Mean Platelet Volume as a Fibrosis Marker in Patients With Chronic Hepatitis B

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Introduction: Many noninvasive tests have been studied for the diagnosis and determining the liver fibrosis score (LFS). In this study, we aimed to research the correlation of mean platelet volume (MPV) and stage of liver fibrosis in patients with chronic hepatitis B (CHB). **Patients and Methods:** Fifty-nine patients with CHB were enrolled retrospectively into the study. Age–sex matched 25 healthy subjects were used as control group. The following data were obtained from computerized patient registry database: HBV-DNA level, hepatitis B e-antigen seropositivity, liver enzymes and function tests, white blood cell count, platelet count, hemoglobin, histological activity index, LFS, and MPV. Patients were divided into two groups: patients without significant fibrosis (F0, F1, or F2) (Group 1) and patients with advanced fibrosis (F3, F4) (Group 2). **Results:** A statistically significant increase in MPV was seen in patients with CHB compared with healthy controls (8.49 ± 0.84 fl vs.

7.65 ± 0.42 fl, $P < 0.001$). Receiver operating characteristic curve analysis suggested that the optimum MPV level cut-off points for CHB was 8.0 fl, with sensitivity, specificity, PPV, and NPV of 68, 76, 86, and 50%, respectively. MPV levels were significantly higher in Group 2 (8.91 ± 0.94 fl, $P: 0.009$) compared with Group 1 (8.32 ± 0.74 fl). ROC curve analysis suggested that the optimum MPV level cut-off points for Group 2 was 8.45 fl, with sensitivity, specificity, positive and negative predictive value of 77, 59, 45, and 85%, respectively. Multivariable logistic regression model, which consisted of HAI, ALT, HBV-DNA, platelet count, and MPV, was performed. We showed that MPV was independently associated with advanced fibrosis ($P: 0.031$). **Conclusion:** We suggest that MPV might help in the assessment of fibrosis in CHB. It should not be considered a stand-alone test for this use owing to nonspecificity with other diseases. J. Clin. Lab. Anal. 25:162–165, 2011. © 2011 Wiley-Liss, Inc.

INTRODUCTION

Hepatitis B (HBV) infection is an important worldwide health problem, and it is estimated that 350–400 million people are chronically infected with this virus. About one million people chronically infected with HBV would die of chronic liver diseases per year (1). Consequently, it is important to stop the progression of early-stage fibrosis to cirrhosis (2). Although liver biopsy is the gold standard for assessment of fibrosis, it has some disadvantages, such as poor patient compliance, sampling error, and limited usefulness for dynamic surveillance (3). Considering these restrictions, noninvasive histology predictors are immediately needed (4). A number of noninvasive serum markers have been studied to measure fibrosis, such as serum aspartate

aminotransferase to platelet ratio index (APRI), FIB-4, Forn's index, Fibrometer, Hepascore, and fibrotest–actitest (5–10). However, these serum markers are expensive and not feasible.

Mean platelet volume (MPV) is a parameter generated by full blood count analyzers as part of the routine complete blood count (CBC) test cycle, which is generally ignored by the doctors (11). Recently, MPV have been studied in some patients groups and were found that there was an increase in myocardial

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infarction and cerebrovascular disease (12). MPV is a widely used surrogate markers of platelet function and has been shown to be a sign of inflammation in ulcerative colitis, Crohn's disease, and rheumatoid arthritis (13,14). An association between inactive chronic hepatitis B (CHB) and MPV has been established in one study previously (15). However, its correlation with the stage of liver fibrosis was not investigated.

In this study, we aimed to research the correlation of MPV and stage of liver fibrosis in patients with CHB.

PATIENTS AND METHODS

Fifty-nine patients with CHB were enrolled retrospectively into the study. Age–sex match 25 healthy subjects were used as control groups for CHB patients, respectively. Following data were obtained from computerized patient registry database: HBV-DNA level, hepatitis B e-antigen (Hbe-Ag) seropositivity, alanine transaminotransferase (ALT), aspartate transaminotransferase (AST), gamma-glutamyl transpeptidase, alkaline phosphatase, bilirubin, international numeric ratio, white blood cell count, platelet count, hemoglobin, histological activity index (HAI), liver fibrosis score (LFS), and MPV. 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 (16). According to the METAVIR scoring system, patients were divided into two groups: patients without significant fibrosis (F0, F1, or F2) (Group 1) and patients with advanced fibrosis (F3, F4) (Group 2). Laboratory tests were performed before the treatment in patient group. 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, cirrhosis, portal hypertension, and malignancies.

Statistical Analyses

Data were analyzed with the SPSS software (SPSS 13.0, Chicago, IL). Data were expressed as Mean $\pm$ Standard deviation. Independent *t*-test was used for group comparisons. Categorical variables were compared with the chi-square test. Pearson and Spearman's correlation were used to assess the association between MPV and demographics or laboratory parameters. Logistic regression analysis was performed, in order to evaluate the association between stage of fibrosis and MPV, platelet count, ALT, HAI, and HBV-DNA levels, respectively. Receiver operating characteristic (ROC) curve analysis was used to identify optimal cut-off values of MPV level, to identify with maximum sensitivity and specificity for detection of fibrosis stage. Statistical significance was set at a *P*-value of less than 0.05.

RESULTS

Demographic features and laboratory findings of patient and control groups are reported in Table 1. Age and sex were similar among the groups. Hemoglobin and hematocrit levels were also similar in both groups. Platelet counts, AST, and ALT levels were significantly higher in CHB group (*P*-value, respectively; 0.008, <0.001, <0.001).

A statistically significant increase in MPV was seen in patients with CHB compared with healthy controls (8.49 ± 0.84 fl vs. 7.65 ± 0.42 fl, *P* < 0.001). ROC curve analysis suggested that the optimum MPV level cut-off points for CHB was 8.0 fl, with sensitivity, specificity, PPV, and NPV of 68, 76, 86, and 50%, respectively.

We compared HAI, ALT, HBV-DNA, platelet count, and MPV between patients groups. MPV levels were significantly higher in Group 2 (8.91 ± 0.94 fl, *P*: 0.009) compared with Group 1 (8.32 ± 0.74 fl). ROC curve analysis suggested that the optimum MPV level cut-off points for Group 2 was 8.45 fl, with sensitivity, specificity, PPV, and NPV of 77, 59, 45, and 85%, respectively. HAI was also correlated with LFS

TABLE 1. Demographic and Laboratory Features in Study and Control Groups

	CHB (n: 59)	Controls (n: 25)	P-value
Age	42.93 $\pm$ 11.5	47.7 $\pm$ 11.7	NS
Sex (F/M)	35(% 58.4)/24(% 40.6)	12(% 48)/13(% 52)	NS
AST (IU/ml)	69.4 $\pm$ 8.08	22.4 $\pm$ 6.10	<0.001
ALT (IU/ml)	99.6 $\pm$ 66.89	25.6 $\pm$ 9.89	<0.001
Hemoglobin (gr/dl)	14.5 $\pm$ 1.63	14.6 $\pm$ 0.85	NS
Hematocrit (%)	42.1 $\pm$ 4.60	42.4 $\pm$ 2.35	NS
Platelet count ($\times 10^3/\mu$ l)	210 $\pm$ 55	240 $\pm$ 41	0.008
MPV (fl)	8.49 $\pm$ 0.84	7.65 $\pm$ 0.42	<0.001

NS, non-significant; CHB, chronic hepatitis B.

TABLE 2. Association of Platelet Count and MPV With Advanced Fibrosis in the Patients Group

	Group 1 (n: 41) F0–F1–F2	Group 2 (n: 18) F3–F4	P-value
HAI	6.6±3.9	8.1±2.5	0.027
HBV-DNA (10 ⁷ IU/ML)	1.0±2.0	1.2±2.2	NS
ALT (IU/ml)	104.35±67.9	104.44±70.6	NS
Platelet count (× 10 ³ /μl)	219±55	184±51	0.017
MPV (fl)	8.30±0.74	8.91±0.94	0.009

NS, non-significant.

(*P*: 0.027). However, platelet count was negative correlated with LFS (*P*: 0.017) (Table 2). Multivariable logistic regression model which consisted of HAI, ALT, HBV-DNA, platelet count, and MPV was performed. We showed that MPV was independently associated with advanced fibrosis (*P*: 0.031).

DISCUSSION

In this study, we have found that patients with CHB have significantly higher MPV values compared with control subjects. Also, a positive correlation between MPV and advanced fibrosis was observed in patients with CHB.

HBV infection is an important health problem worldwide. Chronic HBV infection is associated with a broad range of clinical manifestations, from an asymptomatic carrier state with a normal liver histology to severe and chronic liver diseases, including cirrhosis and hepatocellular carcinoma (HCC) (17). There is a particular concern in the region of Asia, where chronic HBV infection is common, with a carrier rate of approximately 10% of chronic HBV carriers. About 25–40% of them will finally die of liver disease (cirrhosis with and without HCC) (18). Liver biopsy has still been the gold standard for staging of liver fibrosis in patients with CHB. 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. However, biopsy is associated with probable morbidity and mortality and has numerous limitations (3,19). In view of all regarding liver biopsy, in the last decade researchers have been investigating noninvasive methods for true information about liver fibrogenesis activity and fibrosis stage in patients with chronic liver diseases. Some studies have suggested the fibrosis-predicting models composed 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, collagen, hyaluronic acid,

matrix metalloproteinase, and tissue inhibitor of metalloproteinase (20). However, these markers are expensive and to carry out clinical practice is not feasible.

MPV is routinely determined by CBC analyzers and a parameter of reflecting the platelet size. MPV is also a marker of platelet function and activation. It can be influenced by the inflammation (11). Increased MPV levels have been reported in patients with metabolic syndromes, which include myocardial infarction, acute ischemic stroke, diabetes, and nonalcoholic fatty liver disease (12,21). MPV has also shown to be a sign of inflammation in ulcerative colitis, Crohn's disease, and rheumatoid arthritis (13,14). To our knowledge, an association between CHB and increased MPV levels has been reported in one study, but the correlation with stage of liver fibrosis was not investigated (15). This study is the first to show significant increased MPV levels and CHB patients with active disease.

Thrombocytopenia is a frequent complication of advanced liver fibrosis and is commonly considered to be a secondary phenomenon via associated portal hypertension or reduced production of thrombopoietin in the liver. The pathogenesis of liver fibrosis is defined as massive production and deposition of several extracellular matrix (ECM) proteins. The accumulation of ECM proteins, as fibrotic scars, slowly distorts liver structure and increases intrahepatic resistance to blood flow, leading to portal hypertension (22,23). Theoretically, decreased platelet counts can be the result of decreased platelet production, enhanced splenic sequestration, or platelet consumption. In some studies with radiolabeled platelets in chronic liver disease indicate that there is a decreased platelet survival. Depending on the capability of the bone marrow to increase platelet production, platelet counts can be reduced or normal. These findings are in accordance with the increased percentage of young platelets in chronic liver disease (24,25). Similar to previous reports, we also found an association between decreased platelet count and advanced fibrosis in patients with CHB. Additionally, we demonstrated a correlation between MPV levels and advanced fibrosis. We can speculate that increased young platelets could be secondary to sequestration of platelets in the spleen without obvious splenomegaly and portal hypertension. On the other hand, several studies have shown that interleukin-6 (IL-6) contribute to hepatic necroinflammation in CHB patients (26). Some authors reported increased IL-6 levels are responsible for inducing platelet production. IL-6 can induce size of platelets by interfering with megakaryopoiesis with subsequent release of big size platelets from the bone marrow (27). Thereby, increased MPV levels may be owing to increased young platelets.

In conclusion, MPV may be an independent predictor of liver fibrosis in patients with CHB. We suggest that

MPV might help in the assessment of fibrosis in CHB. It should not be considered a stand-alone test for this use owing to nonspecificity with other diseases. However, further studies are needed to establish between platelet functions and liver fibrosis.

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