The Predictive Value of Mean Platelet Volume for Liver Fibrosis in Children With Chronic Liver Diseases

Seyed Mohsen Dehghani, Mohammad Reza Bordbar, Rezvan Salimi, Iraj Shahramian, Hadi Mirzae, Siavash Gholami, Fatemeh Sharafi, Ali Bazi, Maryam Ataollahi, Fatemeh Fazeli, Samaneh Hamzeloo

Professor of Pediatrics Gastroenterology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
Pediatric Gastroenterology and Hepatology Research Center, Zabol University of Medical Sciences, Zabol, Iran
Department of Biotechnology, Faculty of Medicine, Zabol University of Medical Sciences, Zabol, Iran
Internal Medicine Department, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

Introduction: Almost all causes of chronic liver damage can culminate in liver fibrosis and ultimately cirrhosis. Studies have suggested a relationship between mean platelet volume (MPV) and liver fibrosis; however, this needs confirmation by further studies. We here assessed the predictive value of MPV for liver fibrosis in children with chronic liver diseases.

Methods: In this study, children <18 years old with chronic liver diseases referred to the Nemazee Hospital of Shiraz during 2013-2016 were studied. The patients underwent liver biopsy for assessing liver fibrosis. Statistical analyses were conducted in SPSS 23.

Results: From 368 studied children, 52.2% were boys. The patients' mean age was 4.5±3.9 years old. Most patients had grade 6 fibrosis (36.7%). Cryptogenic (42.7%) was the most common cause of chronic liver disease, and jaundice was the most prevalent clinical presentation (53%). There was a significant association between the liver fibrosis and MPV (P = 0.025).

Conclusion: MPV was significantly different between patients with different severities of liver fibrosis. However, assigning an appropriate cut off value to distinguish different degrees of fibrosis requires more studies.

Keywords: Chronic liver disease, Liver fibrosis, Mean platelet volume

Please cite this article as follows: Dehghani SM, Bordbar MR, Salimi R, Shahramian I, Mirzae H, Gholami S, Sharafi F, Bazi A, Ataollahi M, Fazeli F, Hamzeloo S. The predictive value of mean platelet volume for liver fibrosis in children with chronic liver diseases. Int J Basic Sci Med. 2020;5(4):131-135. doi:10.34172/ijbsm.2020.23.
presenting clinical symptoms, results of laboratory tests (serum albumin, bilirubin, liver enzymes, sodium, INR, creatinine, white blood cells and platelets counts, red cell distribution width and MPV, MELD/PELD (model for end-stage liver disease/pediatric end-stage liver disease) scores, Child-Pugh score, and results of liver biopsy. In addition, non-invasive fibrosis markers (AAR, APRI, and FIB-4) were calculated. These data were recorded using patients’ medical archives.

The data were analyzed by SPSS version 23 using descriptive and analytical statistics. Kruskal-Wallis test, Spearman correlation, and ROC curve analysis were used.

Results
In this study, 368 patients with chronic liver diseases who had been undergone liver biopsy were assessed. From these, 192 (52.2%) and 176 (47.8%) were males and females, respectively. The mean age of the patients in this study was 4.5±3.9 years old.

Considering the underlying diseases, 84 (22.8%) of patients had biliary atresia as the second most common reason after unknown causes (Table 1). The most common presenting clinical symptom was jaundice (n=195; 53%). Table 2 demonstrates clinical symptoms of the patients. A summary on laboratory features of the patients has been demonstrated in Table 3. Most of the patients revealed severe fibrosis with grades 5 (n=33;9%) and 6 (n=135; 36.7%) (Table 4). There were no association between the severity of fibrosis with underlying causes of liver disease (Table 5).

The average Child-Pugh score was 6.86±1.63 and 138 (37.5%), 185 (50.3%), and 21 (5.7%) of children were in classes A, B, and C, respectively. The average MELD/PELD (model for end-stage liver disease/pediatric end-stage liver disease) score in patients was 4.6±11.3 (range of 12 to 67). Mean values of MPV, AAR, APRI, and FIB-4 were 10.59±1.9, 1.54±0.90, 4.80±12.77, and 0.47±1.37, respectively. According to our findings, MPV was no significantly associated with the grade of fibrosis (Table 6, P=0.144).

Table 1. Distribution of Underlying Causes in Patients With Chronic Liver Disease

| Underlying Diseases       | No. | Percent |
|---------------------------|-----|---------|
| Unknown                   | 157 | 42.7    |
| Biliary atresia           | 84  | 22.8    |
| PFIC                      | 30  | 8.2     |
| Neonatal hepatitis        | 32  | 8.7     |
| Auto immune hepatitis     | 14  | 3.8     |
| Wilson disease            | 9   | 2.4     |
| Tyrosinemia               | 17  | 4.6     |
| Glycogen storage disease  | 12  | 3.3     |
| Other metabolic disorders | 13  | 3.5     |

PFIC, Progressive familial intrahepatic cholestasis

Table 2. Clinical Symptoms of Patients

| Clinical Manifestation | Number | Percent |
|------------------------|--------|---------|
| Jaundice               | 195    | 53      |
| Hepatomegaly           | 84     | 22.8    |
| Splenomegaly           | 70     | 19      |
| Pruritus               | 44     | 12      |
| Ascites                | 27     | 7.3     |
| GI bleeding            | 16     | 4.3     |
| Encephalopathy         | 6      | 1.6     |
| Spontaneous bacterial peritonitis | 3 | 0.8 |

Table 3. Laboratory Tests Results in Children With Chronic Liver Diseases

| Laboratory Parameters            | Mean Values (Minimum-Maximum) |
|----------------------------------|-------------------------------|
| Aspartate aminotransferase (IU/L) | 297.16 ± 421.9 (4-4700)       |
| Alanine aminotransferase (IU/L)  | 236.08 ± 336.6 (9-3604)       |
| Total bilirubin (mg/dL)          | 6.13 ± 7.97 (0-65.2)          |
| Albumin (g/dL)                   | 4.04 ± 0.65 (0-6.6)           |
| Creatinine (mg/dL)               | 0.38 ± 0.25 (0.1-1.8)         |
| Na (mEq/L)                       | 138.94 ± 8.14 (14-153)        |
| International normalized ratio   | 1.53 ± 1.14 (1-141)           |
| White blood cell count (10³/µL)  | 10398 ± 5468.6 (2700-68100)   |
| Hemoglobin (g/dL)                | 10.64 ± 1.88 (5.1-18)         |
| Mean corpuscular volume (fl)     | 83.26 ± 8.76 (56.2-1111)      |
| Red cell distribution width (fl) | 16.73 ± 5.95 (0.715)          |
| Platelet count (10³/µL)          | 305140 ± 173.8 (27-1166)      |
| Mean platelet volume (fl)        | 10.59±1.90 (7.2-23.9)         |

Table 4. Fibrosis Severity in Children With Chronic Liver Disease

| Stage of Fibrosis | Number | Percent |
|-------------------|--------|---------|
| Mild              | 46     | 12.5    |
| Moderate          | 69     | 18.8    |
| Severe            | 135    | 36.7    |
| Total             | 368    | 100.0   |

Table 5. Distribution of Underlying Causes in Patients With Chronic Liver Disease

Considering the severity of liver fibrosis values based on the underlying disease, MPV showed significant difference only in patients with neonatal hepatitis (P=0.020) (Table 7). Statistically significant difference was found between MPV values in children with different Child score (P=0.002).

There was no significant statistical difference between AAR (AST/ALT ratio) and the grade of fibrosis (P>0.05). However, APRI was significantly correlated with the severity of liver fibrosis (P<0.001). The FIB-4 was significantly associated with fibrosis grade (P<0.001) and...
Table 5. Distribution of Underlying Diseases Based on the Severity of Liver Fibrosis in Children With Chronic Liver Diseases

| Underlying Causes       | Severity of Liver Fibrosis | Mild (%) | Moderate (%) | Severe (%) |
|-------------------------|---------------------------|----------|--------------|------------|
| Biliary atresia         |                           | 15 (17.9)| 32 (38.1)    | 37 (44)    |
| PFIC                    |                           | 4 (13.3) | 9 (30)       | 17 (56.7)  |
| Neonatal hepatitis      |                           | 25 (78.1)| 4 (12.5)     | 3 (9.4)    |
| Auto immune hepatitis   |                           | 7 (50)   | 2 (14.3)     | 5 (35.7)   |
| Wilson disease          |                           | 1 (11.1) | 0 (0)        | 8 (88.9)   |
| Tyrosinemia             |                           | 1 (5.9)  | 0 (0)        | 16 (94.1)  |
| Glycogen storage disease|                           | 3 (25)   | 3 (25)       | 6 (50)     |
| Other metabolic disorders|                          | 3 (23.1)| 3 (23.1)     | 7 (53.8)   |

PFIC, Progressive familial intrahepatic cholestasis.

Table 6. Values of MPV, AAR, APRI, and FIB-4 in Various Grades of Liver Fibrosis

| Stage of Fibrosis | Frequency | Minimum | Maximum | Mean | Standard Deviation |
|-------------------|-----------|---------|---------|------|--------------------|
| 0                 | MPV       | 46      | 7.8     | 13.3 | 10.26              |
|                   | AAR       | 46      | 0.34    | 4.76 | 1.61               |
|                   | APRI      | 46      | 0.16    | 31.15| 2.09               |
|                   | FIB-4     | 46      | 0.02    | 1.72 | 0.19               |
| 1                 | MPV       | 47      | 7.9     | 23.9 | 10.88              |
|                   | AAR       | 46      | 0.18    | 3.13 | 1.45               |
|                   | APRI      | 46      | 0.18    | 23.11| 2.55               |
|                   | FIB-4     | 46      | 0.01    | 1.38 | 0.16               |
| 2                 | MPV       | 22      | 7.0     | 11.5 | 9.89               |
|                   | AAR       | 22      | 0.42    | 4.86 | 1.52               |
|                   | APRI      | 22      | 0.07    | 22.22| 3.19               |
|                   | FIB-4     | 22      | 0.01    | 2.69 | 0.42               |
| 3                 | MPV       | 69      | 7.6     | 17.6 | 10.51              |
|                   | AAR       | 68      | 0.04    | 7.00 | 1.41               |
|                   | APRI      | 68      | 0.03    | 14.63| 2.27               |
|                   | FIB-4     | 68      | 0.00    | 2.57 | 0.17               |
| 4                 | MPV       | 16      | 8.6     | 11.9 | 10.05              |
|                   | AAR       | 16      | 0.32    | 4.08 | 1.71               |
|                   | APRI      | 16      | 0.27    | 19.66| 2.61               |
|                   | FIB-4     | 16      | 0.01    | 1.24 | 0.12               |
| 5                 | MPV       | 33      | 8.3     | 16.1 | 11.08              |
|                   | AAR       | 33      | 0.27    | 3.79 | 1.81               |
|                   | APRI      | 33      | 0.54    | 6.22 | 2.22               |
|                   | FIB-4     | 33      | 0.02    | 2.98 | 0.22               |
| 6                 | MPV       | 135     | 7.2     | 19.8 | 10.77              |
|                   | AAR       | 127     | 0.36    | 6.61 | 1.56               |
|                   | APRI      | 127     | 0.06    | 137.93| 8.36               |
|                   | FIB-4     | 127     | 0.02    | 19.02| 0.88               |

Discussion

In this study, 368 patients with chronic liver diseases who had been undergone liver biopsy were surveyed. The most common causes of chronic liver disease were cryptogenic, biliary atresia, neonatal hepatitis, progressive familial intrahepatic cholestasis (PFIC), tyrosinemia with 157 (42.7%), 84 (22.8%), 32 (8.7%), 30 (8.2%), and 17 (4.6%), respective frequencies. The most common clinical sign was jaundice (53%). Most patients (n=135; 36.7%) had Ishak fibrosis degree of 6 (i.e. cirrhosis). There was no association between MPV and fibrosis grade (S0 to S6) (P=0.144). The average MPVs in patients with mild, moderate, and severe fibrosis were 10.45±2.06, 10.42±1.76 and 10.83±1.90, respectively (P=0.025). Also, considering underlying diseases, significant relationship with liver fibrosis severity and MPV was only observed in patients with neonatal hepatitis (MPV=10.64±1.15 vs. 8.4±0.40 in mild, respective frequencies). The results of ROC curve analysis showed that MPV cut off point of 10.4 rendered AUC=0.582 and sensitivity of 34.8% and specificity of 74.8% (Figure 1B). The cut off MPV for detecting any fibrosis was obtained >10.8 with AUC=0.544, sensitivity of 35.7% and specificity of 76.1% (Figure 1C).

Figure 1. ROC Curve Analysis for Mean Platelet Volume. (A) fibrosis grade ≥5, (B) fibrosis grade ≥3, (C) any fibrosis.
In this study, there was a statistically significant difference in APRI among different degrees of liver fibrosis (P<0.001). Therefore, APRI can be used as an applicable marker to differentiate fibrosis severities, especially in patients with biliary atresia and PFIC. The most common causes of cirrhosis which was in line with our report.8 The most common clinical symptom in our patients was jaundice which was in accordance to the previous study in Shiraz.9,10

In this study, a significant difference was observed in MPV values regarding different fibrosis severities which was in parallel to the report of Tahtaci et al on PBC patients,11 Karagoz et al on patients with chronic hepatitis B,12 Purnak et al on patients with chronic hepatitis C,13 and Abdel-Razik et al on AIH patients.14 Furthermore, in our study only, MPV significantly differed in patients with neonatal hepatitis as well. There was no significant statistical relationship between MPV and age or underlying disease which was in line with the report of Giannini et al in Italy.15 In this study, there was no significant statistical differences between values and Child-Pugh score which was in oppose to the report of Giannini et al in Italy,7 and Erdem et al in Turkey.9 No significant link was observed between MPV and MELD/PELD score in our study which was different from the results Giannini et al in Italy,7 and Hu et al in China.16

According to the results of ROC curve analysis, an appropriate cut off did not obtained for MPV to differentiate various degrees of fibrosis. On the other hand, Tahtaci et al11 Karagoz et al12 and Purnak et al13 reported threshold values with better predictability.

In this study, there was no significant statistical difference for AAR in various degrees of fibrosis which was in line with the study of Yang et al in China14 and Yang et al in South Korea.15 In this study, there was a statistically significant difference in APRI among different degrees...
of liver fibrosis which was supported by the reports of Tahtaci et al in Turkey,11 Kim et al in Japan,16 Yang et al in South Korea,15 Yang et al in China,14 and Shokouhi et al in Iran.17 FIB-4 index also showed a significant relationship with the degree of fibrosis in our study which was similar to the studies of Purnak et al in Turkey,6 Yang et al in South Korea,15 and Yang et al in China.14

Conclusion
In conclusion, although MPV was significantly associated with the severity of liver fibrosis, an optimal cut off point to distinguish different degrees fibrosis was not obtained. Therefore, MPV seems to not be a good marker for predicting fibrosis stage in children with cirrhosis.

Ethical Approval
This study was approved by the Ethics Committee in Research of Shiraz University of Medical Sciences (IR.SUMS.MED.REC.1399.122).

Conflict of Interest Disclosure
None to declare.

Acknowledgments
Thanks to the patients’ families for their generous cooperation and Shiraz University of Medical Sciences for financial support.

References
1. Leader A, Pereg D, Lishner M. Are platelet volume indices of clinical use? a multidisciplinary review. Ann Med. 2012;44(8):805-816. doi:10.3109/07853890.2011.653391
2. Bath PM, Butterworth RJ. Platelet size: measurement, physiology and vascular disease. Blood Coagul Fibrinolysis. 1996;7(2):157-161.
3. Celikbilek M, Gürsoy S, Deniz K, Karaman A, Zararsiz G, Yurci A. Mean platelet volume in biopsy-proven non-alcoholic fatty liver disease. Platelets. 2013;24(3):194-199. doi:10.3109/09537104.2012.688098
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(130):456-459.
5. Karagoz E, Ucay A, Tanoglu A, et al. Clinical usefulness of mean platelet volume and red blood cell distribution width to mean platelet ratio for predicting the severity of hepatic fibrosis in chronic hepatitis B virus patients. Eur J Gastroenterol Hepatol. 2014;26(12):1320-1324. doi:10.1097/meg.0000000000000203
6. Purnak T, Olmez S, Torun S, et al. Mean platelet volume is increased in chronic hepatitis C patients with advanced fibrosis. Clin Res Hepatol Gastroenterol. 2013;37(1):41-46. doi:10.1016/j.clinre.2012.03.035
7. Giannini EG, Moscatelli A, Brunacci M, Zentilin P, Savarino V. Prognostic role of mean platelet volume in patients with cirrhosis. Dig Liver Dis. 2016;48(4):409-413. doi:10.1016/j.dld.2015.10.018
8. Erdem MG, Çil EÖ, Tüpek T, Helvacı ŞA. Evaluation of platelet and mean platelet volume levels in patients with liver cirrhosis. Archives of Clinical and Experimental Medicine. 2018;3(1):18-21. doi:10.25000/acem.390029
9. Dehghani SM, Imanieh MH, Haghighat M, Malekpour A, Falizkar Z. Etiology and complications of liver cirrhosis in children: report of a single center from southern Iran. Middle East J Dig Dis. 2013;5(1):41-46.
10. Dehghani SM, Sharamhian I, Bazi A, Mohammadi Mofrad M, Mardani S. Evaluation of underlying liver disease and its severity in children referred for liver transplant: a single-center report from Nemazee hospital of Shiraz. Exp Clin Transplant. 2020;18(7):803-807. doi:10.6002/ect.2018.0047
11. Tahtaci M, Yurekli OT, Bolat AD, et al. Increased mean platelet volume is related to histologic severity of primary biliary cirrhosis. Eur J Gastroenterol Hepatol. 2015;27(12):1382-1385. doi:10.1097/meg.0000000000000463
12. Abdel-Razik A, Mousa N, Zakaria S, et al. New predictive factors of poor response to therapy in autoimmune hepatitis: role of mean platelet volume. Eur J Gastroenterol Hepatol. 2017;29(12):1373-1379. doi:10.1097/ meg.0000000000000982
13. Hu Y, Lou Y, Chen Y, Mao W. Evaluation of mean platelet volume in patients with hepatitis B virus infection. Int J Clin Exp Med. 2014;7(11):4207-4213.
14. Yang XZ, Gen AW, Xian JC, Xiao L. Diagnostic value of various noninvasive indexes in the diagnosis of chronic hepatic fibrosis. Eur Rev Med Pharmacol Sci. 2018;22(2):479-485. doi:10.26355/eurrev_201801_14198
15. Yang HR, Kim HR, Kim MJ, Ko JS, Seo JK. Noninvasive parameters and hepatic fibrosis scores in children with nonalcoholic fatty liver disease. World J Gastroenterol. 2012;18(13):1525-1530. doi:10.3748/wjg.v18.i13.1525
16. Kim SY, Seok JY, Han SJ, Koh H. Assessment of liver fibrosis and cirrhosis by aspartate aminotransferase-to-platelet ratio index in children with biliary atresia. J Pediatr Gastroenterol Nutr. 2010;51(2):198-202. doi:10.1097/MPG.0b013e3181da1d98
17. Shokouhi S, Rakhshan M, Gachkar L, Khalej E. Correlation between staging of hepatic fibrosis and biochemical markers in patient with liver fibrosis. Pejouhandeh. 2008;13(2):89-97. [Persian].