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***Retrospective Study***

**Ratio of mean platelet volume to platelet count is a potential surrogate marker predicting liver cirrhosis**

Iida H *et al*. MPV/PLT predicts liver cirrhosis

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**Abstract**

***AIM***

To provide a simple surrogate marker predictive of liver cirrhosis.

***METHODS***

Specimens from 302 patients who underwent resection for hepatocellular carcinoma between January 2006 and December 2012 were retrospectively analyzed. Based on pathologic findings, patients were divided into groups based on whether or not they had liver cirrhosis (LC). Parameters associated with hepatic functional reserve were compared in these two groups using Mann-Whitney U-test for univariate analysis. Factors differing significantly in univariate analyses were entered into multivariate logistic regression analysis.

***RESULTS***

There were significant differences between the LC group (*n =* 100) and non-LC group (*n =* 202) in prothrombin activity, concentrations of alanine aminotransferase, aspartate aminotransferase, total bilirubin, albumin, cholinesterase, type IV collagen, hyaluronic acid, indocyanine green retention rate at 15 min (ICGR 15), maximal removal rate of technitium-99m diethylene triamine penta-acetic acid-galactosyl human serum albumin and ratio of mean platelet volume to platelet count (MPV/PLT). Multivariate analysis showed that prothrombin activity, concentrations of alanine aminotransferase, aspartate aminotransferase, total bilirubin, hyaluronic acid and MPV/PLT ratio were factors independently predictive of liver cirrhosis. The area under the curve value for MPV/PLT was 0.78, with a 0.8 cut-off value having a sensitivity of 65% and a specificity of 78%.

***CONCLUSION***

The MPV/PLT ratio, which can be determined simply from the complete blood count, may be a simple surrogate marker predicting liver cirrhosis.

**Key word**: Mean platelet volume; Platelet count; Liver cirrhosis; Hepatic functional reserve; Liver fibrosis

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**Core tip:** Although liver biopsy is considered the gold standard in the diagnosis of liver fibrosis and cirrhosis, liver biopsy is an invasive procedure, with attendant morbidity. Less-invasive procedures are needed in the diagnosis of liver cirrhosis. Multivariate analysis showed that the mean platelet volume to platelet count ratio was independently predictive of liver cirrhosis. This ratio, which can be determined from a routine complete blood count, may be a simple surrogate marker predicting liver cirrhosis.

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**INTRODUCTION**

Mean platelet volume (MPV) is a machine-calculated measurement of average platelet size, usually included in complete blood count (CBC) testing. Normal MPV ranges from 7.5 to 11.5 fL. Because average platelet size is directly proportional to the numbers of platelets produced, MPV is indicative of platelet production in bone marrow. Moreover, MPV is higher when there is destruction of platelets, as observed in patients with inflammatory bowel disease, immune thrombocytopenic purpura, myeloproliferative diseases, and Bernard-Soulier syndrome[1]. MPV may also be higher in patients with pre-eclampsia and those recovering from transient bone marrow hypoplasia[2]. In contrast, abnormally low MPV values are indicative of thrombocytopenia because of impaired platelet production, as observed in patients with aplastic anemia.

Several studies have reported that liver cirrhosis (LC) and fibrosis are related to MPV [3-6]. Increased MPV, as well as decreased platelet count (PLT), were found to reflect a greater degree of fibrosis. These findings suggested that the ratio of MPV to PLT may correlate strongly with the degree of liver fibrosis. This study was therefore designed to determine whether liver fibrosis and LC are associated with the MPV/PLT ratio or not.

**MATERIALS AND METHODS**

This retrospective study assessed samples obtained from 302 patients who underwent liver resection for hepatocellular carcinoma (HCC) between January 2006 and December 2012. All patients were assessed pathologically by stage of fibrosis in nontumor liver tissue using the new Inuyama classification[7]. F0 was defined as no fibrosis (*n =* 22), F1 as chronic hepatitis with fibrous portal expansion (*n =* 67), F2 as chronic hepatitis with bridging fibrosis (*n =* 62), F3 as chronic hepatitis with bridging fibrosis and architectural distortion (*n =* 51), and F4 as LC with tendency toward nodular formation throughout the whole area. Patients classified as F0-F3 were assigned to the non-LC group (*n =* 202), and those classified as F4 to the LC group (*n =* 100).

Parameters associated with hepatic functional reserve were assessed in all patients; these included MPV, PLT, and the MPV/PLT ratio; prothrombin activity (PT); concentrations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, albumin, cholinesterase, type IV collagen, and hyaluronic acid; indocyanine green retention rate at 15 min (ICGR 15); and the maximal removal rate of technitium-99m diethylene triamine penta-acetic acid (99mTc-DTPA)-galactosyl human serum albumin (GSA-Rmax), a marker of hepatic functional reserve, as determined by scintigraphy.[8, 9] These factors were compared between the LC and non-LC groups. Multivariate regression analysis was performed to identify factors independently predictive of LC, and cut-off values were calculated. In addition, patients were divided by fibrosis stage (F0-F4), and these parameters were compared among the five subgroups.

Comorbidities that could be associated with an increase or decrease in the MPV/PLT ratio such as inflammatory bowel disease, immune thrombocytopenic purpura, myeloproliferative disease, or Bernard-Soulier syndrome were not observed in any of the patients.

***Statistical analysis***

Parameters predictive of hepatic functional reserve in the LC and non-LC groups were compared using the Mann-Whitney U-test. Factors differing significantly in univariate analyses were entered into multivariate logistic regression analysis. Receiver operating characteristic (ROC) curves were used to calculate areas under the curve (AUC) and cut-off values. All analyses were performed using JMP 9 statistical analysis software (SAS Institute Inc., Cary, NC, United States), with a *P* value < 0.05 defined as statistically significant.

**RESULTS**

There were 161 patients with hepatitis C and 53 patients with hepatitis B. The remaining 88 patients were negative for hepatitis B and C. The average age was 69.6 ± 9.7 years in the non-LC group and 68.2 ± 7.6 years in the LC group (*P* = 0.21). The ratio of males to females was larger in the non-LC group, with 164 (81.2%) male and 38 (18.8%) female patients; there were 69 (69.0%) male and 31 (31.0%) female patients in the LC group (*P* = 0.02).

Table 1 compares parameters (univariate analysis) between the LC and non-LC groups. The rate of hepatitis C was greater in the LC group than in the non-LC group (*P* < 0.001). The Edmondson-Steiner grade[10] for HCC grade I was a little smaller and for grade II a little larger in the LC group; however, the difference was not significant (*P* = 0.07). The average PLT was 11.6 ± 4.6 and 18.9 ± 8.1 × 104/µL, respectively, and the average MPV was 10.8 ± 0.9 and 10.2 ± 0.9 fL, respectively (*P* < 0.05 for each). The MPV/PLT ratio was significantly higher in the LC group than in the non-LC group (1.10 ± 0.51 vs. 0.64 ± 0.30, *P* < 0.05). Other factors associated with hepatic functional reserve also differed significantly between the two groups, including PT; the concentrations of AST, ALT, total bilirubin, albumin, cholinesterase, type IV collagen, and hyaluronic acid; ICGR15 and GSA-Rmax (*P* < 0.05 for each).

Table 2 shows multivariate analysis of factors predictive of LC in these patients. MPV/PLT ratio, PT; and concentrations of AST, ALT, total bilirubin and hyaluronic acid were independent predictors of LC. The highest odds ratio was 3.71 for the MPV/PLT ratio. Although albumin, cholinesterase, and type IV collagen concentrations, as well as ICGR15 and GSA-Rmax, were also predictors of LC on univariate analysis, they were not independently predictive on multivariate analysis.

The ROC curves of all six independently predictive factors (MPV/PLT ratio, PT; and concentrations of AST, ALT, total bilirubin and hyaluronic acid) are shown in Figure 1. Calculation of AUC for all six factors showed that the MPV/PLT ratio had the highest AUC, 0.78. A cut-off value of 0.8 had a sensitivity of 65% and a specificity of 78% in predicting LC. This ratio was a better predictor of LC than other parameters of hepatic functional reserve.

Patients were also divided by individual fibrosis stage and MPV/PLT ratio determined for each stage. The average MPV/PLT ratios for patients classified as F0-1, F2, F3, and F4 were 0.54 ± 0.24, 0.65 ± 0.29, 0.79 ± 0.35, and 1.10 ± 0.51, respectively, with each pairwise difference being statistically significant (Figure 2).

Additionally, we examined the correlation between the MPV/PLT ratio and the pathological inflammation level according to the new Inuyama classification. The average MPV/PLT ratios for patients classified as A0, A1, A2, and A3 were 0.68 ± 0.21, 0.70 ± 0.45, 0.82 ± 0.39, and 0.73 ± 0.10, respectively. There was no significant correlation between MPV/PLT and pathological inflammation level (*P* = 0.214).

**DISCUSSION**

LC is a result of advanced liver disease, in which normal liver tissue is replaced by fibrotic tissue. These changes lead to loss of liver function. LC is most frequently caused by alcoholism, infection with hepatitis B and hepatitis C viruses, and fatty liver disease, but it may have many other causes. LC arising from nonalcoholic steatohepatitis (NASH) was recently shown to be a worldwide problem.

The standard method of diagnosing LC is liver biopsy. However, liver biopsy is an invasive procedure and cannot be performed on patients with severe ascites or severe coagulation disorders. Several studies have therefore assessed surrogate markers in blood predictive of LC; these include FibroTest (FibroSure) and the aspartate aminotransferase platelet ratio index[11]. In addition, elastographic methods such as FibroScan have been reported to be a noninvasive method of predicting LC[12,13]. We could not compare these methods with the MPV/PLT ratio because we do not have these examination devices.

MPV may be another predictor of LC. Higher MPV has been reported in patients with hepatitis B[14], and LC, fibrosis level, and MPV have been reported to correlate in patients with chronic hepatitis B[3-5]. MPV may also be predictive of LC in patients with chronic hepatitis C[6].

MPV has been associated not only with fibrosis stage but with degree of liver inflammation[15]. For example, higher MPV has been observed in patients with NASH[16], and MPV has been found to correlate with the presence of nonalcoholic fatty liver disease (NAFLD)[17], although another study reported no correlation[18]. In addition, MPV may or may not correlate with insulin resistance, which is closely related to NAFLD[19,20]. To date, however, the relationship between NAFLD and MPV has not been determined.

MPV has been reported to strongly correlate with the prognosis of patients with non-small cell lung cancer[21]. In addition, high MPV and MPV/PLT have been found to be associated with a high risk for HCC[22,23]. An examination of the correlation between MPV/PLT ratio and postoperative prognosis of patients undergoing hepatic resection for HCC found that the MPV/PLT ratio was unrelated to overall or recurrence-free survival rate after resection.

This study had several limitations, including its retrospective design, performance at a single center, and small sample size. Moreover, all patients included had undergone resection for HCC. Therefore, the results should not be generalized to patients without HCC before verification. Prospective, multicenter studies with large numbers of patients are needed to confirm these findings.

In conclusion, we found that the MPV/PLT ratio was predictive of LC, suggesting that this ratio may be a simple surrogate marker predictive of LC.

**COMMENTS**

***Background***

Several noninvasive methods for predicting cirrhosis have been reported, but liver biopsy is the only method for obtaining a definitive diagnosis. However, liver biopsy is invasive, and a noninvasive diagnostic method is desirable. MPV, the size of platelets, can be determined from routine CBC data of blood samples. Generally, if bone marrow hematopoietic function decreases, MPV decreases. In contrast, if spleen function increases, new platelets are made rapidly and MPV increases. In recent years, the relationship between MPV and liver disease has attracted attention.

***Research frontiers***

There are reports that MPV correlates with liver function, and there are reports that MPV is related to the incidence of HCC. However, there is no report to evaluate the correlation between MPV/PLT and liver function, so we undertook this study.

***Innovations and breakthroughs***

The authors studied only patients who were diagnosed with cirrhosis histopathologically after liver resection. The MVP/PLT ratio could predict cirrhosis more sensitively than other general liver function tests.

***Applications***

The MPV/PLT ratio also correlated with the degree of hepatic fibrosis according to the Inuyama classification. We examined the relationship between prognosis after hepatic resection of HCC and the value of the MPV/PLT ration, but unfortunately no correlation was found.

***Terminology***

MPV/PLT; ratio of mean platelet volume to platelet count, HCC; hepatocellular carcinoma, LC; liver cirrhosis, NASH; non-alcoholic steatohepatitis, CBC; complete blood count, PT; prothrombin activity, AST; aspartate aminotransferase, ALT; alanine aminotransferase, ICGR 15; indocyanine green retention rate at 15 min, GSA-Rmax; maximal removal rate of Tc-GSA

***Peer-review***

It is useful as a simple surrogate marker for liver cirrhosis. From now on, it is necessary to compare with noninvasive method of predicting cirrhosis using ultrasound and other modalities.

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Grade E (Poor): 0

**Figure 1 Receiver operating characteristic curve analysis of parameters differing significantly in the liver cirrhosis and non-liver cirrhosis groups on multivariate analysis.** The AUC of mean platelet volume to platelet count (MPV/PLT) was the highest. A MPV/PLT ratio of 0.8 had a sensitivity of 65% and a specificity of 78%.



**Figure 2 Relationship between mean platelet volume to platelet count ratio and fibrosis stage.** There were significant differences between each pair of stages.

**Table 1 Univariate analysis of factors in non-liver cirrhosis and liver cirrhosis groups**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Non-LC group (*n =* 202)** | **LC group (*n =* 100)** | ***P*-value** |
| EtiologyHBVHCVNBNC | 43 (21.2%)89 (44.1%)70 (34.7%) | 10 (10.0%)72 (72.0%)18 (18.0%) | < 0.001 |
| Edmonson-Steiner grade |  |  |  |
| I | 30 (30.0%) | 36 (17.8%) | 0.07 |
| II | 64 (64.0%) | 151 (74.8%) |  |
| III | 4 (4.0%) | 13 (6.4%) |  |
| IV | 2 (2.0%) | 2 (1.0%) |  |
| PLT (×104/µL) | 18.9 ± 8.1 | 11.6 ± 4.6 | < 0.0001 |
| MPV (fL) | 10.2 ± 0.9 | 10.8 ± 0.9 | < 0.0001 |
| MPV/PLT ratio | 0.64 ± 0.30 | 1.10 ± 0.51 | < 0.0001 |
| PT (%) | 92.9 ± 11.7 | 82.5 ± 11.1 | < 0.0001 |
| AST (IU/L) | 42 ± 26 | 51 ± 23 | < 0.0001 |
| ALT (IU/L) | 40 ± 30 | 47 ± 33 | 0.02 |
| Total-bilirubin (mg/dL) | 0.67 ± 0.23 | 0.90 ± 0.34 | < 0.0001 |
| Albumin (g/dL) | 3.8 ± 0.5 | 3.6 ± 0.4 | 0.01 |
| Cholinesterase (IU/L) | 235 ± 80 | 193 ± 60 | < 0.0001 |
| Type 4 collagen (ng/mL) | 6.3 ± 2.4 | 9.1 ± 4.4 | 0.04 |
| Hyaluronic acid (ng/mL) | 147 ± 179 | 312 ± 318 | < 0.0001 |
| ICGR15 (%) | 14.1 ± 8.3 | 22.1 ± 12.1 | < 0.0001 |
| GSA Rmax (mg/min) | 0.62 ± 0.21 | 0.44 ± 0.17 | < 0.0001 |

All results reported as mean ± standard deviation. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GSA-Rmax: Maximal removal rate of 99mTc-DTPA-galactosyl human serum albumin; HBV: Positive for hepatitis B antigen; HCV: Positive for hepatitis C antibody; ICGR 15: Indocyanine green retention rate at 15 min; LC: Liver cirrhosis; MPV: Mean platelet volume; PLT: Platelet count; PT: Prothrombin activity.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | **Odds ratio** | ***P*-value** | **95%CI** |
| MPV/PLT ratio | ≥ 0.71, *n =* 151< 0.71, *n =* 151 | 3.71 | < 0.0001 | 1.94-7.28 |
| PT (%) | ≥ 89.0, *n =* 151< 89.0, *n =* 151 | 2.68 | 0.0018 | 1.44-5.06 |
| AST (IU/L) | ≥ 39, *n =* 155< 39, *n =* 147 | 3.30 | 0.01 | 1.30-9.09 |
| ALT (IU/L) | ≥ 34, *n =* 153< 34, *n =* 149 | 2.57 | 0.04 | 1.02-7.09 |
| Total-bilirubin (mg/dL) | ≥ 0.7, *n =* 177< 0.7, *n =* 125 | 1.89 | 0.04 | 1.00-3.61 |
| Albumin (g/dL) | ≥ 3.8, *n =* 168< 3.8, *n =* 134 | 0.95 | 0.89 | 0.47-1.89 |
| Cholinesterase (IU/L) | ≥ 211, *n =* 152< 211, *n =* 150 | 0.98 | 0.96 | 0.48-1.98 |
| Type 4 collagen (ng/mL) | ≥ 6.5, *n =* 166< 6.5, *n =* 136 | 0.95 | 0.86 | 0.51-1.72 |
| Hyaluronic acid (ng/mL) | ≥ 124, *n =* 153< 124, *n =* 149 | 2.28 | 0.008 | 1.23-4.26 |
| ICGR15 (%) | ≥ 14.3, *n =* 151< 14.3, *n =* 151 | 1.40 | 0.30 | 0.72-2.68 |
| GSA Rmax (mg/min) | ≥ 0.555, *n =* 151< 0.555, *n =* 151 | 1.51 | 0.24 | 0.75-3.04 |

**Table 2 Multivariate analysis of factors predicting liver cirrhosis**

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GSA-Rmax: Maximal removal rate of 99mTc-DTPA-galactosyl human serum albumin; ICGR 15: Indocyanine green retention rate at 15 min; MPV: Mean platelet volume; PLT: Platelet count; PT: Prothrombin activity.