Increased mean platelet volume is related to histologic severity of primary biliary cirrhosis

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Aim To evaluate the main platelet volume (MPV) as a severity marker in patients with primary biliary cirrhosis (PBC).
Materials and methods Thirty-nine patients with biopsy-proven and as yet untreated PBC followed between January 2008 and January 2015 were included in this study. Liver biopsies were categorized as early stage (stage 1 and 2 according to Scheuer's histological stage) and late stage (Scheuer's stage 3 and 4). As part of the routine evaluation, all PBC patients had their full blood count and biochemistry profile determined, where MPV, white blood cell count, hemoglobin, platelet count, red cell distribution width (RDW), alanine aminotransferase, aspartate aminotransferase (AST), gamma glutamyl transferase, alkaline phosphatase, and total bilirubin values were evaluated. Both groups were compared in terms of the RDW/platelet ratio, the AST platelet ratio index, and the neutrophil lymphocyte ratio.
Results Eighteen patients had early-stage disease (46.2%), whereas 21 PBC patients had late-stage disease (53.8%). There were no differences between groups in terms of routine hematological parameters (white blood cell count, platelet count, hemoglobin, RDW) or biochemical parameters (alanine aminotransferase, AST, gamma glutamyl transferase, alkaline phosphatase, total bilirubin, albumin) ($P > 0.05$). Similarly, there were no differences in AST platelet ratio index, RDW/platelet ratio, or neutrophil lymphocyte ratio values between groups (P values 0.08, 0.19, and 0.14, respectively). The MPV and direct bilirubin were significantly higher in the advanced stage group compared with the early-stage group (11.08 vs. 9.73 fl, respectively, $P = 0.01$ and 0.44 vs. 0.28 mg/dl, respectively, $P = 0.03$). The area under the curve, cut-off value, sensitivity, and specificity of MPV and direct bilirubin for detecting advanced stage were 0.721, 10.3, 71%, and 66%, respectively, and 0.698, 0.23, 71%, and 66%, respectively.
Conclusion MPV can be used as a noninvasive, simple, and effective parameter in patients with PBC to predict histological severity of the disease. Eur J Gastroenterol Hepatol 27:1382–1385
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Introduction

Primary biliary cirrhosis (PBC) is characterized by chronic immune-mediated destruction of small-sized and medium-sized bile ducts [1]. The diagnosis of PBC can be put forward in the presence of two of the three diagnostic criteria identified by the following: (a) increased alkaline phosphatase levels (ALP) as biochemical evidence of cholestasis, (b) presence of antimitochondrial antibody (AMA), and (c) destructive and suppurative changes in histology in small-sized and medium-sized bile ducts [2]. Liver biopsy is invasive and is not a requisite for PBC diagnosis so it is not generally performed in diagnostic workup of PBC except for certain circumstances. However, evaluation of the histological specimen provides valuable information on the stage of the disease and aids in follow-up of the response for treatment, therefore providing information on the prognosis [3]. Utilization of noninvasive diagnostic methods is limited because of cost and limited access in most centers.

Mean platelet volume (MPV) is a parameter of routine blood count that provides an insight into platelet function and activation [4]. The value of MPV changes in evaluation of disease activity, severity, and predicting prognosis has been evaluated in various different diseases [5]. In patients with nonalcoholic fatty liver disease, MPV values were found to be significantly elevated compared with the healthy population [6]. Increased MPV had been reported to be an independent predictor of liver cirrhosis in chronic hepatitis B infection [7]. In patients with chronic hepatitis B and C, increased MPV had been found to be correlated positively with liver fibrosis [8,9]. The MPV had been proposed as a candidate marker for the diagnosis of hepatocellular carcinoma in patients with chronic liver disease [10]. To our knowledge, there are no studies investigating MPV values in patients with PBC.

We aimed to evaluate the relationship of MPV values with the severity of histological grade in patients with PBC.

Materials and methods

Study population

This was a retrospective case–control study evaluating patients with PBC. Sixty-three patients were diagnosed

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with PBC during the aforementioned period. A total of 23 patients without liver biopsies and one patient whose MPV values could not be measured in the complete blood count were excluded from the study. As a result, 39 patients with biopsy-proven and untreated PBC at the time of liver biopsy were included in the final analyses.

Laboratory assessment

The following data were obtained retrospectively from the computerized patient registry database and personal patient files: alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase, ALP, total bilirubin, white blood cell count, platelet count, hemoglobin, red cell distribution width (RDW), MPV, and AMA. The AST platelet ratio index (APRI) was obtained by dividing serum AST levels into serum platelet levels, whereas the RDW platelet ratio (RPR) was obtained by dividing serum RDW levels into serum platelet levels. Finally, the neutrophil lymphocyte ratio (NLR) was obtained by dividing the absolute neutrophil count by the absolute serum lymphocyte count. Laboratory values closest to the date of liver biopsy were chosen for analyses.

Histological assessment

Histological evaluation was performed on the basis of the staging system defined by Scheuer [11]. Disease stage can be categorized into four stages according to this histologic staging system. Florid duct lesions are seen in stage 1, ductular proliferation in stage 2, scarring in stage 3, and finally cirrhosis in stage 4. The cases were divided into two groups as early stage (Scheuer's stage 1 and 2) and late stage (Scheuer's stage 3 and 4) of PBC.

Statistical analysis

Preliminary analyses were completed for frequencies, means, SEs, and percentages where applicable. Categorical variables were analyzed using the χ^2-test. Continuous variables were analyzed using the Mann–Whitney *U*-test. Receiver operating characteristic curve analysis was used to determine the optimal cut-off value of MPV to identify sensitivity and specificity for the detection of PBC stage. Statistical significance was set at *P* less than 0.05 for all analyses. Statistical analysis was carried out using SPSS, version 17.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Thirty-nine patients with biopsy-proven PBC were included in this study. Eighteen patients (46.2%) were categorized as early stage on the basis of histological evaluation and the remaining 21 patients (53.8%) were categorized as late stage. Percentage of female patients and the mean age of the patients (year ± SEM) in early and late stages of the disease were 77.8%, 50.55 ± 2.94, and 81%, 50.90 ± 2.76, respectively. There were no statistically significant differences between the groups in terms of sex and mean age ($P > 0.05$).

Patients were found to be AMA positive in the early and late stages of the disease: 83.3 and 66.7%, respectively. This difference in the prevalence of AMA positivity was not found to statistically significant ($P = 0.29$). There were no statistically significant differences between early and late disease stage patients in terms of routine hematologic (white blood cell count, platelet count, hemoglobin, RDW) and biochemical (ALT, AST, gamma glutamyl transferase, ALP, total bilirubin) parameters ($P > 0.05$). Direct bilirubin was significantly higher in the advanced stage group compared with the early-stage group (0.44 vs. 0.28 mg/dl, respectively, $P = 0.03$). The area under the curve (AUC), cut-off value, sensitivity, and specificity of direct bilirubin for detecting advanced stage were 0.698, 0.23, 71%, and 66%, respectively. There were also no statistical differences between groups in terms of APRI, RPR, and NLR values (*P* values 0.08, 0.19, and 0.14, respectively). Only MPV values were found to be significantly elevated in late-stage PBC patients ($P = 0.01$) (Table 1). The AUC value for MPV was found to be 0.721. The cut-off level of 10.3 to indicate late-stage disease resulted in 71.4% sensitivity and 66.7% specificity. The receiver operating characteristic analysis of MPV and direct bilirubin for identification of early and late stage is presented in Fig. 1.

Discussion

To our knowledge, this is the first study evaluating MPV in PBC patients. This study shows that MPV can be a simple and efficient parameter to discriminate early-stage and late-stage disease. In patients with PBC, MPV can be as effective as liver biopsy in predicting prognosis and evaluating response to the treatment. Also, RDW, RPR, and NLR, which are parameters proposed to indicate fibrosis, have been first evaluated in PBC patients in this study.

PBC is a rare autoimmune liver disease mainly affecting females characterized by immune-mediated destruction of intrahepatic bile ducts [12]. Disease is usually slowly progressive and asymptomatic. In symptomatic patients, pruritus and fatigue generally predominate. Signs of decompensated liver cirrhosis can be seen in late-stage disease. Cholestatic-type liver enzyme elevation, mainly

Table 1. Comparison of hematological and biochemical characteristics with early and advanced stage

	Early stage ($n = 18$)	Late stage ($n = 21$)	*P* value
AST (U/l)	56.16 ± 7.24	62.19 ± 7.08	0.60
ALT(U/l)	82.50 ± 12.2	70.14 ± 9.79	0.32
GGT (U/l)	286.27 ± 34.58	264.23 ± 45.24	0.49
ALP (U/l)	300.88 ± 42.74	295.23 ± 36.97	0.97
Total bilirubin (mg/dl)	0.67 ± 0.08	0.85 ± 0.12	0.56
Direct bilirubin (mg/dl)	**0.28 ± 0.05**	**0.44 ± 0.08**	**0.03**
Albumin (g/dl)	4.25 ± 0.06	4.11 ± 0.08	0.29
Hemoglobin (g/l)	12.25 ± 0.38	12.67 ± 0.40	0.36
WBC ($\times 10^9$/l)	7.13 ± 4.38	5.62 ± 4.55	0.07
Platelet ($\times 10^9$/l)	257.66 ± 18.89	205.9 ± 19.22	0.06
Neutrophil ($\times 10^9$/l)	4.04 ± 0.41	3.11 ± 0.28	0.07
Lymphocyte ($\times 10^9$/l)	2.05 ± 0.20	1.91 ± 0.19	0.63
MPV (fl)	**9.73 ± 0.37**	**11.08 ± 0.33**	**0.01**
RDW	14.69 ± 0.44	14.71 ± 0.49	0.88
RPR	0.06 ± 0.00	0.10 ± .02	0.19
NLR	2.91 ± 0.64	1.85 ± 0.17	0.14
APRI	0.42 ± 0.17	0.36 ± 0.05	0.08
ALT/platelet ratio	0.45 ± 0.10	0.40 ± 0.07	0.83

Parameters were expressed as mean with SE.
Statistically significant values are marked in bold.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; APRI, AST platelet ratio index; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; MPV, main platelet volume; NLR, neutrophil lymphocyte ratio; RDW, red cell distribution width; RPR, red cell distribution width platelet ratio; WBC, white blood cell count.

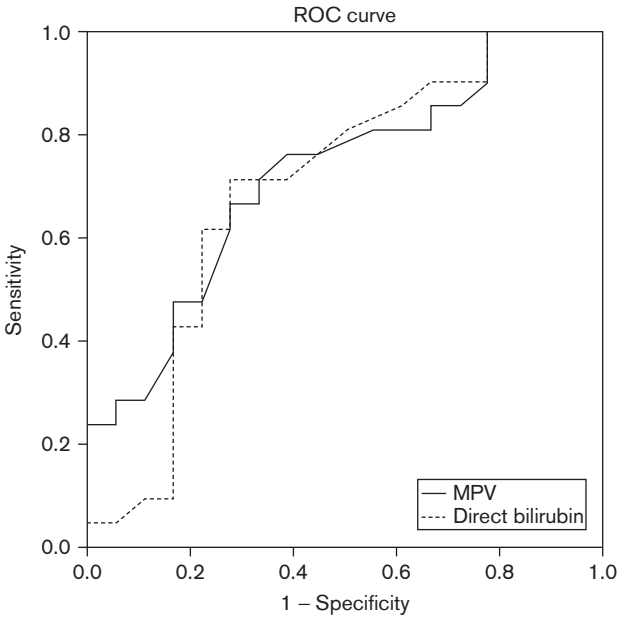

Fig. 1. ROC analysis of MPV and direct bilirubin for identification of early and advanced stage. MPV, main platelet volume; ROC, receiver operating characteristic.

elevation of ALP and AMA positivity, is generally enough for diagnosis. Liver biopsy is generally performed in AMA-negative cases or if there is a suspicion of liver disease other than PBC. Nonetheless, liver histology is very useful in predicting disease prognosis [13]. Information on the histological stage of the disease can help in predicting the response to the treatment. Patients with early-stage disease generally show good clinical and biochemical response to ursodeoxycholic acid treatment [14]. Being invasive, histological staging is not usually used despite the fact that it is very important in predicting the prognosis and response to the treatment.

Routine hematological and biochemical parameters are easy to obtain, and inexpensive and noninvasive tools presenting an attractive alternative to determine the clinical and histological severity of the disease. There are several studies comparing hematological and biochemical parameters with histological stages in patients with chronic liver disease, especially in patients with chronic viral hepatitis B and C. In contrast, studies investigating the role of noninvasive markers in predicting the stage of PBC are limited.

Recently, routine blood count parameters such as RDW, RPR, NLR, and determination of their ratios have gained popularity in predicting the degree of liver fibrosis. Elevated RDW and RPR levels have been reported to be predictors of liver fibrosis in chronic hepatitis B patients [8]. However, factors that increase RDW and RPR levels such as iron deficiency anemia and vitamin B12 deficiency were not evaluated in this study. In our study, no significant decrease was detected in terms of RDW and RPR levels between PBC histological stages.

The NLR is a marker that can be calculated easily from routine blood count parameters showing subclinical inflammation and immune response. Low NLR has been shown to be correlated negatively with fibrosis in inactive hepatitis B patients [15]. In contrast, it is shown to be correlated positively with histological activity and fibrosis in nonalcoholic steatohepatitis patients [16]. The NLR was not found to be a significant marker for predicting PBC disease severity in our study. NLR can be affected by various factors such as coronary artery disease, smoking, and obesity [17]. As this was a retrospective study, these factors could not be investigated in our PBC patients. Furthermore, NLR might not be specific enough to predict disease severity. As a result, all of these factors might be responsible for our negative results with NLR.

MPV is a routine parameter of full blood count. MPV is closely related to platelet activation and function [4]. MPV has been investigated in various clinical fields, especially cardiovascular and hematological diseases [5]. MPV tends to increase or decrease depending on inflammation severity and disease-specific pathophysiological reasons [18]. MPV generally decreases in diseases with high-grade inflammation, whereas MPV has been proposed to increase in diseases with low-grade inflammation [18]. MPV was also found to decrease significantly in early-stage PBC patients in our study. This implies that there may be significant inflammation in the early stage of the PBC. Prominent destruction of liver architecture and decreased inflammation in late-stage disease might be responsible for increased MPV levels in these patients.

In patients with PBC, bilirubin levels have been shown to be an independent predictor of prognosis [19]. We could not detect any significant difference between early-stage and late-stage patients in terms of biochemical and hematologic parameters, except for direct bilirubin. In our hepatology unit, we usually do not perform liver biopsy on patients with esophageal varices, serious thrombocytopenia, and ascites implying cirrhotic liver disease. This might be the reason for the lack of significant differences in albumin or platelet levels, which are indicators of cirrhosis between late and early stages of PBC.

Studies investigating the relationship of biochemical markers between histological stages are limited in PBC. APRI has been found to be correlated positively with histological stage in PBC patients [20]. The ALT/platelet ratio and the AST/platelet ratio have been reported to be significantly decreased in late-stage disease in a study, but AUC levels were reported to be 0.412 and 0.362, respectively, in this study [21]. There were no significant differences between early-stage and late-stage disease in terms of AST platelet or ALT platelet ratios in our study. These markers might not be sensitive enough to detect fibrosis. Our staging system was different from the aforementioned study. These factors might explain the different results of our study.

In a study comparing histological stage and fibrosis with transient elastography for histological stage ≥ 3, AUC was 0.92 [22]. In our study, AUC values for MPV were found to be lower than transient elastography. Nevertheless, MPV results can be obtained much more easily than transient elastography.

There are a few limitations in the current study: (a) the sample size is small. To compare biochemical and hematological parameters with liver biopsy findings, we selected PBC patients with liver biopsy. As liver biopsy is not necessary for the diagnosis of PBC, the number of patients with liver biopsy is limited. (b) The liver biopsy scoring system proposed to provide better staging for severity of disease was not used. Instead, mostly the staging system

was used [23]. We chose the staging system as a new scoring system has not been validated as yet with large prospective studies.

Our study showed that MPV could be a new cheap and easily obtained marker for the determination of PBC severity without liver biopsy. Treatment and follow-up of patients can be optimized when disease severity could be estimated. In terms of MPV cut-off levels, patients with low MPV levels can be treated with effective ursodeoxycholic acid dosing, whereas patients with high MPV can be referred to variceal and hepatocellular carcinoma screening. We believe that our findings need to be confirmed with larger scale prospective studies.

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Conflicts of interest

There are no conflicts of interest.

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