ORIGINAL ARTICLE

Mean platelet volume is an important predictor of hepatitis C but not hepatitis B liver damage

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Background: The mean platelet volume (MPV) is the most commonly used measure of platelet size and is a potential marker of platelet reactivity. In this study, we aimed to explore the relationship between hepatic histopathology in viral hepatitis and MPV levels, which are associated with platelet count and activity. **Materials and Methods:** We performed a retrospective case-control study of baseline histological and clinical parameters in chronic hepatitis B and C patients in our tertiary reference center between January 2005 and January 2011. Two hundred and five chronic hepatitis B patients and 133 chronic hepatitis C patients who underwent liver biopsy were included in the study. The patients were divided into two groups: Chronic hepatitis B and chronic hepatitis C and were additionally divided into groups of two according to histological activity index (HAI) and fibrosis scores obtained by liver biopsy results (according to the Ishak scoring system). The clinical characteristics of chronic viral hepatitis patients, including demographics, laboratory (especially MPV), and liver biopsy findings, were reviewed. **Results:** One hundred and forty-three patients were male (69.1%), and the mean age was 41.9 ± 12.75 with an age range of 18-71 years in hepatitis B patients. In the classification made according to HAI, 181 patients were in the low activity group (88.3%) and 24 in the high activity group (11.7%). In the evaluation made according to fibrosis score, 169 patients were found to have early fibrosis (82.4%) and 36 were found to have advanced fibrosis (17.6%). In patients with hepatitis B, there was no statistically significant difference in terms of their MPV values between the two groups, separated according to their degree of activity and fibrosis. Sixty-three patients were male (47.3%), and the mean age was 50.03 ± 12.75 with an age range of 19-75 years. In the classification made according to HAI, 109 patients were in low activity group (81.9%) and 24 in high activity group (18.1%). In the evaluation made according to fibrosis score, 101 patients were found to have early fibrosis (75.9%) and 32 have advanced fibrosis (24.1%). There was a statistically significant difference between the activity and fibrosis groups of the hepatitis C patients ($P = 0.04$ and $P = 0.02$, respectively). **Conclusion:** MPV values are more reliable in hepatitis C patients than hepatitis B for predicting the advanced damage in liver histology. This finding might be useful for the detection of early fibrosis and also starting early treatment, which is important in hepatitis C.

Key words: Fibrosis, hepatitis B, hepatitis C, mean platelet volume

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INTRODUCTION

Accurate determination of the presence and degree of liver fibrosis is essential for the prognosis and treatment option for patients with chronic viral hepatitis. It is generally accepted that percutaneous liver biopsy is the gold standard method for the determination of liver damage. However, this method is invasive and carries a significant rate of complications ranging from 1.0% to 5.0%, and risk of mortality ranging from 1 in 1000 to 1 in 10,000.[1] These risks are mainly related to the experience and training of the operator.[2] Recently, noninvasive methods of assessing liver fibrosis, utilizing laboratory methods, and imaging (platelet count, Forns' index, elastography, etc.) have been developed to reduce the need for biopsy.

The mean platelet volume (MPV) is the most commonly used measure of platelet size and is a potential marker

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of platelet reactivity. There is uncertainness about the most accurate method for measuring MPV; however, it is routinely available inexpensive method based on a complete blood count measurement in the inpatient and outpatient setting. Larger platelets are metabolically and enzymatically more active and have greater prothrombotic potential. Higher MPV is observed in patients with diabetes mellitus, hypertension, hypercholesterolemia, smoking, and obesity; all of which are known as prothrombotic conditions. This suggests a common mechanism whereby these factors may increase the risk of cardiovascular disease.[3]

In patients with chronic hepatitis, thrombocytopenia was used for many years as an important indicator of the advanced pathology. In this study, we aimed to explore the relationship between liver histopathology in viral hepatitis and MPV levels, which are known to associate with platelet count and activity.

MATERIALS AND METHODS

Study design and participants

We performed a retrospective case-control study of baseline histological and clinical parameters in chronic hepatitis B and C patients in our tertiary reference center (Uludag University, Faculty of Medicine, Department of Gastroenterology) between January 2005 and January 2011. A total of 338 patients with viral hepatitis (205 with chronic hepatitis B and 133 with chronic hepatitis C) were seen at our clinic and analyzed.

Cases with chronic hepatitis B and C infection were included in this study and defined by positive hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV) detection in the serum for a 6-month period. Percutaneous liver biopsies were made with a 16 G 16 cm automatic Tru-Cut biopsy needle. Liver biopsy specimens that included 11 or more complete portal tracts and longer than 20-25 mm were eligible for pathological assessment. Staining, including hematoxylin and eosin, Masson's Goldner, Masson's trichrome, and reticulin, was performed in a blinded fashion. All pathologic specimens were evaluated by a skilled pathologist in the Laboratory of Pathology, Uludag University.

Patients were excluded from the study if they were diagnosed with chronic hepatitis B virus (HBV) infection or HCV and co-infected with human immunodeficiency virus or hepatitis D virus. Patients were also excluded if they had nonalcoholic or alcoholic steatohepatitis, autoimmune liver diseases (such as autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis), or hereditary and metabolic liver diseases (such as Wilson's disease, hemochromatosis, α1-antitrypsin deficiency, and hepatocellular carcinoma). Patients with conditions that might affect the MPV and platelet count, including splenectomized patients, patients with atherosclerotic heart disease, celiac disease, diabetes mellitus, acute and chronic renal failure, hyperlipidemia, chronic obstructive lung disease, hematologic disorders, and malignancies were excluded from the study. Patients receiving drugs such as inhibitors of platelet function including aspirin, ticlopidine, clopidogrel, nonsteroid anti-inflammatory drugs, and any other drugs that might potentially interact with platelet function and size were also excluded from the study. Moreover, patients with low mean corpuscular volume in complete blood count (CBC) analysis (MCV <80 fL) were excluded from the study, since small red blood cells might be counted mistakenly as platelets by the analyzer.

Measurements

Laboratory results of these patients obtained at most 1 week before the biopsy were evaluated retrospectively as biochemical parameters. All CBC analyses were performed in the hematology laboratory of our hospital. CBC analysis was performed using a Beckman Coulter (High Wycombe, UK) Gen-S automated analyzer within 2 h after collecting the blood samples. Platelet count and MPV were recorded at the time of admission. Venous blood samples were obtained between 8.00 and 9.00 am after an overnight fast of 8-12 h. Serum levels of alanine transaminase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), total alkaline phosphatase (ALP), and albumin were determined by automated techniques (Roche Modular System). International normalized ratio (INR) was determined by hemostasis analyzer (BCSXP; Siemens); HCV-ribonucleic acid and HBV-deoxyribonucleic acid (DNA) levels were determined using the Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV amplification test and COBAS® AmpliPrep/COBAS® TaqMan® HBV test, v2.0, respectively.

Patients were divided into two groups: Chronic hepatitis B and chronic hepatitis C. These groups were subsequently divided into groups consisting of histological activity index (HAI) and fibrosis scores obtained by the liver biopsy results. According to the evaluation made with Ishak score, patients with HAI between 0 and 12 were defined as low activity and those with HAI between 13 and 18 as high activity; patients with fibrosis score of 0-2 were defined as early fibrosis and those with a score between 3 and 6 as advanced fibrosis, and comparisons were made accordingly.[4]

Statistical analysis

All statistical analyses were carried out by Statistical Package for Social Sciences (SPSS) version 18 software (SPSS Inc., Chicago, IL, United States). Results were expressed as mean ± standard error of the mean. For comparing the

categorical variables, we used χ^2 test. In order to determine whether data were distributed normally, Kolmogorov-Smirnov test was used. All normally distributed data were analyzed using the independent Student's *t*-test. Data found to be nonnormally distributed were analyzed using the Mann-Whitney U-test. Receiver operating characteristic (ROC) curve analysis was used to identify optimal cut-off values of MPV with maximum sensitivity and specificity for the differentiation of advanced histopathology from mild. The relation between liver histopathology and clinical and laboratory parameters was determined with Pearson or Spearman correlation analysis. A statistical significance level was considered if the *P* value was <0.05.

RESULTS

Overall, 205 patients who underwent liver biopsy due to chronic hepatitis B were included in the study. One hundred and forty-three patients were male (69.1%), and the mean age was 41.9 ± 12.75 with an age range of 18-71 years. In the classification made according to HAI, 181 patients were in the low activity group (88.3%) and 24 in the high activity group (11.7%). In the evaluation made according to fibrosis score, 169 patients were found to have early fibrosis (82.4%) and 36 were advanced fibrosis (17.6%). No significant difference was found between HAI groups in terms of ALT, ALP, HBV-DNA, and MPV levels. In the patient groups with a high activity score, age, AST, GGT, and INR levels were found to be significantly high, and platelet and albumin values were significantly low. In the low activity group, the mean MPV level was 8.72 ± 1.4 (fL), while it was 9.23 ± 1.7 (fL) in high activity group (*P* = 0.14). No difference was found between the two groups with regard to sex (*P* = 0.64). No significant difference was found between the fibrosis groups in terms of ALP, HBV-DNA, and MPV levels. However, in the patient group with advanced fibrosis, score, age, ALT, AST, GGT, and INR levels were found to be significantly higher, and platelet and albumin values were found to be significantly lower. In early fibrosis group, mean MPV level was 8.80 ± 1.4 (fL), while it was 8.66 ± 1.6 (fL) in advanced fibrosis group (*P* = 0.58) [Table 1]. There was no difference between two groups in terms of sex (*P* = 0.07).

Overall, 133 patients who underwent liver biopsy due to chronic hepatitis C were included in the study. Sixty-three patients were male (47.3%), and the mean age was 50.03 ± 12.75 with an age range of 19-75 years. In the classification made according to HAI, 109 patients were in low activity group (81.9%) and 24 in high activity group (18.1%). In the evaluation made according to fibrosis score, 101 patients were found to have early fibrosis (75.9%) and 32 have advanced fibrosis (24.1%). No significant difference was found between HAI groups in terms of GGT, ALP, albumin, and HBV-DNA levels. In the patient groups with high activity score, age, ALT, AST, INR, and MPV levels were found to be significantly high, and platelet values were significantly low. In the low activity group, the mean MPV level was 8.88 ± 1.6 (fL), while it was 9.70 ± 1.6 (fL) in the high activity group (*P* = 0.03). No difference was found between the two groups with regard to sex (*P* = 1.00). No significant difference was found between the fibrosis groups in terms of GGT, ALP, and HBV-DNA levels. In the patient group with an advanced fibrosis score, age, ALT, AST, INR, and MPV levels were found to be significantly higher, and platelet and albumin values were found to be significantly lower [Table 2]. In the early fibrosis group, the mean MPV level was 8.88 ± 1.6 (fL), while it was 9.51 ± 1.7 (fL) in the advanced fibrosis group (*P* = 0.02) [Table 3]. There was no difference between two groups in terms of sex (*P* = 0.84).

The correlation analysis of the age and laboratory parameters of the both activity and fibrosis groups are given in Tables 2 and 4. It has been shown that higher INR value has the best correlation with the activity and also higher GGT level has the best correlation with the fibrosis in the hepatitis B patients. The lower platelet count was found to be the strongest predictor of the liver damage in hepatitis C patients. In addition, MPV values show positive

Table 1: The mean age and laboratory results in chronic hepatitis B patients according to their HAI and fibrosis scores

Parameter	Low activity (HAI = 0-12)	High activity (HAI = 13-18)	*P**	Early fibrosis (stage 0-2)	Advanced fibrosis (stage 3-6)	*P**
Age (years)	41.15±12.9	48.12±9.7	<0.001	40.83±12.9	47.31±10.4	<0.001
ALT (IU/L)	72.11±72.2	99.8±83.09	0.08	69.44±68.2	102.92±92.2	<0.001
AST (IU/L)	45.29±42.2	70.2±52.4	<0.001	44.18±42.3	67.03±49.7	<0.001
GGT (IU/L)	38.85±44.7	66.54±44.5	<0.05	34.63±42.2	68.83±49.6	<0.001
ALP (IU/L)	78.99±23.3	81.18±27.9	0.72	77.51±22.5	85.71±27.6	0.10
Albumin (g/dl)	4.61±0.47	4.35±0.41	<0.05	4.63±0.46	4.36±0.47	<0.05
Platelet ($\times 10^3$/ml)	226.82±61.2	183.75±88.3	<0.001	229.24±59.7	186.75±82.8	<0.001
INR	1.04±0.08	1.15±0.15	<0.001	1.04±0.09	1.12±0.14	<0.001
HBV-DNA (IU/ml)	$2.07\times10^7\pm1.03\times10^8$	$2.17\times10^7\pm3.60\times10^8$	0.97	$2.26\times10^7\pm1.05\times10^8$	$7.38\times10^6\pm1.50\times10^7$	0.56
MPV (fl)	8.72±1.4	9.23±1.7	0.14	8.80±1.4	8.66±1.6	0.58

Values are mean ± SD. **P* value for independent samples *t*-test or Mann-Whitney U-test as appropriate. AST = Aspartate aminotransferase; ALT = Alanine aminotransferase; GGT = Gamma-glutamyl transferase; ALP = Total alkaline phosphatase; INR = International normalized ratio; MPV = Mean platelet volume; HAI = Histological activity index; HBV-DNA = Hepatitis B virus-deoxyribonucleic acid; SD = Standard deviation

correlation, although it is weak, with both activity and fibrosis in hepatitis C patients.

ROC curve analysis suggested that the optimum MPV level cut-off point for advanced fibrosis group was 9.11 fL with sensitivity, specificity, and positive and negative predictive values of 53, 63, 30, and 80%, respectively (area under the ROC curve = 0.630) [Figure 1]. For the high activity group, the optimum MPV level cut-off point was 9.09 fL with sensitivity, specificity, and positive and negative predictive values of 52, 61, 23, and 85%, respectively (area under the ROC curve = 0.630) [Figure 2].

DISCUSSION

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. Under normal circumstances, there is an inverse relationship between platelet size and number. Therefore, the total platelet mass, the product of the MPV, and platelet count (or "plateletcrit") are closely regulated. When platelets decrease in number, bone marrow megakaryocytes are stimulated by thrombopoietin (TPO) and their nucleus becomes hyperlobulated with much higher DNA content (greater ploidy). These stimulated megakaryocytes produce larger platelets.[5,6]

TPO is the physiologically relevant regulator of platelet production. It is produced primarily in the liver parenchymal cells. Several cytokines, inflammatory mediators, and growth factors may affect MPV with subsequent production of larger and more reactive platelets. It has been shown that TPO plays a role in some inflammatory conditions.[7] Thus, TPO may have a relevant role in augmenting MPV in hepatic diseases.[8]

The first report on the link between MPV and liver disease was demonstrated in chronic noncirrhotic patients and healthy controls in 1984. In this study, MPV and platelets were found lower in the patient group.[9] MPV values found higher in inactive HBsAg carriers when compared with healthy controls in another study.[10] Recently, studies have been published about nonalcoholic steatohepatitis (NASH) because of the association with atherosclerosis. Higher MPV values were found in the NASH group compared to the healthy controls in one of these studies.[11-13] In a different study, high MPV values were found in alcoholic cirrhotic patients compared with patients with alcoholic or NASH.[14]

Recently, some positive results were shown from the studies about the significance of MPV in the diagnosis of hepatic fibrosis in hepatitis B patients. A statistically significant increase in MPV level was observed in patients with chronic hepatitis B compared with healthy controls in a study.

Table 2: The correlation analysis of clinical and laboratory parameters with fibrosis in viral hepatitis groups

Parameters	Hepatitis B		Hepatitis C	
	R	*P*	*R*	*P*
Age	0.19	<0.001	0.22	<0.05
MPV	−0.03	0.58	0.19	<0.05
ALT	0.17	<0.001	0.29	<0.001
AST	0.25	<0.001	0.43	<0.001
ALP	0.14	0.1	0.17	0.07
GGT	0.38	<0.001	0.12	0.26
INR	0.24	<0.001	0.37	<0.001
Platelet	−0.24	<0.001	−0.48	<0.001
Albumin	−0.22	<0.05	−0.24	<0.05
HBV-DNA	−0.05	0.56		
HCV-RNA			0.01	0.86

AST = Aspartate aminotransferase; ALT = Alanine aminotransferase; GGT = Gamma-glutamyl transferase; ALP = Total alkaline phosphatase; INR = International normalized ratio; MPV = Mean platelet volume; HBV-DNA = Hepatitis B virus-deoxyribonucleic acid; HCV-RNA = Hepatitis C virus-ribonucleic acid

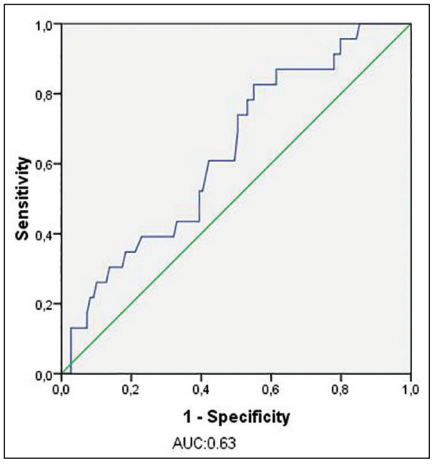

Figure 1: Receiver operating characteristic curve of the mean platelet volume values in the activity group of hepatitis C patients

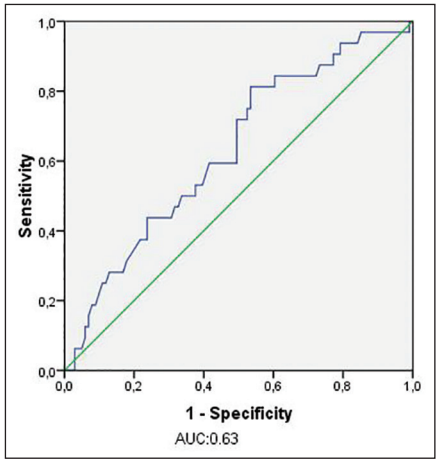

Figure 2: Receiver operating characteristic curve of the mean platelet volume values in the fibrosis group of hepatitis C patients

Table 3: The mean age and laboratory results in chronic hepatitis C patients according to their HAI and fibrosis scores

Parameter	Low activity (HAI = 0-12)	High activity (HAI = 13-18)	*P**	Early fibrosis (stage 0-2)	Advanced fibrosis (stage 3-6)	*P**
Age (years)	48.68±13.3	56.17±6.8	<0.05	48.19±13.6	55.84±6.8	<0.05
ALT (IU/L)	65.07±62.7	87.50±69.38	<0.05	63.19±63.5	87.87±63.6	<0.001
AST (IU/L)	47.14±40.8	71.27±37.6	<0.001	45.16±41.4	71.50±33.5	<0.001
GGT (IU/L)	48.57±41.4	63.93±48.3	0.22	48.31±42.2	60.79±43.8	0.26
ALP (IU/L)	77.62±25.9	88.15±27.6	0.10	76.81±25.2	87.71±28.4	0.07
Albumin (g/dl)	4.56±0.43	4.35±0.54	0.06	4.59±0.4	4.33±0.56	<0.05
Platelet (×10^3/ml)	245.53±69.4	170.47±73.3	<0.001	251.41±63.7	170.67±78.4	<0.001
INR	1.01±0.01	1.07±0.27	<0.001	1.00±0.01	1.09±0.25	<0.001
HCV-RNA (IU/ml)	2.18×10^6±4.13×10^6	2×10^6±3.16×10^6	0.86	2.11×10^6±4.15×10^6	2.27×10^6±3.33×10^6	0.86
MPV (fl)	8.88±1.6	9.70±1.6	<0.05	8.88±1.6	9.51±1.7	<0.05

Values are mean ± SD. **P* value for independent samples *t*-test or Mann-Whitney U-test as appropriate. AST = Aspartate aminotransferase; ALT = Alanine aminotransferase; GGT = Gamma-glutamyl transferase; ALP = Total alkaline phosphatase; INR = International normalized ratio; MPV = Mean platelet volume; SD = Standard deviation; HAI = Histological activity index; HCV-RNA = Hepatitis C virus-ribonucleic acid

Table 4: The correlation analysis of clinical and laboratory parameters with activity in viral hepatitis groups

Parameters	Hepatitis B		Hepatitis C	
	R	*P*	*R*	*P*
Age	0.18	<0.001	0.21	<0.05
MPV	0.11	0.11	0.18	<0.05
ALT	0.12	0.08	0.20	<0.05
AST	0.22	<0.001	0.30	<0.001
ALP	0.03	0.72	0.15	0.10
GGT	0.20	<0.05	0.13	0.22
INR	0.26	<0,001	0.29	<0.001
Platelet	−0.20	<0.001	−0.36	<0.001
Albumin	−0.19	<0.05	−0.17	0.06
HBV-DNA	0.003	0.97		
HCV-RNA			−0.01	0.86

AST = Aspartate aminotransferase; ALT = Alanine aminotransferase; GGT = Gamma-glutamyl transferase; ALP = Total alkaline phosphatase; INR = International normalized ratio; MPV = Mean platelet volume; HBV-DNA = Hepatitis B virus-deoxyribonucleic acid; HCV-RNA = Hepatitis C virus-ribonucleic acid

In addition, the same results were seen in the advanced fibrosis group in hepatitis B patients and these suggested that MPV might help in the assessment of fibrosis in chronic hepatitis B.[15] They hypothesized that increased levels of interleukin-6 production secondary to inflammation in the fibrosis process may cause elevated circulating young platelets that are responsible for increased MPV in CHB with advanced fibrosis. A study from Korea showed also higher MPV levels in chronic hepatitis B patients than controls.[8] The results of the recent study showed that the MPV is an independent variable determining the severity of liver inflammation, but not liver fibrosis.[16] In a more recent study, the authors suggested that elevated MPV level might be an independent predictor for cirrhosis in patients with chronic HBV infection.[17] In one study, authors concluded that MPV may increases in patients with chronic hepatitis B as it does in other infectious diseases. However, they showed this increase was not associated with liver histopathology.[18]

There are limited studies that investigate the relationship between chronic hepatitis C patients and MPV. In a recent study, the results showed MPV was increased in chronic hepatitis C patients with advanced fibrosis. They suggested that two main mechanisms were responsible for increased MPV in CHC patients. One of them was inflammation, which is the important cause of metabolic syndrome and its complications. The other one was secondary to chronic changes caused by liver pathology in CHC.[19]

In our study, we compared MPV values in two viral hepatitis groups separated according their activation and fibrosis scores. We found no reliable results in hepatitis B groups. Conversely, MPV levels were useful in predicting the advanced damage in liver histology in hepatitis C patients.

CONCLUSION

It is difficult to make assumptions about the value of our findings due to the limited number of studies about the association between MPV and viral hepatitis. However, we suggest that MPV values are more valuable in hepatitis C patients than hepatitis B to predict the advanced damage in liver histology. This finding might be useful for the detection of early fibrosis and also starting prompt treatment which is important in hepatitis C. Therefore, examining the correlation between MPV levels and hepatitis C with larger prospective studies are needed to validate these findings.

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Conflicts of interest

There are no conflicts of interest.

AUTHOR'S CONTRUBITIONS

ATE contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. MIU contributed in the conception of the work, approval of the final version of the manuscript, and agreed for all aspects of the work. TA contributed in the conception of the work, conducting the study, and agreed for all aspects of the work. KI contributed in the conception of the work and agreed for all aspects of the work. MK contributed revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. SG contributed approval of the final version of the manuscript and agreed for all aspects of the work. ED contributed approval of the final version of the manuscript and agreed for all aspects of the work. MG contributed approval of the final version of the manuscript and agreed for all aspects of the work. SGN contributed approval of the final version of the manuscript and agreed for all aspects of the work.

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