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ARAŞTIRMA / RESEARCH

Relationship between liver histology and platelet parameters in patients with chronic hepatitis B

Kronik hepatit B hastalarında karaciğer histolojisi ile platelet parametreleri arasındaki ilişki

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Abstract

Purpose: Many noninvasive tests have been studied for the diagnosis and determining the liver fibrosis score. In this study, we aimed to research the correlation of platelet parameters and stage of liver fibrosis in patients with chronic hepatitis B (CHB).

Materials and Methods: A total of 140 biopsy-proven naive CHB cases were included in the study. HBV-DNA level, liver enzymes and function tests, white blood cell count, platelet parametres, hemoglobin, histological activity index (HAI) and other routine biochemical parameters were tested. Patients were divided into two groups as F0-2 and F3-6 with Ishak scoring system according to the severity of liver fibrosis.

Results: There was no significant difference between the groups F0-2 and F3-6 in terms of, platelet (PLT), mean platelet volume (MPV), platelet distribution width (PDW) and plateletcrit (PCT). There was a significant difference between these two groups for HAI, aspartate aminotransferase (AST), gamma glutamyl transpeptidase (GGT), age and lymphocyte (LYM) parameters. The formulation of (AST x Age x LYM) / √PLT)which was formed from many different combinations, was investigated in order to be used in predicting the liver fibrosis stage.

Conclusion: Although our new index is more sensitivitythan other noninvasive scoring systems, it is needed to have a larger sample size in patients with severe stage liver fibrosis in order to be used safely as a noninvasive marker.

Keywords: Chronic hepatitis B, Fibrosis, Platelet

Öz

Amaç: Karaciğer fibrozis tanı ve skorunun belirlenmesi için birçok noninvaziv test çalışılmıştır. Bu çalışmada, kronik hepatit B (KHB) olan hastalarda platelet parametrelerinin ve karaciğer fibrozisin evresi arasındaki ilişkiyi araştırmayı amaçladık.

Gereç ve Yöntem: Çalışmaya toplam 140 biyopsi ile kanıtlanmış naiv KHB olgusu dahiledildi. HBV-DNA düzeyi, karaciğer enzimleri ve fonksiyon testleri, beyaz kan hücresi sayısı, platelet parametreleri, hemoglobin, histolojik aktivite indeksi (HAI) ve diğer rutin biyokimyasal parametreler test edildi. Karaciğer biyopsi örnekleri modifiye Ishak skorlama sistemi kullanılarak incelendi. Hastalar karaciğer fibrosis şiddetine göre modifiye İshak puanlama sistemi ile F0-2 ve F3-6 olarak iki gruba ayrıldı.

Bulgular: F0-2 ve F3-6 grupları arasında platelet (PLT), ortalama platelet hacmi (MPV), platelet dağılım genişliği (PDW) ve platelecrit (PCT) açısından anlamlı fark yoktu. Bu iki grup arasında HAİ, aspartat transaminaz (AST), gama glutamil transaminaz (GGT), yaş ve lenfosit parametreleri açısından anlamlı fark vardı. Karaciğer fibrozis evresini tahmin etmede kullanılmak üzere birçok farklı kombinasyondan oluşan (AST x Yaş x Lenfosit) /√PLT) formülasyonu araştırıldı.

Sonuç: Yeni indeksimiz diğer noninvaziv skorlama sistemlerine göre daha sensitivitesi yüksek olmakla birlikte noninvaziv belirteç olarak güvenle kullanılabilmesi için ileri karaciğer fibrozis düzeyine sahip olan hastaların daha fazla olduğu, daha geniş örneklem büyüklüğüne sahip çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Kronik hepatit B, Fibrozis, Platelet

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INTRODUCTION

Hepatitis B virus (HBV) infection, a serious health problem affecting over 400 million persons worldwide, is the leading cause of cirrhosis and hepatocellular carcinoma (HCC)[1]. Timely evaluation of the severity of liver inflammation and fibrosis is important in the treatment of chronic hepatitis B (CHB) and pathological observation of liver biopsy samples are the gold standart for diagnosis[2]. However, this procedure is costly and the invasive nature of this method restricts its usage in some patient groups because of its complications and contraindications[1]. Therefore, noninvasive parameters have been used to estimate liver histology[3-6]. Liver damage can be indirectly defined by blood concentrations of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma glutamyl transpeptidase (GGT), whilst total bile acid (TBA) and total bilirubin (TBIL) can reflect hepatic function. On the other hand, levels of transaminase enzymes are affected by the compensative volume of the liver[7,8]. Red blood cell distribution width (RDW), platelet distribution width (PDW), mean platelet volume (MPV), which are largely unnoticed, are routine tests that are part of complete blood counts (CBC). To evaluate the association between these parameters and the histological outcomes of diseases related to the liver in patients with CHB, a limited number of studies have been performed. This study was designed to investigate whether RDW, PDW, MPV, and red blood cell distribution width to platelet ratio (RPR) are variables that determine the severity of fibrosis in HBV-infected patients.

Chronic HBV infection is associated with a serious series of clinical findings from a severe asymptomatic carrier with normal liver histology and chronic liver diseases including cirrhosis and HCC[9]. There is a specific fear in the region of Asia, where chronic HBV infection is common, with a carrier rate of nearly 10% of chronic HBV carriers. Approximately 25–40% of them will terminally die of liver disease cirrhosis with and without HCC[10]. Liver biopsy is the gold standard for determining the severity of liver fibrosis. Liver biopsy has a lot of advantages for obtaining direct information not only about fibrosis but also about many useful parameters, such as inflammation, necrosis, and steatosis[11]. However, the liver biopsy restricts its use in disease follow-up[12]. It is not possible to perform a liver biopsy due to contraindications in some patients. In the light of these issues, various parameters have been researched in the prediction of liver histology. Some studies have commited the fibrosis-predictive models consists of several potential serum markers, including AAR (AST/ ALT ratio), PGA (prothrombin time, g-GT, apolipoprotein A1), PGAA index (prothrombin time, g-GT, apolipoprotein A1, a2-macroglobulin), FibroTest, Forns fibrosis index, APRI (AST-to-PLT ratio) index, collagen, hyaluronic acid, matrix metalloproteinase, and tissue inhibitor of metalloproteinase[13].

MATERIALS AND METHODS

This was a retrospective study conducted among patients with chronic HBV-infection. Our study contained in patients diagnosed with CHB at Hitit University Erol OlcokTraining and Research Hospital between January 2010 and October 2017. This study included 140 patients who were diagnosed with CHB and performed liver biopsy. CHB is diagnosed when serum hepatitis surface antigen is positive for more than 6 months, and when persistent or intermittent increases in ALT, AST levels, and histopathological changes in liver biopsy are present. Patients with underlying diseases such as cardiac diseases, renal diseases, diabetes mellitus, atherosclerotic disease, chronic infections, history of hypertension, coinfection with hepatitis C virus, human immunodeficiency virus and hepatitis D virus, malignancy, autoimmune disorders, rheumatic diseases, hematological diseases, and chronic obstructive lung diseases, as well as patients taking drugs such as aspirin heparin, warfarin, antidiabetics, antihypertensives and hyperlipidemics were excluded from this study. The number of CHB patients excluded from exclusion criteria was 120.

The CBC variables used included white blood cell (WBC), hemoglobin (HB) level, hematocrit (HTC) value, platelet (PLT) count, RDW, MPV and PDW. Serum levels of AST, ALT, TBIL, albumin (ALB), and other routine biochemical parameters were determined. Liver biopsy was performed on all of our patients and biopsy samples were studied using the Ishak scoring system. Patients were divided into two groups on the basis of the fibrosis score: patients without significant fibrosis (F0, F1, or F2) were assigned to group 1 and patients with advanced fibrosis (F3, F4, F5, or F6) were appointed to group 2. Groups were then compared with RDW, MPV and PDW to determine whether any of these variables was significantly associated with the severity of liver

fibrosis score. Additionally, data of the patients were evaluated by using alsoFibrosis-4 score (FIB-4), APRI, platelet-lymphocyte ratio (PLR), fibro-quotient (FibroQ) and platelet count (2)/[monocyte fraction (%) x segmented neutrophil fraction (%)]indices (P2/MS), which are used widely in the literatüre[13]. Ethics committee decision was taken from Hitit University Medicine Faculty for this study.

Statistical analysis

Statistical analyses of the data obtained in our research were performed via SPSS (Version 22.0, SPSS Inc. Chicago, IL, USA, Licensed to Hitit University). Data were presented as mean ± SD. Between group comparisons were made using independent sample *t*-test. Receiver operatör characteristic (ROC) graphs were drawn by ROC analysis method to determine the discrimination of the power of the index (Maximum sensitivity and specificity) that can be used in prediction of liver fibrosis, and the area under the curve (AUC) and %95 confidence interval were calculated. Youden index was used to determine the best cut-off point in ROC analysis. In order to determine the effective candidate variables for the success of classifying before the ROC analysis, logistic regression (LR)analysis was performed. In the LR analysis, significant variables that could be effective to discriminate the groups were investigated by backward Wald method. Statistical significance level was chosen $p<0.05$.

RESULTS

Of the 140 cases, 80 (57. 1%) were men and 60 (42.9%) were women. The mean age of the patients was 44.79±12.19 (20-85). The mean age of the group F0-2 was 43.25±11.53 (20-65). The mean age of the group F3-6 was 47.63±12.96 (29-85). There was significant difference between the mean ages according to the fibrosis groups (p=0.042, Table 1). There were 20 (14.3%) patients with HBeAg positive, and 120 (85.7%) with HBeAg negative.

There were 91 (65%) patients in the group F0-2 and 49 (35%) in F3-6. There was statisticallysignificant difference between these two groups for histological activity index (HAI), AST, GGT and lymphocyte (LYM) parameters (p< 0.001, p=0.007, p=0.014, p=0.438 respectively) (Table 1). Although we did not detect a significant difference between the two groups for PLT, MPV, PDW, PCT.

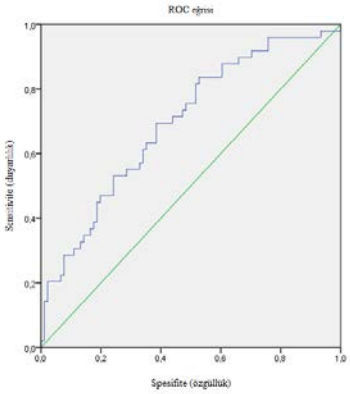

Figure 1. ROC curve results of our new index

In LR analysis, the independent variables determining the severity of fibrosis were age, AST and LYM (p=0.039, p=0.009, p=0.042 respectively; Table 2). As a result of LR analysis, we found a new candidate index which gave the highest area under the ROC curve value from many different combinations using age, AST, GGT, LYM and PLT variables. For our new index (AST x Age x $\mathrm{LYM})/(\sqrt{\mathrm{PLT}})$ AUROC was found 0.695 (Figure 1).

Two cut-off points of 299.85 and 159.81 were found in consequence of Youden index. Fibrosis classification results for the ones whose candidate index values are >159.81 and ≤ 299.85. When the our new index value was > 159.81, sensitivity was found 83.7%, specificity 47.3%, negative predictive value (NPV) 84.3% and positive predictive value (PPV) 46.1% in discriminating the group F3-6. When the cut-off value of our candidate index was determined ≤ 299.85, specificity was found 81.3%, sensitivity 44.9%, NPV 73.3%, and PPV 56.4% in discriminating the group F0-2. The index we found (AST x Age x $\mathrm{LYM})/(\sqrt{\mathrm{PLT}})$ was compared with the indices that have been widely used in the literature before and the other alternative indices that we formed according to the area under the ROC curve values.

In the study, ROC area, cut-off, specificity and sensitivity analyses of the indices with a ROC area value of higher than 0.600 were presented in Table 3.

As the ROC area values of other indices were not accepted statistically significant, their cut-off, specificities and sensitivities were not calculated.

Table 1. Comparison of cases with liver fibrosis scores 0-2 and 3-6.

	F0-2 (n=91)				F3-6 (n=49)				p
	Mean±SD	**Median**	**Min**	**Max**	**Mean ± SD**	**Median**	**Min**	**Max**	
Age	43.25 ± 11	45	20	65	47.63 ± 12.96	52	29	85	0.042[a]
HAI	5.21 ± 2.01	5.00	2.00	11.00	8.35 ± 2.49	9.00	4.00	14.00	<0.001 [b]
HBsAg (S/CO)	3738.67± 1668.70	4153.00	294.00	6545.00	3668.82 ± 1626.26	3665.00	361.00	7591.00	0.696 [b]
HBV DNA (IU/mL)	39363734 ± 161660897	40198	2467	1190000000	17805264 ± 47430681	251000	1208	170000000	0.093 [b]
Glu (mg/dL)	93.69 ±9.90	94.00	67.00	117.00	96.06 ± 11.89	92.00	75.00	121.00	0.598 [b]
Urea (mg/dL)	29.14 ±8.13	28.10	12.00	50.00	28.77 ± 8.26	28.50	14.30	48.70	0.800[a]
Cre (mg/dL)	0.72 ±0.16	0.70	0.46	1.12	0.76 ± 0.14	0.77	0.50	1.00	0.056 [b]
Alb (g/dL)	4.40±0.30	4.40	3.60	5.20	4.39 ± 0.32	4.40	3.80	5.10	0.897 [a]
AST (U/L)	35.00±27.87	26.00	10.00	202.00	52.94 ± 50.24	35.00	14.00	264.00	0.007 [b]
ALT (U/L)	52.26±59.36	34.00	11.00	437.00	86.71 ± 117.40	47.00	12.00	669.00	0.099 [b]
ALP (U/L)	78.05 ±25.03	71.00	37.00	154.00	92.65 ± 50.16	81.00	27.00	301.00	0.054 [b]
GGT (U/L)	24.46 ±16.31	21.00	8.00	118.00	38.51 ± 48.45	26.00	7.00	311.00	0.014 [b]
T. Bil (mg/dL)	0.72 ±0.33	0.68	0.15	1.80	0.78 ± 0.39	0.70	0.28	2.14	0.618 [b]
INR	1.01 ± 0.09	1.01	0.81	1.39	1.05 ± 0.11	1.03	0.83	1.41	0.058 [b]
WBC (10^9/L)	6.75±1.48	6.70	3.80	11.80	6.92± 1.57	6.70	3.80	10.40	0.546 [a]
HB (g/dL)	14.77±1.47	14.90	11.40	17.40	14.89 ± 1.49	14.70	11.00	17.60	0.634 [b]
HTC (%)	44.83±3.78	44.80	37.00	51.20	44.89± 4.45	44.50	34.30	52.80	0.896 [b]
MCV (fL)	88.60±4.31	88.50	77.30	99.40	88.81± 6.23	89.40	69.60	104.30	0.580 [b]
RDW (%)	13.30±0.93	13.10	11.80	17.80	13.42± 1.08	13.30	11.20	16.70	0.297 [b]
PLT (10^9/L)	233.44±47.27	226.00	139.00	379.00	230.47± 81.83	217.00	79.00	561.00	0.265 [b]
MPV (fL)	9.90±1.18	10.00	7.60	12.80	9.71± 1.28	9.60	7.60	12.70	0.367 [a]
PCT (%)	0.2± 30.05	0.22	0.13	0.33	0.22± 0.07	0.21	0.09	0.46	0.141 [b]
PDW	16.13±0.36	16.20	15.30	16.90	16.09 ± 0.42	16.00	15.20	16.90	0.576 [a]
Neut. (10^9/L)	3.91± 1.15	3.67	2.20	8.26	3.83 ± 1.09	3.68	2.07	7.18	0.948 [b]
Lym. (10^9/L)	2.25 ± 0.55	2.24	0.94	4.30	2.45± 0.81	2.19	1.11	4.44	0.438 [b]
Mon. (10^9/L)	0.43± 0.14	0.40	0.21	0.97	0.48± 0.17	0.46	0.21	1.01	0.052 [b]
Eos. (10^9/L)	0.17± 0.13	0.13	0.02	0.79	0.20± 0.19	0.14	0.02	1.13	0.498 [b]
Baso (10^9/L)	0.03 ± 0.01	0.02	0.01	0.07	0.03 ± 0.02	0.03	0.01	0.13	0.879 [b]

[a]Student's *t-test*, [b] Mann-Whitney

Table 2. LR backward Wald method results

B (Estimation coefficients)	p	Odds Ratio	OR for 95% C.I.		
			Min	Max	
Age	0.032	0.039	1.033	1.002	1.065
AST	0.015	0.009	1.015	1.004	1.026
LYM	0.588	0.042	1.801	1.020	3.178

Table 3. Comparison of the indices with higher ROC area values in our study

Index	*P*	ROC Area	Cut-off	Sensitivity (%)	Specificity (%)
Our candidate index	< 0.001	0.695	159.81	83.7	47.3
Our candidate index	< 0.001	0.695	299.85	44.9	81.3
FIB-4	0.002	0.656	1.492	40.8	87.8
GGT/PLT	0.012	0.628	0.113	59.2	68.1
APRI	0.016	0.624	0.912	40.8	91.2
LYM/PCT	0.042	0.605	10.15	67.3	53.8
PLR	0.046	0.603	104.32	71.4	51.6

DISCUSSION

In this study, we aimed to investigate whether exists a relationship between the liver histology and platelet parameters in 140 CHB patients, whose liver biopsies had been performed and routine laboratory tests had been conducted simultaneously. In addition to the platelet parameters, we compared other routine laboratory tests between the two groups. We compared our new index, which has not been used in the literature before and which we have newly created by using many different combinations with the data that significant difference were detected in terms of liver fibrosis, with the indices which are currently used in the literature. In our study, modified Ishak scoring system was used to determine fibrosis in liver biopsy. According to this scoring, the patients were seperated into two groups as F0-2 (No fibrosis or mild fibrosis) and F3-6 (Moderate-severe fibrosis). Significant difference was found in age, AST and LYM parameters (p=0.039, p=0.009, p=0.042 respectively) between the two groups. Statistically significant difference was detected in mean HAI and GGT scores (p< 0.001, p=0.014 respectively) between the two groups. No significant difference was detected in the other parameters between the groups.

Age, AST, GGT and LYM parameters, which was observed to be significant in consequence of the analyses conducted, were used in new formulations. Platelet variable was added to the formulations in order to increase the prognostic power. Contrary to what was expected, it was found that prognostic power decreased in the formulas in which GGT parameter was added. AUROCof our index (AST x Age x $\mathrm{LYM})/(\sqrt{\mathrm{PLT}})$, which we created by using many different combinations in our study, was found 0.695 (0.605-0.786). Two cut-off points of 299.85and 159.81 were found in consequence of Youden index.

The indices that have been used in the literature were compared between the two groups in our study. In this study, ROC area, cut-off, specificity and sensitivity analyses of the indices with a ROC area value of higher than 0.600 were presented in Table 3.

AUROC value of our candidate index (0.695) was found to be superior to AUROC values of other indexes that are used in the literature. In our patient group, it was found that sensitivities of APRI and FIB-4 indices, which have successful ROC values and are frequently used in the literatürewere lower and their specificities were found higher than those of our candidate index[14].In the literature, there are only a few studies the correlation between MPV and the liver fibrosis score in chronic hepatitis[15-16]. 59 patients with HBV in one of these studies were divided into two groups according to the fibrosis scores in the Metavir scoring system. Those with scores of 0–2 and 3–4. They were compared HAI, platelet count, MPV, serum HBV DNA, and ALT levels.

The findings of this study pointed that MPV is an independent predictor of fibrosis score severity[16]. In another study, 59 patients with CHB virus infection were appreciated, and showed that patients with severe fibrosis had a greater MPV than those with mild fibrosis[15]. In a study Ceylan et al. performed, it

was concluded that low MPV levels and increased RDW levels were associated with severe fibrosis hepatitis B patients[1]. In a study conducted by Hakyemez et al. in 2016 with a total 434 patients with CHB, it was found that PCT was statistically correlated with severe fibrosis stage[17].

It was found that PLR is a prognostic parameter which is an indicator of systemic inflammation in various cancer treatments including HCC[18-20]. In a study conducted by Li et al. when the results of HCC treatment were assessed, it was found that PLR was closely associated with progression[21]. Also, in another study conducted by Meng et al. İt was detected that the grade of liver disease was closely correlated with the PLR in the patients with CHC[22].

Considering all of these results, that there was not homogeneous distribution between the fibrosis groups and the number of the patients who were diagnosed severe fibrosis was limited might be the cause of why the results were different. In histopathological examination in our study, that the number of patients with stage 4 or 5 fibrosis were elimeted and there was not any patients with stage 6 fibrosis are the limitations of the study. Also, in our retrospective study, another limitation is that some of the patients with severe stage fibrosis were excluded from the study because of data losses.

In conclusion, the formulation of (AST x Age x LYM) / $\sqrt{PLT}$) which was formed from many different combinations by using the platelet count and the parameters. AUROC value (0.695) of our candidate index was found superior to AUROC values of other indexes used in the literature. In order for our new index to be used as a noninvasive marker safely, further studies that have larger sample sizes in which there are more patients with severe stage liver fibrosis are needed.

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