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

Hiroya Iida, Masaki Kaibori, Kosuke Matsui, Morihiko Ishizaki, Masanori Kon

Department of Surgery, Kansai Medical University, Osaka 573-1010, Japan

Author contributions: Iida H designed the research and performed the surgical interventions; Kaibori M performed the surgical interventions and contributed to the statistical assessment; Matsui K and Ishizaki M performed the surgical interventions; Kon M performed the surgical interventions and conferred on the final agreement for publication.

Institutional review board statement: The study was reviewed and approved by the Kansai Medical University Institutional Review Board.

Informed consent statement: Since this research was retrospective observation research using medical record information, the authors only gave the patient the opportunity to opt out. Therefore, there is no informed consent statement signed by the patients.

Conflict-of-interest statement: None of the authors have any conflicts of interest or financial disclosures.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Unsolicited manuscript

Correspondence to: Hiroya Iida, MD, Department of Surgery, Kansai Medical University, 2-5-1 Shinmachi Hirakata, Osaka 573-1010, Japan. hiroya0001@mac.com
Telephone: +81-72-8040101
Fax: +81-72-8042578
Received: March 26, 2017
Peer-review started: March 28, 2017

Abstract

AIM
To provide a simple surrogate marker predictive of liver cirrhosis (LC).

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 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, 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 and hyaluronic acid, and MPV/PLT ratio were factors independently predictive of LC. The area under the curve value for MPV/PLT was 0.78,
with a 0.8 cutoff 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 LC.

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

© The Author(s) 2018. Published by Baishideng Publishing Group Inc. All rights reserved.

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.

Iida H, Kaibori M, Matsui K, Ishizaki M, Kon M. Ratio of mean platelet volume to platelet count is a potential surrogate marker predicting liver cirrhosis. *World J Hepatol* 2018; 10(1): 82-87 Available from: URL: http://www.wjgnet.com/1948-5182/full/v10/i1/82.htm DOI: http://dx.doi.org/10.4254/wjh.v10.i1.82

**INTRODUCTION**

Mean platelet volume (MPV) is a machine-calculated measurement of average platelet size, usually included in complete blood count testing. Normal MPV ranges from 7.5 fl 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. MPV may also be higher in patients with pre-eclampsia and those recovering from transient bone marrow hypoplasia. 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. 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. 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 (ICGR15); 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. These factors were compared between the LC and non-LC groups. Multivariate regression analysis was performed to identify factors independently predictive of LC, and cutoff 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 cutoff values. All analyses were performed using JMP 9 statistical analysis software (SAS Institute Inc., Cary, NC, United States), with a P value of < 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 × 10^11/L and 18.9 ± 8.1 × 10^11/L, respectively, and the average MPV was 10.8 ± 0.9 fL 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 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 cutoff 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

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

| Factor                              | Odds ratio | P-value | 95% CI       |
|-------------------------------------|------------|---------|--------------|
| MPV/PLT ratio                       | ≥ 0.71, n = 151 | 3.71     | < 0.0001     | 1.94-7.28 |
|                                     | < 0.71, n = 151 |          |              |          |
| PT, %                               | ≥ 89.0, n = 151 | 2.68     | 0.0018       | 1.44-5.06 |
|                                     | < 89.0, n = 151 |          |              |          |
| AST, IU/L                           | ≥ 39, n = 155  | 3.30     | 0.01         | 1.30-9.09 |
|                                     | < 39, n = 147  |          |              |          |
| ALT, IU/L                           | ≥ 34, n = 153  | 2.57     | 0.04         | 1.02-7.09 |
|                                     | < 34, n = 149  |          |              |          |
| Total-bilirubin, mg/dL              | ≥ 0.7, n = 177 | 1.89     | 0.04         | 1.00-3.61 |
|                                     | < 0.7, n = 125 |          |              |          |
| Albumin, g/dL                       | ≥ 3.8, n = 168 | 0.95     | 0.89         | 0.47-1.89 |
|                                     | < 3.8, n = 134 |          |              |          |
| Cholinesterase, IU/L                | ≥ 211, n = 152 | 0.98     | 0.96         | 0.48-1.98 |
|                                     | < 211, n = 150 |          |              |          |
| Type 4 collagen, ng/mL              | ≥ 6.5, n = 166 | 0.95     | 0.86         | 0.51-1.72 |
|                                     | < 6.5, n = 136 |          |              |          |
| Hyaluronic acid, ng/mL              | ≥ 124, n = 153 | 2.28     | 0.008        | 1.25-4.26 |
|                                     | < 124, n = 149 |          |              |          |
| ICGR15, %                           | ≥ 14.3, n = 151 | 1.40    | 0.30         | 0.72-2.68 |
|                                     | < 14.3, n = 151 |          |              |          |
| GSA Rmax, mg/min                    | ≥ 0.555, n = 151 | 1.51    | 0.24         | 0.75-3.04 |
|                                     | < 0.555, n = 151 |          |              |          |

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CI: Confidence interval; GSA-Rmax: Maximal removal rate of 99mTc-DTPA-galactosyl human serum albumin; ICGR15: Indocyanine green retention rate at 15 min; MPV: Mean platelet volume; PLT: Platelet count; PT: Prothrombin activity.

**Figure 1** Receiver operating characteristic curve analysis of parameters differing significantly in the liver cirrhosis and non-liver cirrhosis groups on multivariate analysis. The area under the curve of MPV/PLT was the highest. A MPV/PLT ratio of 0.8 had a sensitivity of 65% and a specificity of 78%. MPV/PLT: Mean platelet volume to platelet count; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; PT: Prothrombin activity.

**Figure 1** Receiver operating characteristic curve analysis of parameters differing significantly in the liver cirrhosis and non-liver cirrhosis groups on multivariate analysis. The area under the curve of MPV/PLT was the highest. A MPV/PLT ratio of 0.8 had a sensitivity of 65% and a specificity of 78%. MPV/PLT: Mean platelet volume to platelet count; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; PT: Prothrombin activity.
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 AST platelet ratio index[11]. In addition, elastographic methods, such as FibroScan, have been reported to be noninvasive methods 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.

**ARTICLE HIGHLIGHTS**

**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. Mean platelet volume (MPV), the size of platelets, can be determined from routine complete blood count 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/platelet count (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 MPV/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 Ishak classification. The authors examined the relationship between prognosis after hepatic resection of hepatocellular carcinoma and the value of the MPV/PLT ratio, but unfortunately no correlation was found.

**Terminology**

MPV is the size of platelets and can be determined from routine complete blood count data of blood samples. Liver cirrhosis and fibrosis are related to MPV.

**REFERENCES**

1. Liu S, Ren J, Han G, Wang G, Gu G, Xia Q, Li J. Mean platelet volume: a controversial marker of disease activity in Crohn’s disease. *Eur J Med Res* 2012; 17: 27 [PMID: 23058104 DOI: 10.1186/2047-783X-17-27]

2. Lippi G, Filippozzi L, Salvagno GL, Montagnana M, Franchini M, Guidi GC, Targher G. Increased mean platelet volume in patients with acute coronary syndromes. *Arch Pathol Lab Med* 2009; 133: 1441-1443 [PMID: 19722752 DOI: 10.1043/1543-2165-133.9.1441]

3. Karagoz E, Ulcay A, Tanoglu A, Kara M, Turhan V, Erdem H, Oncul O, Gorenek L. Clinical usefulness of mean platelet volume and red blood cell distribution width to platelet ratio for predicting the severity of hepatic fibrosis in chronic hepatitis B virus patients. *Eur J Gastroenterol Hepatol* 2014; 26: 1320-1324 [PMID: 25210777 DOI: 10.1097/MEG.0000000000000203]

4. QI XT, Wan F, Lou Y, Ye B, Wu D. The mean platelet volume is a potential biomarker for cirrhosis in chronic hepatitis B virus infected patients. *Hepatogastroenterology* 2014; 61: 456-459 [PMID: 24901161]
5 Ekiz F, Yuksel O, Coskun E, Yilmaz B, Altuntas A, Coban S, Yuksel I, Uskudar O, Klokli S. Mean platelet volume as a fibrosis marker in patients with chronic hepatitis B. J Clin Lab Anal 2011; 25: 162-165 [PMID: 21567462 DOI: 10.1002/jcla.20450]

6 Purnak T, Olmez S, Turan S, Efe C, Sayilir A, Ozaslan E, Tenlik I, Kalkan IH, Beyazit Y, Yuksel O. Mean platelet volume is increased in chronic hepatitis C patients with advanced fibrosis. Clin Res Hepatol Gastroenterol 2013; 37: 41-46 [PMID: 22572524 DOI: 10.1016/j.clinre.2012.03.035]

7 Ichida F, Tsuji T, Omata M, Ichida T, Inoue K, Kamimura T, Yamada G, Hino K, Yokosuka O, Suzuki H. New Inayama classification: new criteria for histological assessment of chronic hepatitis. Int Hepatol Commun. 1996; 112

8 Ha-Kawa SK, Tanaka Y. A quantitative model of technetium-99m-DTPA-galactosyl-HSA for the assessment of hepatic blood flow and hepatic binding receptor. J Nucl Med 1991; 32: 2233-2240 [PMID: 1744708]

9 Kwon AH, Matsui Y, Ha-Kawa SK, Kamiyama Y. Functional hepatic volume measured by technetium-99m-galactosyl-human serum albumin liver scintigraphy: comparison between hepatocyte volume and liver volume by computed tomography. Am J Gastroenterol 2001; 96: 541-546 [PMID: 11232703 DOI: 10.1111/j.1572-0241.2001.03556.x]

10 Edmondson HA, Steiner PE. Primary carcinoma of the liver: a study of 100 cases among 48,900 necropsies. Cancer 1954; 7: 462-503 [PMID: 13160935]

11 Castéra L, Vergniol J, Foucher J, Le Bail B, Chanteloup E, Haaser M, Darriet M, Couzigou P, De Lédinghen V. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. Gastroenterology 2005; 128: 343-350 [PMID: 15685546]

12 Sandrin L, Fournet B, Hasquenoph JM, Yon S, Fournier C, Mal F, Christidis C, Ziol M, Poulet B, Kazemi F, Beaugrand M, Palau R. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. Ultrasound Med Biol 2003; 29: 1705-1713 [PMID: 14698338]

13 Foucher J, Chanteloup E, Vergniol J, Castéra L, Le Bail B, Adhoute X, Bertet J, Couzigou P, De Lédinghen V. Diagnosis of cirrhosis by transient elastography (FibroScan): a prospective study. Gut 2006; 55: 403-408 [PMID: 16020491 DOI: 10.1136/gut.2005.069153]

14 Turhan O, Coban E, Inan D, Yalcin AN. Increased mean platelet volume in chronic hepatitis B patients with inactive disease. Med Sci Monit 2010; 16: CR202-CR205 [PMID: 20357720]

15 Ceylan B, Fincanci M, Yardimci C, Eren G, Tozalgan U, Muderresoglu C, Pasaoğlu E. Can mean platelet volume determine the severity of liver fibrosis or inflammation in patients with chronic hepatitis B? Eur J Gastroenterol Hepatol 2013; 25: 606-612 [PMID: 23325286 DOI: 10.1097/MEG.0b013e32835d08da]

16 Shin WY, Jung DH, Shim JY, Lee HR. The association between non-alcoholic hepatic steatosis and mean platelet volume in an obese Korean population. Platelets 2011; 22: 442-446 [PMID: 21751850 DOI: 10.3109/09537104.2010.540049]

17 Ozhan H, Aydin M, Yazici M, Yazgan O, Basar C, Gongur A, Onder E. Mean platelet volume in patients with non-alcoholic fatty liver disease. Platelets 2010; 21: 29-32 [PMID: 19947902 DOI: 10.3109/09537100903391023]

18 Kilciler G, Genc H, Tapan S, Ors F, Kara M, Karaduman N, Ercin CN, Karsioglu Y, Kilic S, Bagci S, Erbil MK, Dogru T. Mean platelet volume and its relationship with carotid atherosclerosis in subjects with non-alcoholic fatty liver disease. Ups J Med Sci 2010; 115: 253-259 [PMID: 20731535 DOI: 10.3109/03009734.2010.508062]

19 Arslan N, Makay B. Mean platelet volume in obese adolescents with nonalcoholic fatty liver disease. J Pediatr Endocrinol Metab 2010; 23: 807-813 [PMID: 21073123]

20 Celikbilek M, Gurosoy S, Deniz K, Karaman A, Zararsiz G, Yurci A. Mean platelet volume in biopsy-proven non-alcoholic fatty liver disease. Platelets 2013; 24: 194-199 [PMID: 22646469 DOI: 10.3109/09537104.2012.688988]

21 Inagaki N, Kibata K, Tanaka T, Shimizu T, Nomura S. Prognostic impact of the mean platelet volume/platelet count ratio in terms of survival in advanced non-small cell lung cancer. Lung Cancer 2014; 83: 97-101 [PMID: 24189108 DOI: 10.1016/j.lungcan.2013.08.020]

22 Cho SY, Yang JJ, You E, Kim BH, Shim J, Lee HJ, Lee Wl, Suh JT, Park TS. Mean platelet volume/platelet count ratio in hepatocellular carcinoma. Platelets 2013; 24: 375-377 [PMID: 22835043 DOI: 10.3109/09537104.2012.701028]

23 Kurt M, Onal IK, Sayilir AY, Beyazit Y, Oztas E, Kekilli M, Turhan N, Karaman K, Akdogan M. The role of mean platelet volume in the diagnosis of hepatocellular carcinoma in patients with chronic liver disease. Hepatogastroenterology 2012; 59: 1580-1582 [PMID: 22683976 DOI: 10.5754/heg10444]