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Research article

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Predictors of eligibility for reimbursement of antiviral treatment in HBe-Ag negative chronic hepatitis B patients with high ALT levels

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Ethics Committee Approval
The study was approved by the local ethical committee of Haseki Training and Research Hospital (approval date / number: 22.02.2017/455)
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: A liver biopsy is required for the reimbursement of antiviral therapy in Hepatitis B e-antigen (HBe-Ag) negative chronic hepatitis B patients. Liver biopsy is an invasive procedure with potential complications, such as bleeding, pain, pneumothorax, and even death. The study aimed to evaluate simple and non-invasive parameters that may help predict histological criteria that would be eligible for antiviral treatment reimbursement.

Methods: HBeAg-negative chronic hepatitis B patients with alanine transaminase (ALT) levels > upper normal limit (40 IU/L) and HBV DNA viral load > 2000 IU/ml who underwent liver biopsy were enrolled in this retrospective cohort study. ALT, aspartate aminotransferase (AST), alpha-fetoprotein (AFP) values, hepatitis B virus (HBV) DNA levels, platelet count, and hepato-steatosis grade based on ultrasonography were used to predict the eligibility for antiviral therapy reimbursement. Eligibility for reimbursement of antiviral treatment regarding histological criteria defined by National Social Security Institution is based on the hepatitis activity index (HAI) score ≥ 6 and/or fibrosis score ≥ 2 according to Ishak's scoring system.

Results: One hundred and fifteen patients were included in the study; 79 patients (68.7%) were male. The mean age of patients was 46.51 (11.39). Sixty-two patients (53.9%) had a fibrosis score ≥ 2, and 80 (69.6%) patients had an HAI score ≥ 6. Ninety-two (80%) of the patients fulfilled histological criteria for antiviral treatment reimbursement. Multivariate analysis revealed that age and platelet count were independent predictors of eligibility for antiviral treatment reimbursement. The platelet count cut-off point was 198 x 10^9 /L for predicting eligibility for antiviral treatment reimbursement.

Conclusion: Most patients (92/115, 80%) with high ALT and DNA viral load were eligible for antiviral treatment reimbursement. Platelet count and age may be used as simple non-invasive parameters for predicting the eligibility for antiviral treatment reimbursement in terms of histological findings.

Keywords: Chronic hepatitis B, HBeAg-negative, High ALT, Reimbursement

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Introduction

Chronic hepatitis B is still a high burden for public healthcare systems. In 2015, it was estimated that 257 million people worldwide were infected with chronic hepatitis B virus (HBV) [1]. The prevalence of HBS Ag positivity is 4% in Turkey [2].

Cumbersome complications such as cirrhosis and hepatocellular carcinoma may develop as a consequence of chronic HBV infection [3]. Regular follow-ups and timely initiation of antiviral treatment is crucial to prevent those unfavorable outcomes. The European Association for the Study of the Liver (EASL) guidelines recommend that all patients with HBeAg-positive or -negative chronic hepatitis B, HBV DNA level > 2,000 IU/ml, alanine transaminase (ALT) > upper limit of normal (ULN), cut-off value ~ 40, and/or at least moderate liver necroinflammation or fibrosis, should be treated [4]. In our country, HBV DNA levels ≥ 2000 IU/ml with an HAI score ≥ 6 or fibrosis score ≥ 2 based on results from a liver biopsy is required for reimbursement of antiviral treatment in HBe Ag-negative patients.

Liver biopsy is the gold standard for assessing the histology of liver in patients with chronic hepatitis B. Owing to its invasive nature, liver biopsy has cumbersome complications, such as bleeding, pneumothorax, vasovagal reactions, and death [5]. It is uncomfortable and undesirable for a patient as it is associated with pain and anxiety [6]. Therefore, non-invasive methods have gained popularity for assessing hepatic fibrosis. Fibroscan and Fibrotouch are ultrasound imaging techniques that help to assess the degree of fibrosis in liver. However, these pieces of equipment are not widely available. Biochemical markers, such as aspartate aminotransferase (AST)-to-platelet ratio index (APRI) and the fibrosis index based on four factors (FIB-4) are also used in the assessment of hepatic fibrosis [7, 8]. APRI and FIB-4 are not practical as they require the combination with other indexes and increase the workload. Therefore, this study aimed to evaluate simple and non-invasive parameters in HBeAg-negative chronic hepatitis B patients with high ALT level that may help to predict histological criteria eligible for reimbursement of antiviral treatment.

Materials and methods

This single-center retrospective cohort study was conducted as a thesis study with the approval of Haseki Training and Research Hospital Ethical committee (Approval date/ number: 22.02.2017/455). Medical records of 283 chronic hepatitis B patients with HBV DNA levels ≥ 2000 IU/ml who underwent liver biopsy were reviewed. Of those 283 patients, 115 HBeAg-negative chronic hepatitis B patients with ALT levels > ULN were taken for statistical analysis. 40 IU/L was accepted as ULN of ALT according to the EASL guidelines.

Patients younger than 18 years old, with HCV and/or HIV co-infections, delta virus (HDV) infection, liver comorbidities (such as auto immune hepatitis, Wilson disease), and chronic alcohol consumers were excluded from the study.

ALT, AST, and alpha-fetoprotein (AFP) values, hepatitis B virus (HBV) DNA levels, platelet count, and hepato-steatosis grade based on ultrasonography were recorded. HBV DNA was measured quantitatively using commercially available kits (Realtime PCR Rotor-Gene Q, QIAGEN, Hamburg/GERMANY). FIB-4 and HAI were scored using the Ishak scoring system [9].

Eligibility for reimbursement of antiviral treatment regarding histological criteria defined by National Social Security Institution was an HAI score ≥ 6 and/or fibrosis score ≥ 2.

Statistical analysis

All statistical analyses were performed using IBM SPSS for Windows version 20.0 (SPSS, Chicago, IL, USA) and MedCalc 14. Kolmogorov–Smirnov and Shapiro–Wilk's tests were used to assess the assumption of normality. Numeric variables were presented with or median (25^{th}–75^{th} percentile). Categorical variables were summarized as counts (percentages). Comparisons of numeric variables between groups were carried out using independent sample t-test or Mann–Whitney U test, whichever was appropriate. The association between two categorical variables was examined using the chi-squared test. Logistic regression analysis was used to determine the factors affecting the outcome variable. Receiver operator characteristic (ROC) analysis was used to determine the area under the curve (AUC), sensitivity, specificity, and cut-off values. A *P*-value < 0.05 was considered statistically significant.

Results

One hundred and fifteen patients were included in the study; 79 patients (68.7%) were male. The mean age of patients was 46.51 (11.39). Baseline characteristics of the study population are shown in Table 1.

Table 1: Baseline parameters of the study population

		Patients (n = 115)
Age, years	mean (SD)	46.51 (11.39)
Sex, n (%)	Male	79 (68.7)
	Female	36 (31.3
ALT (IU/l)	median (25^{th}–75^{th} percentile)	80 (56–140)
AST(IU/L)	median (25^{th}–75^{th} percentile)	56 (40–96)
AFP(ng/ml)	median (25^{th}–75^{th} percentile)	2.78 (2.02–3.85)
Platelet count, $x10^9$/L	median (25^{th}–75^{th} percentile)	193 (152–254)
HBV DNA (log_{10}IU/ml),	mean (SD)	6.15 (1.36)
HAI	mean (SD)	7.49 (3.08)
Fibrosis stage	mean (SD)	2.06 (1.42)
Hepato-steatosis, n (%)	Grade 0	79 (68.7)
	Grade 1	24 (20.9)
	Grade 2	12 (10.4)

ALT: alanine aminotransferase, AST: aspartate aminotransferase, AFP: alpha-fetoprotein, HAI: histological activity index, HBV: hepatitis B virus, SD: standard deviation

All patients had HBV DNA levels > 2000 IU/ml. The mean HBV DNA level was 6.15 (1.36) log 10 IU/ml. Sixteen patients (13.9%) had HBV DNA levels < 4.27 log 10 (20000) IU/ml, 19 patients (16.4%) had HBV DNA levels between 4.27 and 5.38 log10 (20000–200000) IU/ml, 80 patients (69.7%) had DNA levels > 5.38 log10 (200000 IU/ml).

Histopathological findings are given in Table 2. Sixty-two patients (53.9%) had a FIB-4 score ≥ 2 and 80 (69.6) patients had an HAI score ≥ 6. Ninety-two (80%) patients fulfilled histological criteria for reimbursement of antiviral treatment (HAI ≥ 6 or F ≥ 2).

Table 2: Histopathological findings in liver biopsy specimens of chronic hepatitis B patients with high alanine aminotransferase, according to the Ishak scoring system

Histopathological findings	n (%)
Fibrosis stage (F)	
0	12 (10.4)
1	41 (35.7)
2	17 (14.8)
3	26 (22.8)
4	12 (10.4)
5	6 (5.2)
6	1 (0.9)
HAI	
1–5	35 (30.4)
≥ 6	80 (69.6)
HAI ≥ 6 or F ≥2	
Negative	23 (20)
Positive	92 (80)

HAI: Histological activity index

Univariate and multivariate analysis of factors associated with eligibility for reimbursement

The association of age, sex, AST, ALT, AFP, platelet count, HBV DNA (log_{10}IU/l), and hepato-steatosis with reimbursement eligibility was analyzed (Table 3). In univariate analysis, platelet count was associated with reimbursement eligibility. Patients eligible for treatment had lower mean platelet counts (195.37 [74.09] x 10^9/L versus 234.35 (62.45) x 10^9/L; *P* = 0.007).

Multivariate analysis revealed that age (odds ratio [OR] 1.070, 95% confidence interval CI 1.016–1.1126; *P* = 0.010) and platelet count (< 193 x 10^9/L; OR 4.448, 95% CI 1.476–13.401) were independent predictors of eligibility for reimbursement of antiviral treatment (Table 4).

Table 3: Univariate analysis of factors associated with eligibility for reimbursement of antiviral treatment

		Eligible for reimbursement		
		None	Yes	*P*-value
Age, years	mean (SD)	42.61 (11.67)	47.49 (11.18)	0.066[i]
Sex	Female	9(25.0)	27(75.0)	
	Male	14(17.7)	65(82.3)	0.366[ii]
ALT	min–max(median)	41–335 (67)	41–412 (81)	
	mean (SD)	97.35 (71.24)	111.12 (78.54)	0.206[iii]
AST	min-max(median)	25–434 (39)	26–250 (59)	
	mean (SD)	77.43 (87.63)	77.33 (51.10)	0.060[iii]
AFP	min-max(median)	1–8 (2.89)	1–56 (2.77)	
	mean (SD)	3.04 (1.80)	4.53 (7.24)	0.531[iii]
Platelet count,	min-max(median)	115–386 (223)	113–504 (182.5)	
x10^9/L	mean (SD)	234.35 (62.45)	195.37 (74.09)	0.007[iii]
HBV DNA	min-max(median)	3.70–8.77(5.37)	3.47–8.23(6.51)	
(log_{10}IU/ml),	mean (SD)	5.83 (SD)	6.23 (0.13)	0.213[iii]
Hepatosteatosis,	Grade 0	15 (19.0)	64 (81.0)	
n (%)	Grade 1	4 (16.7)	20 (83.3)	0.509[ii]
	Grade 2	4 (27.3)	8 (72.7)	

[i] Student's t-test, [ii] Pearson chi-squared test, [iii] Mann–Whitney U test

Table 4: Multivariate analysis for eligibility of treatment reimbursement

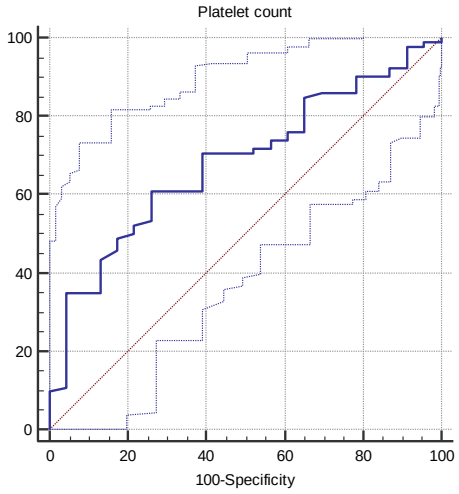
Reimbursement criteria	Multivariate analysis		
	OR	95% CI	*P*-value
Age	1.070	1.016–1.1126	0.010
Sex	0.552	0.187–1.631	0.282
Platelet group	4.448	1.476–13.401	0.008
HBV DNA(log_{10}IU/ml) group	1.757	0.454–6.801	0.415

OR: odds ratio, CI: confidence interval, HBV: hepatitis B virus, HBV DNA(log10IU/ml) group: 3.30-4.30 vs > 4.30

AUC for the association of platelet count with eligibility for reimbursement

Platelet count was used to predict the probability of being eligible for antiviral therapy reimbursement in HBe Ag-negative patients with high ALT. The cut-off point for platelet count was 198x10^9 /L. The AUC of the platelet value associated with eligibility for reimbursement of antiviral treatment was 0.682 (95% CI 0.589–0.766; sensitivity = 60.87%, specificity = 73.97%; *P* = 0.001) as shown in Figure 1.

Figure 1: ROC curve of platelet value associated with eligibility of reimbursement of antiviral therapy in HBeAg-negative patients with hih-ALT levels. (AUC = 0.682, 95% CI 0.589–0.766; sensitivity = 60.87%, specificity = 73.97%, *P* = 0.001)



Discussion

In the present study, the association of laboratory and demographic parameters with eligibility for antiviral treatment reimbursement in HBeAg-negative chronic hepatitis B with high ALT levels was analyzed. Platelet count and age were found to be statistically significant independent parameters for predicting eligibility for reimbursement of antiviral treatment.

Age is an important parameter that affects the degree of liver damage. Older patients probably have a longer duration of disease, and their immune-tolerance and immune clearance phases are relatively longer which predispose them to more severe liver damage [10]. Papatheodoridis et al. [11] found that histological indication for treatment was more likely in patients older than 45 years old compared to ones younger than 45 years. In two previous studies from our country, the age cut-off for age in predicting the requirement of treatment in HBeAg negative chronic hepatitis B patients was 46 years [10, 12]. Parallel with previous studies, patients in our study who were eligible for reimbursement of antiviral treatment were older compared to non-eligible patients which did not reach statistical significance (47.49 [11.18] versus 42.61 [11.67]). However, logistic regression analysis showed that age could predict eligibility for reimbursement (OR: 1.070, 95% CI 1.016–1.126).

Thrombocytopenia is a well-known feature of liver cirrhosis, usually resulting from portal hypertension and hypersplenism that leads to splenic sequestration [13]. Besides splenic sequestration, a decrease in platelet production due to diminished synthesis of thrombopoietin and/or other humoral factor(s) by the liver also contributes to thrombocytopenia in cirrhosis [14]. However, before the development of cirrhosis, platelet count may begin to gradually decline during the course of chronic hepatitis as fibrosis progresses. Studies have shown a negative correlation between platelet count and FIB-4 score [15, 16]. In this present study, it was also found that patients eligible for antiviral treatment reimbursement had lower mean platelet counts compared to non-eligible patients.

HBV DNA viral load is also an important determinant of the requirement for antiviral treatment. Papatheodoridis et al. [11] found that histological indications for treatment increased as HBV viral loads increased. A similar result was found in a study

from our country [12]. On the other hand, Ormeci et al. [10] reported an opposite finding. In contrast to the previously described studies, patients requiring treatment were more likely to present HBV DNA levels between 2000 and 20000 IU/ml compared to levels > 20000 IU/ml. In our study, the difference in HBV viral loads between eligible and non-eligible patients for antiviral treatment was not statistically significant. As a high percentage of patients (80%, 92/115) patients were eligible for reimbursement of antiviral treatment, the difference might not have reached statistical significance. The first two studies included patients with high and normal ALT values. In a study by Ormeci et al., only patients with normal ALT values were included, whereas our study consisted of patients only with high ALT levels. This difference may explain the discrepancy in the results.

Limitations

Some limitations of the study should be mentioned. The retrospective nature of the study is an important limitation. A small sample size is also an important limitation. Thus, it is necessary to design a multicenter study with a larger study population to obtain more definite results.

Conclusion

In conclusion, platelet count and age may be used as non-invasive parameters for predicting the eligibility for reimbursement of antiviral treatment in terms of histological findings.

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