Original Paper

The Role of Mean Platelet Volume in the Diagnosis of Hepatocellular Carcinoma in Patients with Chronic Liver Disease

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ABSTRACT

Background/Aims: Hepatocellular carcinoma (HCC) has poor long-term prognosis so we need new diagnostic techniques and markers to detect HCC in the early phases. The aim of this study was to analyze the levels of serum mean platelet volume in HCC. **Methodology:** The clinical data of 230 subjects with normal, chronic hepatitis, cirrhosis and HCC were retrospectively analyzed at our hospital between January 2009 and December 2009. The levels of MPV were determined in patients with liver disease and compared between patient groups and with healthy persons. **Results:** Serum MPV levels were significantly increased compared to the patients with chronic hepatitis, cirrhosis, and the control group (p<0.01). The cut-off value for MPV for the detection of HCC in cirrhotic patients was calculated as ≥9.2fl using ROC analysis [Sensitivity: 68.3%, specificity: 62.1%, AUC: 0.676 (0.580-0.773), p<0.001]. Additionally, serum MPV levels show higher sensitivity for diagnosis of HCC than AFP. An AFP of more than 7.4IU/mL and an MPV of ≥9.2fl, both put together, had a specificity of 95.2%, while when used separately, they have a sensitivity of 87.5 %. **Conclusions:** MPV may be a potential or adjunctive marker of HCC in patients with chronic liver disease.

INTRODUCTION

HCC is the most common primary malignancy of the liver, being the fifth most frequent cancer worldwide and the third most frequent cause of mortality among oncological patients (1). The incidence of HCC is on the increase and it is becoming more significant both clinically and epidemiologically. HCC is frequently associated with liver cirrhosis, which masks symptoms of cancer progression. The clinical course of HCC is mostly asymptomatic. Suspected focal liver changes are often detected incidentally while monitoring the patient's condition during abdominal ultrasonography examination and are often too large and too advanced for the tumor to be subjected to potentially effective and radical therapy (2). Although it is obvious that development of new diagnostic modalities will significantly increase the detection rate of HCC, there is still a dire need for early detection methods.

For more than 3 decades, information on the platelet size has been widely available to health care practitioners, as part of the data provided in the full blood count, but it is rarely taken into consideration in the diagnosis of patients (3-5). Mean platelet volume (MPV) is one of the most widely used surrogate markers of platelet function and has been shown to increase in acute myocardial infarction, acute ischemic stroke, pre-eclampsia, renal artery stenosis and rheumatoid arthritis (6,7). The diagnostic value of the platelet size in neoplastic disorders particularly in gastric cancer has recently been shown to be elevated (8). To establish whether MPV has diagnostic value for HCC in patients with chronic liver disease, we conducted a retrospective study evaluating MPV levels and its relation with HCC in a standard clinical practice setting.

METHODOLOGY

This study was undertaken at the Gastroenterology clinic for Turkiye Yuksek Ihtisas Teaching and Research Hospital. The medical records of all patients who underwent a liver biopsy for chronic hepatitis, patients with liver masses which were pathologically confirmed to be hepatocellular carcinomas and all cirrhotic patients admitted for palliative management of ascites and hepatic encephalopathy between January 2009 and December 2009 were reviewed. Patients with any signs of infection (cellulitis, urinary tract infection, spontaneous bacterial peritonitis, cholangitis, *etc.*) and/or patients who had fever were excluded from the study. The control group consisted of patients with no known chronic disease who presented to the gastroenterology clinic with dyspepsia, but who had normal laboratory and ultrasonographic findings. Results of complete blood count, biochemistry, AFP levels and ultrasonographic findings on presentation were evaluated.

Samples for full blood count analysis were collected into ethylenediaminetetraacetic acid (EDTA) anticoagulated tubes. Measurements were performed on Advia 2120, Siemens, Germany. Reference values of the MPV for the Advia 2120, Siemens, Germany equipment is 6.1-8.9fl at our institution. MPV assay was standardized according to the manufacturer's instructions. All measurements with the ADVIA 2120 device were performed using the flow cytometric technique.

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TABLE 1. Clinical and laboratory characteristics of the study population.

	Normal	Chronic hepatitis	Cirrhosis	HCC	P1	P2
Number of patients	63	49	58	60		
Age (yrs)	45.8 (17.8-79.0)	45 (19.6-58.9)	55.1 (25.0-81.3)	65.5 (23.1-83.0)	<0.001	<0.001
Gender (M/F)	23/40	29/20	36/22	41/19	0.002	0.475
AFP (0-7.4IU/mL)		2.2 (0.9-60.6)	2.0 (0.5-240.4)	11.6 (0.9-2479)	<0.001	<0.001
MPV (6.1-8.9fl)	8.8 (7.5-11.4)	8.6 (7.0-11.0)	9.1 (7.0-12.1)	9.7 (7.9-14.5)	<0.001	0.001
Child-Pugh score			8 (5-14)	6 (5-12)		0.016
MELD score			12.5 (7-33)	10 (6-25)		0.004
Hemoglobin (13.3-17.2g/dL)	13.9±1.4	14.9±1.4	11.4±2.3	12.4±1.83	<0.001	0.016
White blood cell (3.7-9.7x10^3µL)	7.08 (3.2-10.3)	6.4 (4.3-9.5)	4.8 (1.2-19.8)	4.9 (1.3-17.5)	<0.001	0.489
Platelet (150-373x10^3µL)	294 (166-609)	244 (152-551)	99 (18-430)	116.5 (18-337)	<0.001	0.076
Spleen size			163±38.7	145.8±29.4		0.033

M/F: Male or Female; AFP: Alpha-Fetoprotein; HCC: Hepatocellular Carcinoma; MPV: Mean Platelet Volume; MELD: Model for End-Stage Liver Disease. P2: *p* value, for comparison between cirrhosis and HCC groups.

TABLE 2. Sensitivity and specificity of AFP and MPV values for the diagnosis of HCC.

	Sensitivity (%)	Specificity (%)
AFP >7.4IU/mL	62.5	89.5
MPV ≥9.2fl	68.3	69.2
AFP or MPV	87.5	62.9
AFP and MPV	48.2	95.2

AFP: Alpha-Fetoprotein; MPV: Mean Platelet Volume.

Statistical analysis

Statistical analysis was performed using PASW Statistics 18 (SPSS, Chicago, IL, USA). Statistically significant differences were analyzed by the χ^2 test for categorical variables. Continuous variables were tested for normality by the Kolmogorov-Smirnov test. Normally distributed data are presented as mean and standard deviations (SDs). We used the Kruskal-Wallis (more than 2 subgroups) and the Mann-Whitney U test (2 subgroups) for independent subgroups and the Wilcoxon test for dependent subgroups. Independent samples *t*-test was used for parametric groups. A two-tailed *p* value below 0.05 was considered statistically significant. The sensitivity and specificity of MPV level for a diagnosis of HCC were calculated under various cut-off ranges and the receiver operating characteristic (ROC) curves were drawn.

RESULTS

Two-hundred and thirty patients were deemed suitable for inclusion in the study. Patients were divided into 4 groups; normal (63 patients), non-cirrhotic (49 patients), cirrhotic (58 patients) and hepatocellular carcinoma (60 patients) (**Table 1**). There was no correlation between AFP and MPV (Spearman correlation, r=0.242). A cut-off point of 7.4IU/mL of serum AFP was found to be 62.5% sensitive and 89.5% specific for a diagnosis of HCC, with a kappa value of 0.521.

The cut-off value for MPV for the detection of HCC in cirrhotic patients was calculated as ≥9.2 fl using ROC analysis [sensitivity: 68.3%, specificity: 62.1%, AUC: 0.676 (0.580-0.773), *p*<0.001] (**Figure 1**). In our study, the sensitivities of AFP and MPV in detecting HCC in the chronic hepatitis, cirrhotic and HCC groups were 62.5% and 68.3%, respectively (**Table 2**). An AFP of more than 7.4IU/mL and an MPV of ≥9.2fl, both put together, had a specificity of 95.2%, while when used separately, they have a sensitivity of 87.5 % (**Table 2**).

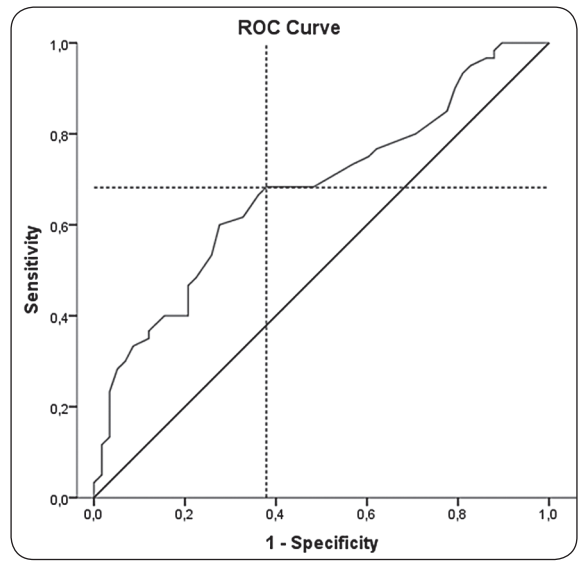

FIGURE 1. Receiver operating characteristic (ROC) analysis for MPV.

DISCUSSION

Our study showed that the patients with chronic liver disease (CLD) have a significantly elevated MPV compared to control subjects. MPV was also higher among patients with hepatocellular carcinoma compared to patients with CLD. These findings suggest that MPV may be a potential marker of hepatocellular carcinoma in patients with CLD.

Thrombocytopenia (platelet count <150,000/lL) is a common complication in patients with chronic liver disease (CLD) that has been observed in up to 76% of patients. Moderate thrombocytopenia (platelet count, 50,000/lL–75,000/lL) occurs in approximately 13% of patients with cirrhosis (9). Spleen platelet sequestration, bone marrow suppression by chronic hepatitis C infection and antiviral treatment with interferon-based therapy can contribute to the development of thrombocytopenia. Reductions in the level or activity of the hematopoietic growth factor thrombopoietin (TPO) may also play a role (10). MPV has an inverse, non-linear relation with platelet count, while platelet volume heterogeneity has a direct, non-linear relation with MPV (11). So, higher MPV levels in patients with CLD are understandable. On the other hand the routine blood count allows classification of patients into 9 categories: high, low, or normal MPV and high, low or normal platelet count. An analysis

of 1244 patients showed that all of the 11 patients who are in the high MPV and low platelet category had hyperdestructive causes (12). Bone marrow is not a usual site of metastases in patients with HCC. The overall incidence of bone marrow metastasis was reported as 14.7 % in autopsy series of HCC and stromal fibrosis was rare in these cases (13). For this reason higher MPV values in HCC cannot be explained by invasion and destruction of bone tissue matrix by tumor cells in most of the cases.

Interleukin-6 (IL-6) is a broad spectrum cytokine that exhibits potent effects on megakaryocytic maturation (14-16). When used in combination with the early acting cytokine IL-3, IL-6 is synergistic, promoting increased growth of megakaryocytic and early hematopoietic progenitor cells (14-16). IL-6 is capable of progressively augmenting platelet diameter. This observation suggests that the cytokine (directly or indirectly) modifies terminal maturation of megakaryocytes (17). The substantial proportion of platelets may achieve extremely large size (up to 19.1% in three normal dogs administered 80kg/kg/d of IL-6) due to the effect of IL-6 (17). Circulating levels of IL-6 increase markedly during development and progression of tumors of different etiologies such as cancers of the breast, pancreas, lung, ovary and prostate (18). As far as HCC is concerned, higher IL-6 levels were found in cirrhotic patients with HCC in comparison to cirrhotic patients without HCC; furthermore, in patients with HCC, a significant correlation of serum IL-6 levels with the Okuda stage classification of the disease was observed (19-21). In another series high serum IL-6 level was found to predate the development of HCC in chronic hepatitis B patients and it had moderate accuracy in predicting future cancer (22). Regarding the effects of IL-6 on megakaryocytopoies, high concentration of this cytokine may explain for the higher MPV values in patients with HCC.

It is not known if the enlarged platelets are hemostatically superior to the other platelets, but the platelets in the HCC patients have been suggested to store more brain-derived-neurotropic factor (BDNF) than in the normal population or patients with cirrhosis. BDNF is a novel functional protein that could promote tumor cell growth in a rat HCC model. It was also demonstrated that BDNF mRNA was over expressed in human HCC tumor tissue compared with that in non-tumorous tissue, cirrhotic or normal liver tissues (23). Whether the higher MPV is an epiphenomenon in HCC or increased platelet volume due to storage of various mediators contributes to the pathogenesis needs further clarification.

Our data has limitations due to the retrospective nature of the study. The cut-off value for MPV for the detection of HCC in cirrhotic patients was calculated as ≥9.2 in our series. Prospective follow-up of the patients with CLD and higher MPV values (≥9.2) to observe the development of HCC would provide more reliable data. On the other hand our series is the only one who documented the possible relationship between MPV and HCC to the best of our knowledge.

Measurement of MPV is non-invasive, cheap and quick, and may therefore serve as a predictor of HCC in patients with CLD. Low sensitivity and specificity, on the other hand, suggests that this may be an adjunctive parameter to some other markers like AFP. Further studies with larger samples are needed to determine the association of MPV with HCC.

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