Research Article/ Araştırma Makalesi

Use of platelets and their properties in predicting fibrosis and activity in HBV infection

Platelet ve özelliklerinin HBV enfeksiyonunda aktivite ve fibrozis tahmininde kullanımı

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ABSTRACT

Aim: Although liver biopsy is the gold standard diagnostic method for showing histological activity and fibrosis today, there are some non-invasive methods using biochemical calculations as an alternative since it is an invasive procedure. In our study, we aimed to examine the relationship between platelets and some related parameters and histopathology in patients who underwent liver biopsy due to chronic hepatitis B virus (HBV).

Material and Method: 70 patients diagnosed with chronic HBV and followed up between 2009 and 2013 were included. Demographic data, liver histopathological results and laboratory parameters of all patients were documented. The relationship between histopathology and platelets and some related laboratory parameters was examined.

Results: A total of 70 patients, 28 (40%) of whom were women, were included in the study. A statistically significant relationship was detected between hepatic activity index (HAI) and AST (p=0.001), ALT (p=0.001), Sedimentation (p=0.026, r=0.5) and aspartate aminotransferase and alanine aminotransferase ratio (AAR), aspartate aminotransferase to platelet ratio index (APRI), fibrosis index based on the 4 factor (FIB-4) (p<0.05). A statistically significant relationship was found between fibrosis and International Normalized Ratio (INR), between PDW/Platelet count, and between Platelet count/PDW (p<0.05). Additionally, the relationship between fibrosis and APRI, FIB4 and red cell distribution (RDW) width to platelet ratio (RPR) was statistically found significant. (p<0.05). No correlation was found between HAI and Platelet, RDW, PDW (p>0.05).

Conclusions: Platelet, RPR and RDW have been shown to be associated with the degree of fibrosis. It is thought that RPR, which is an inexpensive and easily calculable index, can predict significant fibrosis and cirrhosis with relatively high accuracy in chronic hepatitis patients, potentially reducing unnecessary liver biopsies.

Key Words: Fibrosis, Chronic hepatitis B, Inflammation, Platelet, RPR.

ÖZ

Amaç: Günümüzde histolojik aktiviteyi ve fibrozisi göstermede altın standart karaciğer biyopsisi olmasına karşın invaziv bir işlem olması nedeniyle alternatif olarak biyokimyasal hesaplanan bazı noninvaziv yöntemler bulunmaktadır. Biz de çalışmamızda kronik hepatit B virüsü (HBV) nedeniyle karaciğer biyopsisi yapılan hastalarda platelet ve ilişkili bazı parametrelerin histopatoloji ile olan ilişkisini incelemeyi amaçladık.

Gereç ve yöntem: Kronik HBV tanısı ile 2009 ile 2013 yılları arasında takipli, 70 hasta dahil edildi. Tüm hastaların demografik verileri, karaciğer histopatolojik sonuçları ile laboratuvar parametreleri dökümante edildi. Histopatoloji ile platelet ve ilişkili olduğu bazı laboratuar parametreleri arasındaki ilişki incelendi.

Bulgular: Çalışmaya 28 (%40) kadın olmak üzere toplamda 70 hasta alındı. Hepatik aktivite indeksi (HAİ) ile AST (p=0.001), ALT (p=0.001), Sedimantasyon (p=0.026, r=0.5) ve aspartat aminotransferaz ve alanin aminotransferaz oranı (AAR), aspartat aminotransferaz/trombosit oranı indeksi (APRI), 4 faktöre dayalı fibrozis indeksi (FIB-4) arasında istatistiksel olarak anlamlı ilişki saptandı (p<0.05). Fibrozis ile İNR arasında, PDW/Platelet arasında, Platelet/PDW arasında (p<0.05) istatistiksel olarak anlamlı ilişki bulundu. Ayrıca Fibrozis ile APRI, FIB4 ve kırmızı hücre dağılımı ile RPR arasındaki ilişki istatistiksel olarak anlamlı bulundu (p<0.05). HAİ ile Platelet, RDW, PDW korelasyonu bulunamadı (p>0.05).

Sonuç: Trombosit, RPR ve RDW'nin fibrozisin derecesi ile ilişkili olduğu gösterildi. Pahalı olmayıp kolay hesaplanabilir bir index olan RPR, potansiyel olarak gereksiz karaciğer biyopsilerini azaltarak kronik hepatit hastalarında nispeten yüksek doğruluk oranıyla belirgin fibrozis ve sirozu tahmin etmeyi sağlayabileceği düşünülmüştür.

Anahtar kelimeler: Fibrozis, Kronik hepatit B, İnflamasyon, Platelet, RPR.

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Introduction

Hepatit B virus (HBV) is a member of the hepa-DNA virus family, and HBV infection is one of the most important causes of cirrhosis and hepatocellular carcinoma. HBV, for which there is an effective vaccine, continues to be a serious public health problem all over the world (1, 2). Liver fibrosis is a chronic process that is seen in the course of all chronic liver diseases, regardless of their etiology, and ends with the development of cirrhosis if it is not treated. Liver fibrosis and cirrhosis are the most important causes of morbidity and mortality in chronic hepatitis B patients. Although antiviral treatment significantly reduces the risk of fibrosis and cirrhosis, advanced fibrosis and cirrhosis may develop in some patients (1, 2).

Laboratory (serum transaminases), serological diagnosis, molecular diagnosis and pathological diagnosis methods are used in the diagnosis of chronic viral hepatitis. Histopathological examination of the liver, especially hepatic activity index (degree/grade) and fibrosis (stage/stage), has an important place in the diagnosis and staging of liver disease, estimating the prognosis, and making treatment decisions for patients (3).Treatment decisions are often made based on the results of liver biopsy, which is an invasive procedure. Liver biopsy is the gold standard in determining the histo-pathological results of liver disease (3, 4). However, biopsy is an invasive procedure and involves some complications (4). Therefore, non-invasive, economical and simple methods should be developed to determine the severity of hepatic fibrosis.

In studies conducted on non-invasive tests, it has been thought that some calculated values such as Fibrosis-4 (FIB4), Aspartate Amino Transferase-Platelet Ratio Index (APRI), Aspartate Amino Transferase-Alanine Amino Transferase Ratio (AAR) may be related to fibrosis and histological stage (5, 6). Following the studies carried out, the use of non-invasive methods in places with limited examination was added to the diagnosis and treatment guide by the World Health Organization (WHO) in 2015 (7). Therefore, weaimed to determine whe ther platelets and their properties could be effective in determining histological activity index and fibrosis in HBV infection.

Materials and Methods

70 chronic hepatitis B patients who were diagnosed, treated and followed up by our hospital's Hepatology outpatient clinic between 2009 and 2013 were included in this clinical study. Our study was designed retrospectively. Patients with HBsAg positivity and/or high liver function test levels and HBV-DNA positive results for six months were evaluated as chronic HBV and liver biopsy was performed. Demographic data (age, gender) of all patients were recorded. Histopathological data of the patients were documented. A comparison was made in terms of biochemical parameters in chronic HBV patientgroups.

Biochemical and hematological measurements:

Biochemical parameters were measured from antecubital venous blood samples taken after 8 hours of fasting. Among the biochemical parameters, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl trans peptidase (GGT), total bilirubin, direct bilirubin, albumin, prothrombin time (PT), INR level were measured. Some formulas as were calculated from the biochemical parameter sex amin.

1. AAR=Obtained by dividing AST by ALT (8).

2.APRI=APRI: Calculated using the formula [(AST/Upper Limit of Normal/PLT (10^9/L)] × 100 (9).

3. FIB4=FIB-4 score was calculated using the formula = Age ([year] x AST [U/L]) / ((PLT [109/L]) x (ALT [U/L])(1/2)) (10).

4. RPR= RDW(%) / Platelet (10^9/L) (11).

Liver biopsy and histopathological evaluation

Liver biopsy was performed using a 16 G biopsy needle under ultrasonography guidance. Samples with liver biopsy material length less than 1.5 cm and insufficient number of portal areas for evaluation were excluded from the study. The received materials were evaluated by three different experienced pathologists with out providing clinical information. Knodell histological hepatic activity score was used to make grade and staging (12). The presence of fibrosis in liver biopsies was determined according to the Scheuer score (13).

Ethical Approval

Approval was received for this study from İnönü University Ethics Committee.

Statistical Analysis

The results of our study were analyzed with the program "The Statistical Pack age for the Social Sciences 22.0 (SPSS Armonk, NY: IBM Corp.)". Continuous data were given as mean (± standard deviation), and categorical data were given as frequency and percentage (n,%). Data were tested for normal distribution using the Kolmogorov-Simirnov test, histogram and ± SD. Parametric data of the groups were compared between paired groups were made using post-hoc test. Chi-square test was used to test categorical data. $P<0.05$ were considered statistically significant.

Results

Seventy patients with chronic hepatitis B whounder went liver biopsy were included in the study. 60% (42) of the patients included in the study were male and 40% (28) were female. The a verage age was found to be 42.1±12.8 years (age range 20-67 years).When the laboratory values of the patients are analyzed; AST=44.8±34.9 (14-209) IU/mL, ALT=68.6±59.5 (5-318) IU/mL, ALP=73.1±26.6 (23-153) IU/mL, GGT=36.9±24.1 (9-125) IU/mL, LDH=195.8±72.1 (105-611) IU/mL, INR=1.06±0.9 (0.8-1.3) was detected as. HAI score in our patients; it ranges from 1 to 14, and the average was found to be 5.88 ± 2.4.

The fibrosis score ranged from 0 to 6, with an average of 2.3 ± 1.2 (Figure 1). A significant correlation was detected between fibrosis and HAI (p=0.000 correlation r=0.57). The correlation between HAI and AST (p=0.001) and ALT (p=0.001) was found to be statistically significant. Statistically significant differences were found between HAI and AAR, APRI, FIB4. A correlation was observed between HAI and erythrocyte sedimentation rate (p=0.026, r=0.5). No correlation was found between HAI and Platelet, RDW, PDW. A correlation was observed between fibrosis and INR (p=0.02, r=0.2). A statistically significant difference was found between fibrosis and PDW/PLT. There lationship between fibrosis and APRI, FIB4 and RPR was found to be statistically significant (Table 1). The relationship between HAI, fibrosis scores and PLT and PDW is presented in detail in Figure 2.

Discussion

HBV infection continues to be an important health problem in the world. Although liver biopsy is the gold standard for demonstrating hepatic tissue damage in diagnosis and follow-up, it is an invasive procedure that may have complications. Studies have shown that some laboratory parameters are close to biopsy in showing hepatic fibrosis (14, 15). The examinations are less costly than liver biopsy and provide more advantages in terms of accessibility (2, 15).

In a study conducted by Baode Chen et al. in 2012, they

Table 1. Relationship between HAI and Fibrosis values and laboratory parameters

		HAI	Fibrozis	Wbc	Hgb	Hct
HAI	r value	1	0,572	0,027	-0,103	-0,101
	p value		0	0,822	0,397	0,403
Fibrozis	r value	0,572	1	-0,053	-0,085	-0,093
	p value	0		0,661	0,482	0,446
		MCV	PLT	RDW	PDW	AST
HAI	r value	-0,085	-0,06	0,127	0,058	0,383
	p value	0,486	0,62	0,294	0,635	0,001
Fibrozis	r value	0,024	-0,226	0,032	0,169	0,225
	pvalue	0,843	0,06	0,794	0,162	0,061
		ALT	ALP	GGT	LDH	INR
HAI	r value	0,420	0,007	0,233	0,251	0,093
	pvalue	0	0,954	0,052	0,036	0,445
Fibrozis	r value	0,196	-0,048	0,275	0,177	0,268
	pvalue	0,104	0,69	0,021	0,142	0,025
		T.billirubin	D.billurubin	Albumin	Sedimentation	CRP
HAI	r value	0,048	0,063	0,157	0,510	0,126
	pvalue	0,692	0,606	0,193	0,026	0,682
Fibrozis	r value	0,076	0,069	-0,011	0,267	0,321
	pvalue	0,532	0,572	0,93	0,27	0,285
		PDR/ PDW	AAR	APRI	FIB4	RPR
HAI	r value	0,048	0,063	0,157	0,510	0,126
	pvalue	0,692	0,606	0,193	0,026	0,682
Fibrozis	r value	0,076	0,069	-0,011	0,267	0,321

investigated whether platelets and their properties were related to the development of fibrosis and cirrhosis in HBV ivnfection; RDW has been shown to be positively correlated with significant fibrosis and cirrhosis, while platelets and hemoglobin are negatively correlated with significant fibrosis and cirrhosis. It has been observed that the severity of liver fibrosis is significantly associated with the gradual increase in RDW and the decrease in hemoglobin and platelets. Compared to hemoglobin, platelet count was found to be more closely related to the degree of fibrosis. For this reason, it has been reported that RDW and platelets are the strongest determining risk factors in liver fibrosis (16). Similarly, in their study by Yuyun et al., where 1282 patients were evaluated; it was reported that RPR showed the best accuracy in predicting hepatic fibrosis, regardless of etiology. It has also been reported that combining RPR with white blood cell (WBC) count further increases the accuracy of grading hepatic fibrosis. This study arguest hattheuse of RPR, both alone and in combination with inflammatory parameters, would be beneficial to increase the accuracy of scoring hepatic fibrosis (11).

APRI score; It is a ratio calculated to estimate fibrosis with AST and platelet count parameters measured in the routine follow-up of patients with chronic hepatitis. The scoring system was first used by Wai et al. in patients with hepatitis C (17). In the study in question, the AUROC value of APRI was found to be 0.80 and 0.89, respectively, in the calculations made to predict fibrosis and cirrhosis. In a meta-analysis for the APRI score, the negative predictive value and the probability of excluding cirrhosis increased when the APRI score fell below 0.5; It was determined that when the scores increased above 1.5, the positive predictive value and the probability of cirrhosis increased (18).

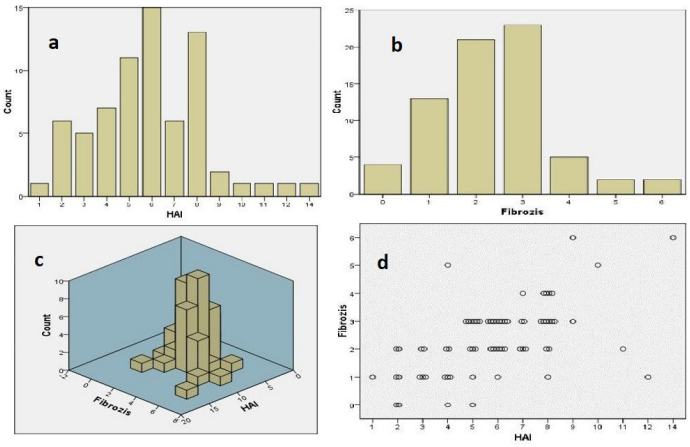

Figure 1. a. HAI (Histological Activity Index) rates of the patients included in the study, b. Fibrosis rates, c. Cross-relationship between HAI and Fibrosis, d. Cross-relationship between HAI and Fibrosis

There are studies in the literature showing that the AAR value is superior to the APRI value in determining fibrosis. In the studies in question, the positive predictive value for showing significant fibrosis was close to 90% when the AAR value was ≥1; It has been shown that in cases where the AAR value is <1, the negative predictive value indicating the absence of significant fibrosis is around 80% (19).

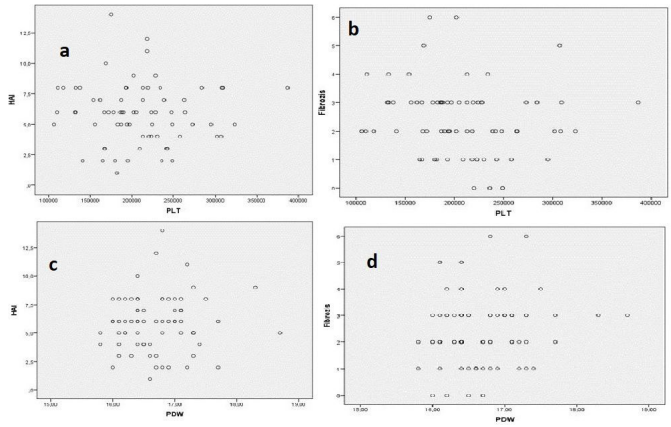

Figure 2. a. Relationship between HAI values and PLT of the patients included in the study, b. Relationship between fibrosis values and PLT, c. Relationship between HAI values and PDW, d. Relationship between fibrosis values and PDW

Fibrosis index (FIB-4), which is based on four parameters; AST is a formulation calculated using the ALT level, platelet count and age of the patient (20). The basic foundations of this approach are; These can be listed as increasing the duration of the disease and therefore fibrosis with age, increasing the AST value more than the ALT value due to the decrease in mitochondrial damage and clearance, and decreasing thrombopoietin and platelet values with periportal fibrosis (21). In the study conducted by Lee et al. in 2021; APRI and FIB-4 scores have been shown to have comparable performance to biopsy in risk stratification of liver-related mortality and morbidity in patients with non-alcoholic fatty liver disease (22).

Although our study is an important study examining the relationship between biochemical parameters and inflammation and fibrosis, it has some limitations. First of all, our study was designed retrospectively and the number of samples was small.

In addition, failure to detectcer tain conditions such as drugs and infections that may affect the level of biochemical parameters may lead to different results. On the other hand, the presence of all fibrosis stages in our patient group and the ability to make comparisons between fibrosis stage sare the strengths of our study.

Conclusion

Platelet and related parameters were shown to have a significant relationship with fibrosis. It has been shown that platelet and related parameters RDW and RPR are related to the degree of fibrosis. It is thought that RPR, which is an inexpensive and easily calculable index, can predict significant fibrosis and cirrhosis with relatively high accuracy in chronic hepatitis patients, potentially reducing unnecessary liver biopsies. However, more comprehensive studies are needed for non-invasive tests to replace liver biopsy.

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