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Mean platelet volume as a fibrosis marker in patients with chronic hepatitis C

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Aim: We designed this study to evaluate the role of mean platelet volume (MPV) as a fibrosis marker in patients with chronic hepatitis C (CHC).

Materials and methods: The study was designed at Kayseri Education and Research Hospital. Ninety-five patients with CHC were enrolled retrospectively into the study. The control group comprised 33 age- and sex-matched healthy individuals. Hepatitis C virus-RNA level, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, prothrombin time (PT), platelet count (PC), serum albumin, histological activity index (HAI), liver fibrosis score (LFS), and MPV were obtained from the patients' files and a computerized database.

Results: Statistically significant differences in MPV and PC were seen in patients with CHC compared to healthy controls (MPV: 9.1 ± 1.31 fL vs. 8.58 ± 0.8 fL, P = 0.008; PC (×103/μL): 219.37 ± 74.31 vs. 258.52 ± 48.34, P = 0.001). In multivariate analysis, 4 variables remained as independent risk factors: AST (OR 1.11, 95% CI 1.02 to 1.21), ALT (OR 0.92, 95% CI 0.86 to 0.99), PT (OR 2.11, 95% CI 1.15 to 3.88), and MPV (OR 2.28, 95% CI 1.22 to 4.25). Cut-off values were calculated for diagnostic performance, and the cut-off value for MPV was 8.4 fL.

Conclusion: We suggest that high MPV levels (especially those over 8.4 fL) may help to predict advanced fibrosis in patients with CHC. However, it should not be forgotten that MPV is not a specific marker for fibrosis, and the negative predictive rate seems more valuable to exclude a high fibrosis ratio in patients with CHC.

Key words: MPV, chronic hepatitis C, fibrosis

1. Introduction

Hepatitis C virus (HCV) was discovered in 1989 (1). It was found to be responsible for the majority of chronic non-A and non-B hepatitis and cryptogenetic liver diseases (2,3). In a study from Turkey, it was found that the prevalence of HCV was 0.4% in blood donors (4). In adults, acute HCV infection leads to chronic infection in approximately 80% of cases. Approximately 120–130 million individuals are chronically infected with HCV worldwide. The risk of chronic hepatitis C (CHC) infection after an acute episode is high. In many studies, 80% to 100% of patients remain HCV-RNA positive, and 60% to 80% have persistently elevated liver enzymes (5). The mechanism responsible for the high prevalence of CHC infection is unclear. It may be related to the genetic diversity of the virus and its tendency toward rapid mutation, allowing HCV to escape immune recognition (6). Host factors may also be involved in the ability of spontaneous clearance of the virus. One of the most influential factors appears to be certain polymorphisms of a site close to the interleukin-28B (IL28B) gene, and polymorphisms are also an important predictor of response to treatment (7). Chronic HCV infection is responsible for chronic hepatitis, which results in cirrhosis in approximately 20% of cases. Patients with cirrhosis are exposed to life-threatening complications, including end-stage liver disease, peritonitis, esophageal

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variceal hemorrhage, and the development of hepatocellular carcinoma, which occurs at an incidence of 4%–5% per year (8). It is essential to stop the progression of early fibrosis to cirrhosis. Liver biopsy is the gold standard for the assessment of liver histology and stage of fibrosis, but it has some problems, such as bleeding, poor patient compliance, sampling error, and coagulation problems. Because of these problems, there is always an effort to find a method or a laboratory test for predicting the stage of fibrosis stage in CHC patients.

Platelet volume is an indicator of platelet function and activation (9). Platelet activity and aggregation capacity can be easily determined by measuring mean platelet volume (MPV) (10). Large platelets have more granules, aggregate more rapidly with collagen, produce higher levels of thromboxane A2, and express more glycoprotein Ib and IIb/IIIa receptors than smaller ones (11). MPV has been reported as a risk factor for atherothrombosis. Elevated MPV values have been shown in atherothrombotic diseases like acute myocardial ischemia, acute myocardial infarction, coronary atherosclerosis, and cerebrovascular events (12–14). Additionally, MPV has been shown to be a sign of inflammation in ulcerative colitis, Crohn's disease, and rheumatoid arthritis (15,16). In a study from Turkey, MPV was reported to be independently associated with advanced fibrosis in patients with chronic hepatitis B (17). In the present study, we aimed to investigate the association of MPV and stage of liver fibrosis in patients with CHC.

2. Materials and methods

Ninety-five patients with biopsy-proven CHC were enrolled in the study. The control group comprised 33 age- and sex-matched healthy subjects. The following data were obtained from a computerized patient registry database: HCV-RNA level, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, prothrombin time (PT), platelet count (PC), serum albumin (ALB), histological activity index (HAI), liver fibrosis score (LFS), and MPV. Laboratory findings of patients were screened before treatment. Exclusion criteria were atherosclerotic heart disease, any medication use that can influence platelet function (e.g., aspirin), diabetes mellitus, asthma, chronic obstructive pulmonary disease, peripheral and cerebral vascular disease, hematological disorders, and malignancies.

2.1. Histopathological evaluation

Fibrosis staging was assessed according to the METAVIR system. LFSs were defined as follows: score for fibrosis (F): F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with rare septa; F3, numerous septa without cirrhosis; and F4, cirrhosis (18). According to the METAVIR scoring system, patients were divided into 2 groups: patients without significant fibrosis (F0, F1, or F2) (Group 1) and patients with advanced fibrosis (F3 or F4) (Group 2).

2.2. Statistical analysis

The Shapiro–Wilk test was used to assess the normality of the data. Accordingly, either an independent samples t-test or Mann–Whitney U tests and one-way analysis of variance were used to compare the differences of continuous variables between groups. For RNA values, a logarithmic transformation was applied because of high skewness. Chi-square analysis was used to compare the differences of categorical variables. Results were expressed as frequencies and percentages, mean ± standard deviation, or median (25th and 75th percentiles). Univariate and multivariate logistic regression analyses were also performed and odds ratios with 95% confidence intervals (CIs) were calculated in order to identify risk factors of liver fibrosis in patients with CHC. Statistically significant variables in univariate analysis were taken to multivariate analysis, and backward stepwise elimination was used at a $P < 0.0.5$ stringency level to identify the independent risk factors of liver fibrosis. Receiver operating characteristic (ROC) curves were drawn for these risk factors, and the areas under the ROC curve (AUC) values with 95% CIs were calculated and compared with each other. A cut-off value was determined for each factor. Sensitivity, specificity, positive predictive rate (PPR), negative predictive rate (NPR), and accuracy rate (AR) diagnostic measures were calculated, and Kappa tests were performed for each factor with the given cut-off value. Matthew's correlation coefficient (also referred to as the phi coefficient and similar to the Pearson correlation coefficient in its interpretation) was also calculated because the fibrosis classes were of different sizes (19). A probability level of $P < 0.05$ was considered statistically significant. MedCalc (Version 9.2.0.1) and SPSS 15.0 (SPSS Inc., Chicago, IL, USA) software were used for all analyses.

3. Results

Demographic data and laboratory findings of patient and control groups are reported in Table 1. Age and sex were similar among the groups. Statistically significant differences in MPV and PC were seen in patients with CHC compared to healthy controls (MPV: 9.1 ± 1.31 fL vs. 8.58 ± 0.8 fL, $P = 0.008$; PC ($\times 10^3/\mu L$): 219.37 ± 74.31 vs. 258.52 ± 48.34, $P < 0.001$).

Serum AST, ALT, PT, bilirubin, ALB, PC, and MPV were significantly different between groups 1 and 2. Univariate logistic regression analysis revealed an association between fibrosis in CHC patients and serum AST, ALT, ALB, PT, PLT, and MPV values (Table 2). In multivariate analysis, 4 variables remained as independent risk factors: AST (OR 1.11, 95% CI 1.02 to 1.21), ALT (OR 0.92, 95% CI 0.86 to 0.99), PT (OR 2.11, 95% CI 1.15 to 3.88), and MPV (OR 2.28, 95% CI 1.22 to 4.25) (Table 2).

Table 1. Demographic parameters of control and patient groups.

	Control (n = 33)	CHC (n = 95)	P
Age (years)	55.12 ± 8.12	54.28 ± 10.72	0.56
Sex (female/male)	18 (54.5%)/15 (45.5%)	63 (66.3%)/52 (33.7%)	0.318
Platelet count ($\times 10^3$ μL)	258.52 ± 48.34	219.37 ± 74.31	0.001
MPV (fL)	8.58 ± 0.80	9.10 ± 1.31	0.008

Values are expressed as n (%) or mean ± standard deviation.

Table 2. Demographic characteristics and laboratory findings of CHC patients.

	Between-group comparisons			Logistic regression analysis	
	Group 1 (n = 72) F0, F1, F2	Group 2 (n = 23) F3, F4	P	Univariate OR (95% CI)	Multivariate OR (95% CI)
Age (years)	53.89 ± 10.48	55.52 ± 11.62	0.528	1.02 (0.97–1.07)	-
Sex (female*/male)	50 (69.4%)/22 (30.6%)	13 (56.5%)/10 (43.5%)	0.374	1.75 (0.67–4.59)	-
AST (IU/L)	33.00 (25.00–48.00)	51.00 (34.50–81.75)	0.002	1.03 (1.01–1.05)	1.11 (1.02–1.21)
ALT (IU/L)	42.00 (28.25–50.75)	63.00 (29.50–96.50)	0.050	1.02 (1.00–1.03)	0.92 (0.86–0.99)
PT (s)	13.27 ± 1.33	14.37 ± 1.18	0.001	1.97 (1.28–3.04)	2.11 (1.15–3.88)
BIL (mg/dL)	0.70 (0.45–0.90)	0.90 (0.60–1.18)	0.037	2.99 (0.88–10.13)	-
ALB (mg/dL)	4.10 (4.00–4.33)	3.90 (3.45–4.20)	0.018	0.14 (0.04–0.56)	-
log (RNA)	5.78 ± 0.72	5.42 ± 0.96	0.083	0.58 (0.31–1.09)	-
PC ($\times 10^3$ μL)	235.14 ± 66.13	170.00 ± 78.24	<0.001	0.98 (0.97–0.99)	-
MPV (fL)	8.91 ± 1.24	9.67 ± 1.39	0.015	1.56 (1.07–2.27)	2.28 (1.22–4.25)

AST, aspartate aminotransferase; ALT, alanine aminotransferase; PT, prothrombin time; BIL, bilirubin; ALB, albumin; RNA, ribonucleic acid; PC, platelet count; MPV, mean platelet volume. Values are expressed as n (%), mean ± SD or median (25th and 75th percentiles). *Reference category for logistic regression analysis.

Comparison of ROC curves for the diagnostic performance of AST, ALT, PT, and MPV in identifying fibrosis in CHC is shown in Figure 1a. AUC values for AST, ALT, PT, and MPV were 0.74 (0.63–0.82), 0.66 (0.55–0.76), 0.73 (0.63–0.82), and 0.66 (0.55–0.76), respectively, and the differences of these values between parameters were not statistically significant (P > 0.05). A plot to obtain a cut-off value for MPV that displays sensitivity and specificity variation for each MPV value and a dot diagram that plots the distribution of CHC samples with mild and severe fibrosis around an 8.4-fL cut-off value are shown in Figures 1b and 1c. In addition, sensitivity, specificity, PPR, NPR, and AR were demonstrated for the independent risk factors AST, ALT, PT, and MPV (Table 3).

4. Discussion

CHC infection often follows a progressive course over years and may result in cirrhosis, hepatocellular carcinoma, and the need for liver transplantation. Because of the long course of the disease, the natural history of CHC has not been clearly defined. Many studies have provided estimates of the proportion of patients with CHC infection who develop cirrhosis within 20 years (20,21).

The MPV is the geometric mean of the transformed lognormal platelet volume data in impedance technology systems. In some optical systems, MPV is the mode of the measured platelet volume (22). There is an inverse relationship between platelet size and number. Therefore, the total platelet mass, the product of the MPV and

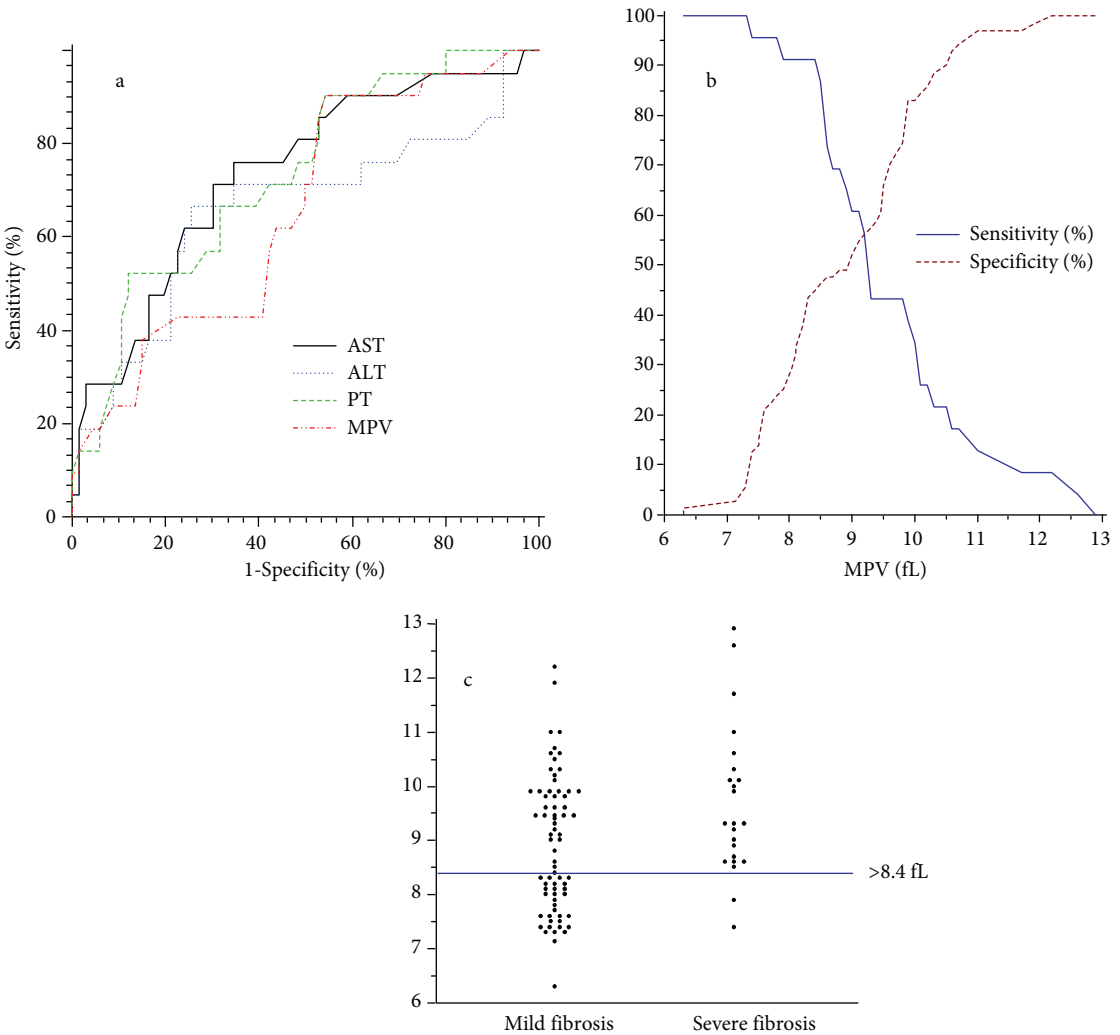

Figure 1. a) Comparison of ROC curves for the diagnostic performance of AST, ALT, PT, and MPV in identifying fibrosis in CHC. AUC values were 0.74 (0.63–0.82), 0.66 (0.55–0.76), 0.73 (0.63–0.82), and 0.66 (0.55–0.76), respectively, and the differences of these values between parameters were not statistically significant (P > 0.05). b) A plot to obtain a cut-off value for MPV that displays sensitivity and specificity variation for each MPV value. c) A dot diagram that plots the distribution of CHC samples with mild and severe fibrosis around an 8.4-fL cut-off value.

Table 3. Diagnostic measures and Kappa test results of parameters in the detection of liver fibrosis.

Parameters	Diagnostic measures						Kappa test	
	SEN (95% CI)	SPE (95% CI)	PPR (95% CI)	NPR (95% CI)	AR (95% CI)	MCC (95% CI)	κ	P
AST (42.0 IU/L)	72.7 (49.8–89.3)	66.7 (54.6–77.3)	40.0 (24.9–56.7)	88.9 (77.4–95.8)	68.1 (57.7–77.3)	33.7 (14.8–52.7)	0.307	0.001
ALT (51.0 IU/L)	63.6 (40.7–82.8)	75.0 (63.4–84.5)	43.8 (26.4–62.3)	87.1 (76.2–94.3)	72.3 (62.2–81.1)	34.5 (14.2–54.8)	0.334	<0.001
PT (14.7 s)	50.0 (28.2–71.8)	85.1 (74.3–92.6)	52.4 (29.8–74.3)	83.8 (72.9–91.6)	76.4 (66.2–84.8)	35.6 (13.4–57.9)	0.356	<0.001
MPV (8.4 fL)	91.3 (72.0–98.9)	43.7 (31.9–56.0)	34.4 (22.7–47.7)	93.9 (79.8–99.3)	55.3 (44.7–65.6)	31.5 (16.9–46.1)	0.224	0.002

SEN, sensitivity; SPE, specificity; PPR, positive predictive rate; NPR, negative predictive rate; AR, accuracy rate; MCC, Matthew's correlation coefficient.

platelet count, is closely regulated. When platelets decrease in number, bone marrow megakaryocytes are stimulated by thrombopoietin and their nucleus becomes hyperlobulated, with much higher DNA content. These stimulated megakaryocytes produce larger platelets. Thus, platelets with a higher MPV are expected to be seen in destructive thrombocytopenia when megakaryocytic stimulation is present. Conversely, platelets with a lower MPV are expected in thrombocytopenic states associated with marrow hypoplasia or aplasia. An exception to this relationship occurs with splenic sequestration, in which a low MPV is seen because the spleen sequesters large platelets. In hyposplenic states a higher MPV is seen, since there is no spleen to sequester the larger platelets (23–25).

There are many studies on the relationship between MPV and some thrombotic and cardiac disorders, but there are few on inflammatory diseases. Beyazit et al. (26) reported that overall accuracy of MPV in predicting disease severity according to computerized tomography severity index was not superior compared with other inflammation markers in patients with acute pancreatitis. Zubcevic et al. (22) reported that one of the most reliable indicators of activity of Crohn's disease was MPV; however, it was not sensitive enough to distinguish the relationship between moderate and severe disease. A decrease in MPV reflects the activation and participation of platelets in the inflammatory process of colon mucosa, and so MPV may be a useful marker of active ulcerative colitis (27). Korkmaz et al. (28) reported that higher MPV may reflect increased atherosclerotic burden and cardiovascular risk. Yazici et al. (29) reported that MPV may prove to be useful as a prognostic marker in patients with metabolic syndrome and ST elevation in myocardial infarction. Köşüş et al. (30) reported that mild glycemic disorders are associated with increased MPV. Increased MPV might be associated with elevated baseline cardiovascular risk factors. Individuals with these glycemic disorders might be more aggressively targeted with strategies to lower cardiovascular disease risk.

In this study, our aim was to investigate whether MPV could be a marker for fibrosis in CHC patients. We found that MPV was significantly higher in patients with CHC when compared to control subjects. In contrast, PC was significantly lower in CHC patients. Portal hypertension and hypersplenism in some of the subjects with advanced fibrosis may be the cause of this significant difference. Patients were divided into 2 groups according to severity of fibrosis. AST, ALT, ALB, PT, PC, and MPV were significantly different between the groups. Therefore, we suggest that these parameters are affected by the degree of fibrosis in CHC. The independent risk factors for fibrosis were AST, ALT, PT, and MPV in this study. The cut-off value for MPV to predict advanced fibrosis in patients with CHC was 8.4 fL. At this cut-off value, sensitivity was 91.3% and specificity was 43.7%. The predictive role of some laboratory tests in the detection of liver fibrosis was previously investigated in patients with CHC. Kandemir et al. (31) reported that PC and the GUCI (Goteborg University Cirrhosis Index, calculated using AST, PC, and PT) can discriminate to some degree of accuracy patients with severe fibrosis. We also found AST, ALT, PT, and MPV to have diagnostic values in identifying severity of fibrosis in this study.

The question of this study is why MPV is related to advanced fibrosis. It is well known that a high MPV in a thrombocytopenic patient indicates active marrow production of platelets, whereas a low MPV is indicative of bone marrow suppression (32). The PC of patients with advanced fibrosis was significantly lower in our study. This finding could be one reason for the higher MPV ratio in patients with advanced fibrosis.

Hepatic steatosis and insulin resistance as a part of metabolic syndrome in CHC patients are associated with hepatic fibrosis (33). A high MPV ratio has been observed in some diseases associated with metabolic syndrome (28,34,35). The relationship between CHC infection and metabolic syndrome and its components may be another reason for the higher MPV ratio in patients with CHC.

The higher MPV and lower PCs in patients with advanced fibrosis can lead to thrombocytopenia and platelet–endothelial adhesion dysfunction, which affect clot formation and contribute to a relative hypocoagulable situation in patients with advanced fibrosis. The surface phospholipids of platelets provide the platform for factor complexes, amplification, and propagation of clot formation. Many theories exist regarding the genesis of thrombocytopenia in patients with liver disease. Decreased thrombopoietin levels (36), splenic sequestration of platelets due to portal hypertension, auto-antibody destruction of platelets (37), and bone marrow suppression due to underlying liver disease can all contribute to thrombocytopenia. Decreased platelet count may mobilize young platelets (with high MPV) in bone marrow in patients with CHC. Here we want to point out the quite high NPR at this cut-off value (93.9%), which reveals the absence of severe fibrosis in CHC under this value.

In conclusion, we suggest that high MPV levels (especially those over 8.4 fL) may help to predict advanced fibrosis in patients with CHC. However, it should not be forgotten that MPV is not a specific marker for fibrosis, and a high NPR seems to be more important in helping to exclude a high fibrosis ratio in patients with CHC.

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