Gender (male)	0.453	0.434	0.296	1.574	0.673-3.681

β: Regression coefficient, SE: Standard error, OR: Odds Ratio, CI: Confidence interval, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: Gamma-glutamyl transpeptidase, AFP: Alpha-fetoprotein

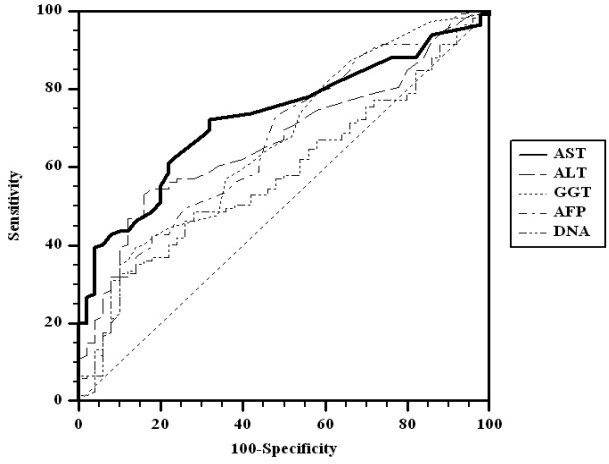

Figure 1. ROC analysis of laboratory results

ROC: Receiver operating characteristic, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transpeptidase, AFP: Alpha-fetoprotein

ROC curve analysis was performed and the optimal cut-off ALT, AST, GGT, and AFP values were determined for identifying CH. The AUC values were derived as 0.658 (95% confidence interval (CI)=0.594 to 0.719) for ALT, 0.694 (95% CI=0.631 to 0.753) for AST, and 0.649 (95% CI=0.582 to 0.712) for GGT. AST levels higher than 29 U/L have 63.52% sensitivity and 67.57% specifity for CH. Similarly AFP levels higher than 2.5 U/L have 71.9% sensitivity and 50.98% specifity for CH. The results of ROC curve analysis are shown in Table 3.

Multivariate logistic regression analysis was performed in order to identify factors associated with CH. Age, AST, and AFP were the significant independent risk factors for CH. The results of multivariate logistic regression analysis are shown in Table 4.

Discussion

In this study, we investigated associations between CH and some demographic and laboratory parameters such as age, gender, ALT, AST, GGT, AFP, and HBV-DNA in HBeAg-negative CHB patients. According to our results, age, gender, ALT, AST GGT, AFP, and HBV-DNA levels >100.000 IU/mL were associated with CH in univariate analysis. However in multivariate analysis only age, AST and AFP levels were associated with CH.

AST and ALT are normally contained in liver cells. In liver diseases such as in viral hepatitis, the liver cells spill the enzymes into the blood, raising the enzyme levels in the blood and signaling that the liver was damaged (8). In a study which was investigated relationship between histopathological features of liver and serum transaminase levels, AST was found a better laboratory screening test for finding the severity of liver injury than ALT in HBeAg-negative CHB patients (9). Similarly, our results showed that AST levels are more useful in showing liver damage than ALT. The normal limits of AST have been investigated in very few studies. It is recommended to adopt 40 U/L as the upper limit of AST (10). This value may be different in cases who have stage 3 or higher fibrosis, which was very low in our study. Inthis study the cut off level of AST was found to be 29 U/L. This suggests that normal AST levels in our country should be determined by large epidemiological studies.

Our results indicate that high levels of AFP was the second independent laboratory parameter related with CH. AFP is a glycoprotein that normally produced in early pregnancy by the fetal yolk sac, liver and gastrointestinal tract (11). In adults, AFP levels are elevated in acute or chronic viral hepatitis, chronic liver disease, non-alcoholic fatty liver disease, and especially in gonadal tumors and hepatocellular carcinoma (12). Also, it was shown that elevated serum AFP levels are associated with hepatic steatosis and ≥stage 2 fibrosis (13). Elevated serum AFP levels in these hepatic diseases are depend on the ongoing inflammation, altered hepatocyte-hepatocyte interaction or the loss of normal achitectural arrangements (14). According to our results, the cut off point of AFP is 2.5 ng/mL. However, this cut-off value is under the ULN value for AFP. This situtation might be related with observer difference in our pathologists.

Age was another parameter found as a prognostic factor for CH. The relationship between age and fibrosis was found in multiple studies. the average age was found lower in patients with mild fibrosis than in those with severe fibrosis (15). In another study, positive correlation was found between age and fibrosis, too (16). It should be noted that the duration of the disease may also be related to the fibrosis score. Our results revealed that the average age was higher in HBeAg-negative CHB patients with CH than in those with NL (43.5 years vs 37 years). Interestingly, according to our results, HBV-DNA level does not predict the necroinflammation and fibrosis. This finding has also been mentioned in other studies. Lu et al. (17) and Aktug Demir et al. (16) reported no correlation between the viral load, inflammatory activity, and the fibrosis score. As the risk of CH increases with age, patients should be followed up very closely after the age of 40 years and liver biopsy should be considered even if HBV-DNA levels and other liver tests such as

ALT are not too high. This is also important in determining the age at which treatment begins. Patients more than 40 years old should be evaluate for treatment be carefully because this age is critical for fibrozis.

Study Limitations

Before any conclusion we should declare our limitations. One of our limitation is that, we could not evaluate the effect of platelet results for fibrosis. Our other limitation is that, we did not investigate the pathologist observation difference. İf we did it, we could been say more accurate results.

Conclusion

As a result, age, high AST anf AFP levels are associated with hepatic necroinflammation in HBeAg-negative CHB. Specialist doctors who follow up these patients should evaluate these parameters more carefully.

Ethics

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of Sakarya University Faculty of Medicine (approval number: 2013/71522473.050.01.04/37).

Informed consent: Retrospective study.

Peer-review: External and internal peer-reviewed.

Author Contributions

Concept: E.G., Design: E.G., A.Ö., O.K., Data Collection or Processing: E.G., A.Ö., M.K., O.K., Analysis or Interpretation: E.G., Ü.E., O.K., Literature Search: E.G., A.Ö., Writing: E.G., A.Ö., O.K.

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