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Is mean platelet volume better than other long-used non-invasive parameters in assessing severe fibrosis in patients with chronic hepatitis B?

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ABSTRACT

Aim: This study was aimed at i-) investigating the correlation between the severity of hepatic fibrosis and mean platelet volume (MPV) ii-) comparing the accuracy rate of MPV with that of other long-used non-invasive parameters in predicting severe hepatic fibrosis in patients with chronic hepatitis B (CHB).

Material and Method: Ninety-nine patients with CHB were enrolled. The patients were assigned to two groups, based on their hepatic fibrosis scores. Those with scores ranging from 0 to 3 (mild to moderate fibrosis) were assigned to Group 1, and those with scores ranging from 4 to 6 (severe fibrosis) were included in Group 2.

Results: The mean age of the patients was 42±13, and 69 (70%) of them were male. Twenty two patients (22%) were in Group 2. Patients in Group 2 displayed significantly lower albumin and platelet count ($p<0.001$), and significantly higher aspartate aminotransferase-to-platelet ratio index (APRI) and MPV ($p<0.001$). Among the parameters in detecting severe fibrosis, the most sensitive (90%) test was MPV at a cut-off value of ≥10 fl, whilst the most specific (95%) test was platelet count at a cut-off value of ≤150x10^3/mm^3. The accuracy rates of albumin, platelet count, MPV, and APRI were 79%, 91%, 90%, and 77%, respectively.

Conclusions: Among the parameters for the detection of severe fibrosis in patients with CHB, the most sensitive test was MPV and the most specific test was platelet count. When assessed for their accuracy rates, it was determined that platelet count was superior to the other parameters.

Keywords: Albumin, aspartate aminotransferase to platelet ratio index, chronic hepatitis B, fibrosis, mean platelet volume, platelet count

INTRODUCTION

According to data published by the World Health Organisation (WHO), it is estimated that worldwide 257 million people are chronically infected with hepatitis B virus (HBV), which is a major cause of hepatic cirrhosis and hepatocellular carcinoma (HCC) (1-3).

The risk of developing HCC and other liver-related complications is higher in chronic hepatitis B (CHB) patients with advanced hepatic fibrosis or cirrhosis. Therefore, the accurate prediction of the severity of hepatic fibrosis in these patients is of major significance (2,4).

Liver biopsy remains the gold standard of detecting hepatic fibrosis. However, being an invasive procedure, liver biopsy is associated with the risk of several complications. To exemplify, following liver biopsy, the risk of developing severe haemorrhage is 3/1000 and the risk of mortality is 3/10000. Furthermore, biopsy specimens represent only a very small portion (1/50000) of the total hepatic volume. Moreover, the examination results of liver biopsy specimens may present with intraobserver and interobserver variability (5). In view of these limitations of liver biopsy, several non-invasive models have been tried to be developed for the assessment of hepatic fibrosis in patients with CHB, and several literature reports have been published (6-8). However, as most of these models have been tested by different researchers in different groups of patients, standardisation has not been achieved. Further to that, some of these models involve the use of expensive blood tests. Thus, it has not been possible to put these non-invasive models into routine clinical use.

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Albumin is a significant plasma protein synthesized in the liver, and its production decreases in the event of chronic hepatic failure and hepatic fibrosis (9,10). Similar to the measurement of the serum albumin level, the platelet count is also a simple and inexpensive laboratory method. Cases of chronic hepatic diseases may be associated with thrombocytopenia due to several reasons, including the splenic sequestration of platelets, the suppression of the bone marrow and the decrease of thrombopoietin production (11). In this respect, both serum albumin level and platelet count have long served as two simple and inexpensive laboratory methods for the demonstration of chronic hepatic failure and hepatic fibrosis.

Mean platelet volume (MPV) is a standard component of routine complete blood counts, and recently, it has been used to determine the severity of inflammatory disorders, and has been suggested as a potential biomarker for proinflammatory and prothrombotic diseases (12). Studies have been carried out on the correlation between non-alcoholic fatty liver disease (NAFLD) and MPV (13,14). However, only very few studies are available on the correlation of hepatic fibrosis and hepatic inflammation level with MPV in CHB patients, and a complete standardisation has not been able to be established for the results of these studies.

Another simple, non-invasive and inexpensive parameter, known to be available before the use of MPV, for the detection of hepatic fibrosis and inflammation, is the aspartate aminotransferase-to-platelet ratio index (APRI) (15).

In this study, we aimed to i-) assess the correlation of hepatic fibrosis level with MPV in CHB patients and ii-) compare the accuracy rate of MPV with that of other long-used parameters (serum albumin, platelet count, and APRI) in predicting severe hepatic fibrosis.

MATERIAL AND METHOD

The study was conducted pursuant to the approval of the Local Ethics Committee. This study was performed at the outpatient clinic of the Department of Gastroenterology of Bursa Yüksek İhtisas Training and Research Hospital. Ninety-nine treatment-naive patients with CHB were enrolled in the retrospective study.

The demographic, clinical, laboratory, and histopathological data of the patients were obtained from a computerized patient registry database. It was confirmed that all laboratory measurements had been performed within one month before or after the liver biopsy.

Hepatic fibrosis staging and histological activity index (HAI) score were assessed according to the Modified Ishak Scoring System (16). The APRI score was calculated with the formula: (Aspartate aminotransferase/40)/ platelet (10^9/L)×100 (15). The patients were divided into two groups, namely, Group 1 and Group 2, according to their hepatic fibrosis scores. Those with scores ranging from 0 to 3 (mild to moderate fibrosis) were assigned to Group 1, and those with scores ranging from 4 to 6 (severe fibrosis) were included in Group 2. The patients were also divided into two groups on the basis of their HAI scores. Those with scores ranging from 0 to 9 (mild to moderate inflammation) were assigned to Group A, and those with scores ranging from 10 to 18 (severe inflammation) were included in Group B.

Patients, who had undergone liver biopsy with a diagnosis of chronic HBV infection and for whom laboratory data was available within one month before or after the biopsy, were included in the study.

Patients, who had a history of atherosclerotic heart disease, diabetes mellitus, hypertension, renal failure, asthma, chronic obstructive pulmonary disease, peripheral/cerebral vascular disease, haematological disorders, cirrhosis, portal hypertension, splenectomy, rheumatic diseases, pregnancy, malignancies, and any medication use capable of influencing platelet function (e.g., aspirin, heparin), were excluded from the study.

Statistical Analyses

The data were analysed using the Statistical Package for the Social Sciences version 20.0 (SPSS Inc., Chicago, Illinois, USA). The Kolmogorov-Smirnov test was used to assess the normal distribution of the continuous variables. Values were expressed as mean ± standard deviation (SD) for normally distributed variables, as median and 25^{th}-75^{th} percentiles for non-normally distributed variables, and count and percent for categorical variables. In univariate analysis, variables were compared using the independent t-test for normally distributed data, the Mann–Whitney U-test for non-normally distributed data, and the chi-square test for categorical data. The Pearson correlation coefficient was used to assess the association between the variables. Receiver-operating characteristic (ROC) curve analysis with a 95% confidence interval (CI) was used to establish optimal cut-off value, sensitivity, specificity, and accuracy rate for MPV, APRI, platelet, and albumin for the detection of severe fibrosis. For all analyses, a P value less than 0.05 was considered to be statistically significant.

RESULTS

Out of the 99 patients enrolled in this study, 69 (70%) were male and their mean age was 42±13 years (range: 18-76). The number of patients found to be positive

for hepatitis B early antigen (HBeAg) and anti-HBeAg were 7 (7%) and 92 (93%), respectively. The median HBV-DNA, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, APRI, and fibrosis of the patients were 60x10³ IU/ml, 32 U/L, 44 U/L, 4.3 g/dl, 0.46, and 2, respectively. Furthermore, the mean total bilirubin, prothrombin time, platelet, MPV, and HAI values of the patients were 0.7 mg/dL, 12.4 s, 200x10³/mm³, 9.5 fl, and 7, respectively (**Table 1**).

Table 1. Demographic and laboratory parameters of the patients (n: 99)

Parameters	Value
Age±SD (years)	42 (±13)
Gender (M/F), n (%)	69/30 (70/30)
HBeAg positivity, n (%)	7 (7)
Anti-HBe positivity, n (%)	92 (93)
HBV DNA* (x10³ IU/mL)	60 (8-3010)
AST* (U/L)	32 (24-51)
ALT* (U/L)	44 (22-81)
Total bilirubin±SD (mg/dL)	0.7 (±0.3)
Protrombin time±SD (s)	12.4 (±1.7)
Albumin* (g/dl)	4.3 (4.0-4.5)
Platelet±SD (x10³/mm³)	200 (±63)
MPV±SD (fl)	9.5 (±1.3)
APRI*	0.46 (0.28-0.76)
HAI±SD	7 (±3)
Fibrosis*	2 (1-3)

SD: Standard deviation, M: Male, F: Female, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, MPV: Mean platelet value, APRI: AST to Platelet Ratio Index, HAI: Histologic activity index, *: Median (25th-75th percentiles)

Based on their hepatic fibrosis scores, 77 (78%) of the patients were assigned to Group 1, and 22 (22%) were assigned to Group 2. The mean age of the patients was 39±12 years in Group 1 and 51±13 years in Group 2. Patients with severe fibrosis were older than those with mild to moderate fibrosis (p=0.01). Group 1 and Group 2 did not differ for sex distribution. The number of HBeAg-positive patients was 3 (4%) in Group 1 and 4 (18%) in Group 2, and the percentage of HBeAg positivity was higher in the group with severe fibrosis (p=0.02). Groups 1 and 2 showed no significant difference for anti-HBe positivity, HBV-DNA, total bilirubin, and ALT levels (p>0.05). In Group 2, the prothrombin time was longer, the AST level was higher and the albumin level and platelet count were lower, when compared to Group 1 (p<0.05). The median APRI value was 0.4 in Group 1 and 0.8 in Group 2 (p<0.001). HAI scores and MPV values were 6.4 and 8.9 fl, respectively, in Group 1, and 10 and 11 fl, respectively, in Group 2. The HAI score and MPV value were significantly higher in the group with severe fibrosis (p<0.001) (**Table 2**).

Based on the HAI, 76 (77%) of the patients were assigned to Group A and 23 (23%) were assigned to Group B. The mean age of the patients was higher in Group B (p=0.01). The HBV-DNA, AST, and ALT levels were significantly higher in Group B, compared to Group A (p<0.05). No difference was detected between the two groups for gender, HBeAg/anti-HBeAg positivity, prothrombin time, and total bilirubin levels. Platelet counts and albumin were significantly lower in Group B, when compared to Group A (p<0.05). MPV, APRI, and fibrosis score were significantly higher in Group B, compared to Group A (p<0.05) (**Table 3**).

Hepatic fibrosis was determined to be positively correlated with MPV (r=+0.77) and APRI (r=+0.50), and negatively correlated with albumin level (r=-0.43) and platelet count (r=-0.42) (p<0.001) (**Figure 1**).

Table 2. Comparison of the patients according to liver fibrosis scores

Parameters	Group 1, n: 77 (78%)	Group 2, n: 22 (22%)	p
Fibrosis score range	0-3	4-6	
Age±SD (years)	39 (±12)	51 (±13)	0.01
Gender (M/F), n (%)	50/27 (65/35)	19/3 (86/14)	0.06
HBeAg positivity, n(%)	3 (4)	4 (18)	0.02
Anti-HBe positivity, n(%)	73 (95)	19 (86)	0.2
HBV DNA* (x10³ IU/ml)	40 (8-1411)	76 (7-11420)	0.25
AST* (U/L)	32 (23-42)	51 (28-150)	0.01
ALT* (U/L)	42 (11-70)	50 (27-149)	0.1
Total bilirubin±SD (mg/dL)	0.6 (±0.3)	0.8 (±0.5)	0.1
Protrombin time±SD (s)	13 (±1.4)	15 (±1.8)	0.001
Albumin* (g/dl)	4.4 (4.2-4.5)	3.8 (3.6-4.0)	<0.001
Platelet ±SD (x10³/mm³)	218 (±56)	136 (±41)	<0.001
MPV±SD (fl)	8.9 (±0.9)	11 (±0.9)	<0.001
APRI*	0.4 (0.3-0.6)	0.8 (0.5-3)	<0.001
HAI±SD	6.4 (±1.7)	10 (±2.4)	<0.001

SD: Standard deviation, M: Male, F: Female, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, MPV: Mean platelet value, APRI: AST to Platelet Ratio Index, HAI: Histologic activity index, *: Median (25th-75th percentiles)

Table 3. Comparison of the patients according to liver histologic activity index scores

Parameters	Group A, n: 76 (77%)	Group B, n: 23, (23%)	p
HAI score range	0-9	10-18	
Age±SD (years)	40 (±13)	48 (±12)	0.01
Gender (M/F), n (%)	51/25 (67/33)	18/5 (78/22)	0.3
HBeAg positivity, n(%)	4 (3)	5 (13)	0.2
Anti-HBe positivity, n(%)	71 (93)	21 (91)	0.7
HBV DNA* (x10³ IU/ml)	24 (7-1487)	693 (45-8560)	0.02
AST* (U/L)	30 (23-41)	74 (31-157)	0.001
ALT* (U/L)	38 (21-68)	91 (28-158)	0.01
Total bilirubin±SD (mg/dL)	0.7 (±0.3)	0.8 (±0.5)	0.1
Protrombin time±SD (s)	13 (±1.4)	14 (±2)	0.1
Albumin* (g/dl)	4.4 (4.2-4.5)	3.9 (3.8-4.2)	0.001
Platelet ±SD (x10³/mm³)	211 (±60)	164 (±65)	0.02
MPV±SD (fl)	9 (±1.1)	11 (±0.9)	0.001
APRI*	0.37 (0.3-0.5)	0.96 (0.4-3.3)	0.001
Fibrosis*	2 (1-3)	3 (2-3)	0.001

SD: Standard deviation, M: Male, F: Female, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, MPV: Mean platelet value, APRI: AST to Platelet Ratio Index, HAI: Histologic activity index, *: Median (25th-75th percentiles)

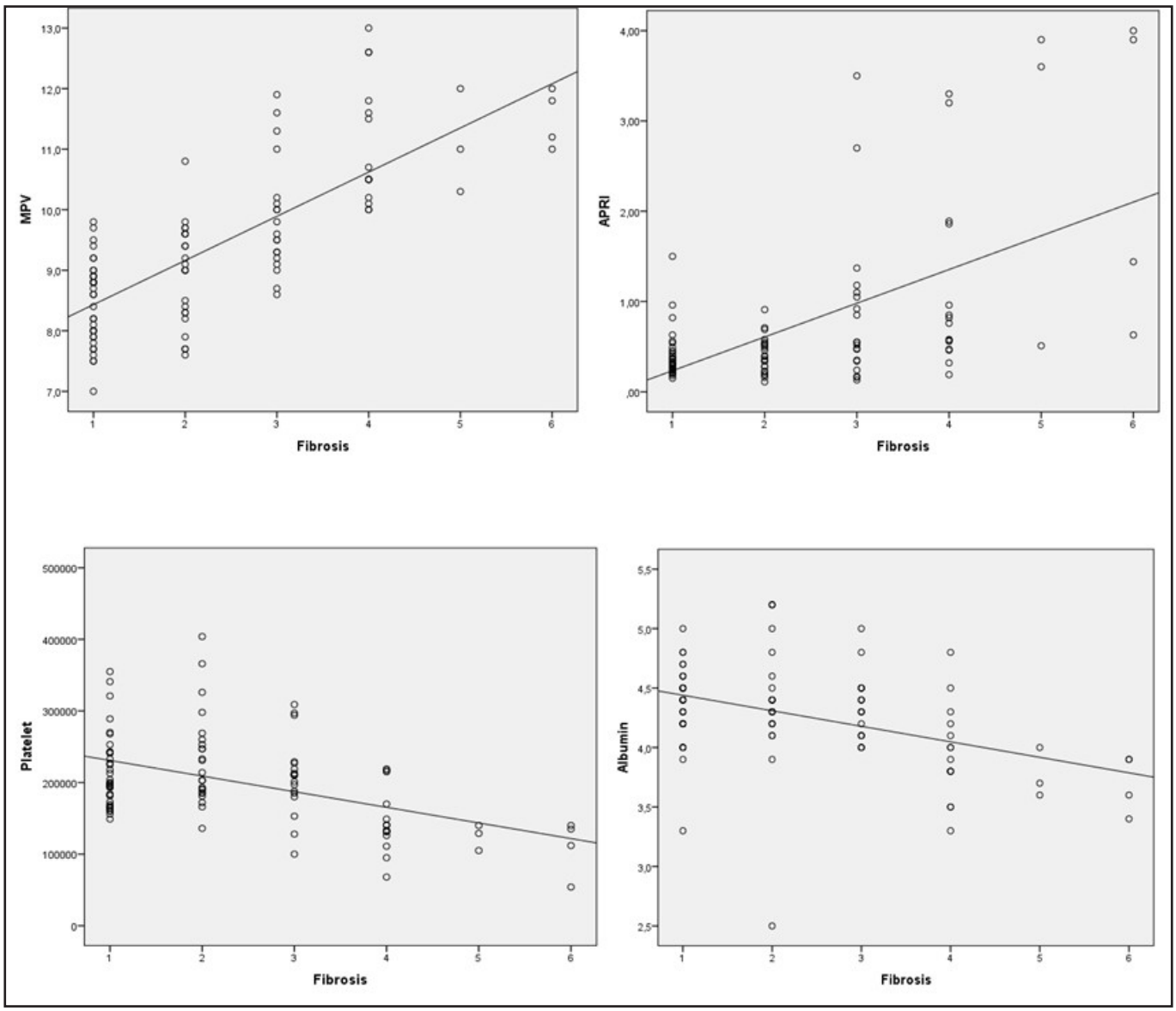

Figure 1. Scatter diagrams showing correlation between fibrosis and different values (MPV: mean platelet value, APRI: Aspartate aminotransferase to Platelet Ratio Index, platelet count, and albümin, respectively). Coefficients (r) and p values were calculated using Spearman correlation analysis. Coefficients (r)/p values for MPV, APRI, platelet, and albumin were +0.77, +0.50, -0.42, and -0.43, respectively (p<0.001).

The ROC analysis performed to determine the accuracy rates of albumin level, platelet count, MPV, and APRI in detecting severe fibrosis revealed area under the curve (AUC) values of 0.86 (0.75-0.96), 0.89 (0.80-0.98), 0.95 (0.92-0.99), and 0.81 (0.71-0.92), respectively, for these parameters (**Figure 2**).

The cut-off values established for albumin level, platelet count, MPV, and APRI for detecting severe fibrosis were ≤4.0 g/dl, ≤150x10^3/mm^3, ≥10 fl, and ≥0.55, respectively. Accordingly, the parameter most sensitive in detecting severe fibrosis was found to be MPV (90%), and the most specific parameter was proven to be platelet count (95%). The accuracy rates were 79%, 91%, 90%, and 77% for albumin level, platelet count, MPV, and APRI, respectively (**Table 4**).

Table 4. Statistical diagnostic measures of different noninvasive variables in the detection of severe fibrosis

Diagnostic measures	Variables and cut-off values			
	Albumin (≤4.0 g/dl)	**Platelet (≤150x10^3/mm^3)**	**MPV (≥10 fl)**	**APRI (≥0.55)**
AUC (95% CI)	0.86 (0.75-0.96)	0.89 (0.80-0.98)	0.95 (0.92-0.99)	0.81 (0.71-0.92)
SEN (%)	81	82	90	77
SPE (%)	80	95	91	78
AR (%)	79	91	90	77
p value	<0.001	<0.001	<0.001	<0.001

MPV: Mean platelet value, APRI: Aspartate aminotransferase to Platelet Ratio Index, AUC: Area under the ROC curve, SEN: Sensitivity, SPE: Specifity, AR: Accuracy rate.

DISCUSSION

Due to liver biopsy being an invasive diagnostic method associated with the risk of several complications, research has been carried out on alternative non-invasive, easily applicable, inexpensive models that can be used for the detection of hepatic fibrosis and inflammation (17). One of the most common models tested for this purpose is APRI (17,18). APRI was first described as a simple, easily detectable and inexpensive marker that could be used to detect significant fibrosis in patients with chronic hepatitis C (CHC) (15). Later, it was also reported as a reliable marker of significant fibrosis in patients with CHB (19). Shoaei et al. determined that APRI was significantly correlated with the Knodell histological activity index and the Ishak fibrosis score in 137 patients with CHB, and suggested that this index would be of use in detecting severe fibrosis and necroinflammation (20). Similarly, the present study demonstrated that APRI values were significantly correlated with advanced hepatic fibrosis and marked necroinflammation.

Serum albumin level and platelet count, both of which have also been long-used as simple, inexpensive, and non-invasive markers similar to APRI in detecting chronic hepatic diseases, have been demonstrated to be negatively correlated with the severity of these diseases (9-11). Likewise, in the present study, both serum albumin levels and platelet counts were observed to be significantly and negatively correlated with hepatic fibrosis and necroinflammation.

Platelets have an essential role in the development of inflammation and the immune response, and antiplatelet treatment is known to reduce mortality rates caused

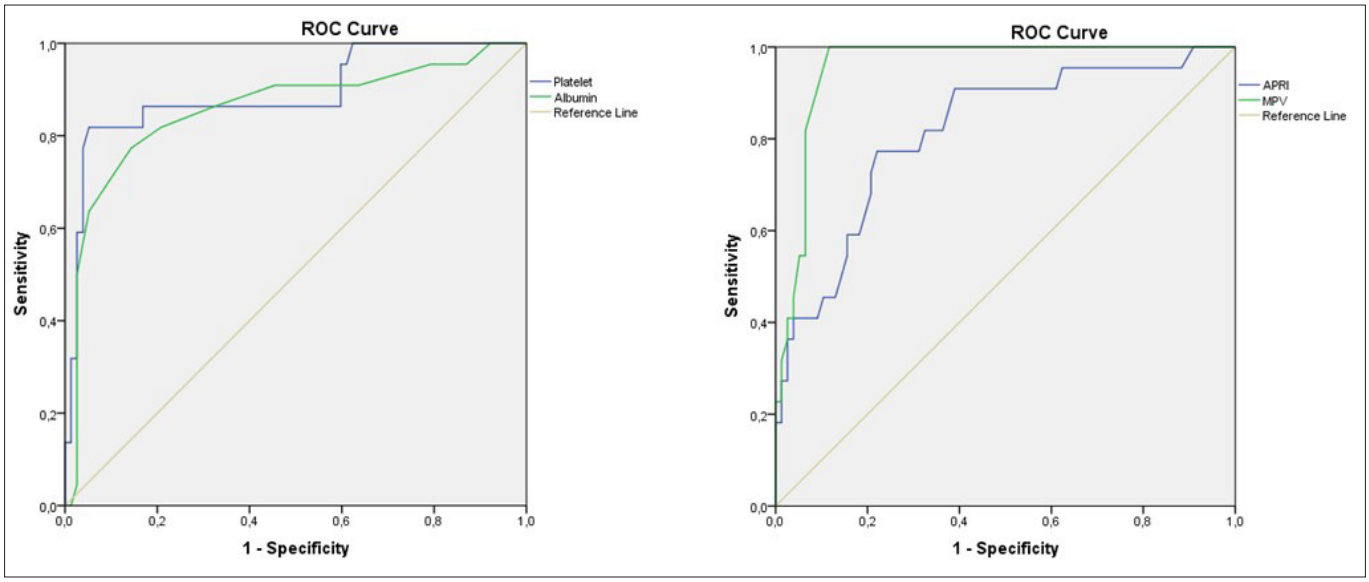

Figure 2. Comparison of receiver operating characteristic curves of albumin, platelet, mean platelet value (MPV), and Aspartate aminotransferase to Platelet Ratio Index (APRI) values in identifying severe fibrosis. For severe fibrosis area under receiver operating characteristic (ROC) curves were 0.86 (0.75-0.96), 0.89 (0.80-0.98), 0.95 (0.92-0.99), and 0.81 (0.71-0.92) for albumin, platelet, MPV, and APRI, respectively and the differences between four areas were statistically significant.

by sepsis and infection (12,21,22). In recent years, the involvement of platelets in inflammation has drawn much interest. MPV, which is a platelet parameter, has been reported to increase in the event of inflammatory diseases, including rheumatoid arthritis (23-25), ulcerative colitis (26), Crohn's disease (27), and acute pancreatitis (28). On the other hand, only very few literature reports are available on the correlation between MPV and chronic hepatic damage. Further to that, the number of studies on the correlation of MPV with hepatic fibrosis and inflammation in CHB patients is particularly low. Research investigating the correlation of NAFLD with MPV has shown that MPV values are higher in cases of NAFLD (13). Abdel-Razik et al. (14) reported that in patients with NAFLD, MPV was positively correlated with the NAFLD activity score, and also determined that MPV was higher in the group with advanced fibrosis (fibrosis=3-4). Therefore, these researchers suggested that MPV could be used in determining advanced cases of hepatic fibrosis. Similarly, in the present study, MPV values were significantly higher in the group with severe fibrosis, in comparison to the group with mild to moderate fibrosis. Different from the study of Abdel-Razik et al. (14), the patients enrolled in the present study had been diagnosed with CHB. In a previous study on patients with chronic inactive hepatitis B and healthy controls, it was determined that MPV values were significantly higher in chronic inactive hepatitis B patients (29). Based on their comparative assessment of 17 patients with acute hepatitis B, 62 patients with CHB, 41 patients with severe chronic hepatitis B, and 58 healthy volunteers, Hu et al. (30) ascertained that MPV values were higher in the patients with CHB and were correlated with the severity of the infection. In another study on patients diagnosed with CHB and CHC, it was observed that in the group with CHC, MPV values were higher in the patients with advanced fibrosis, compared to the patients in the early stage of hepatic fibrosis, yet no such difference was detected in the patients with CHB. Another report on CHB patients indicated that, although statistically insignificant, MPV values were lower in patients with advanced hepatic fibrosis, compared to those with early-stage fibrosis (31). In a more recent study conducted by Hamidi et al. (32) on CHB patients, who had undergone liver biopsy, MPV values were observed to be higher in patients with advanced fibrosis (stages 3-6), compared to those with early-stage fibrosis (stages 1-2). In another study on the correlation between fibrosis and MPV in CHB patients, the comparison of 59 patients with CHB and 25 healthy volunteers demonstrated that MPV values were higher in the infected group. The subgroup analysis of the patients, based on METAVIR scoring, similar to the results of the present study, demonstrated that MPV values were higher in the group with advanced fibrosis (fibrosis=3-4), compared to patients with insignificant fibrosis (fibrosis=0-2), and were also correlated with the severity of hepatic fibrosis (33). In a previous study by Karagoz et al. (34), in agreement with the present study, MPV values were found to be higher in CHB patients with advanced fibrosis (fibrosis=3-6), compared to patients with mild fibrosis (fibrosis=0-2). Differently, in the present study, the group with severe fibrosis included patients with fibrosis scores ranging from 4 to 6, according to the Modified Ishak Scoring Method. Ceylan et al. (35) reported that, in their research on 238 patients diagnosed with CHB, of which those with a HAI score of 0-9 had been assigned to the group with mild to moderate inflammation and those with a HAI score of 10-18 had been assigned to the group with severe inflammation, MPV was proven to be a reliable marker in detecting the severity of inflammation. In the present study, the comparison of the group with the same inflammation score showed that MPV values were higher in the patients with severe inflammation.

The major limitations of the present study are it being a retrospective study covering a relatively small number of patients.

CONCLUSION

Among the simple, non-invasive, and inexpensive parameters (serum albumin level, platelet count, MPV, and APRI) tested in detecting severe fibrosis in treatment-naive CHB patients, the most sensitive test was MPV at a cut-off value of ≥10 fl, whilst the most specific test was platelet count at a cut-off value of $\leq 150x10^3/mm^3$. However, when compared for accuracy rate in predicting severe fibrosis, it was demonstrated that platelet count ($\leq 150x10^3/mm^3$) was superior to the other parameters (serum albumin, MPV, and APRI).

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Ethics Committee of Bursa Yüksek İhtisas Training and Research Hospital (Date: 09 December 2020, Protocol no: 2011-KAEK-25 2020/12-06).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Referee Evaluation Process: Externally peer-reviewed. Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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