

High mean platelet volume-to-platelet count ratio as a diagnostic maker for increased risk of liver function damage in pediatric patients with infectious mononucleosis in China

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Abstract. The aim of the present study was to provide novel laboratory indexes for infectious mononucleosis (IM) in pediatric patients. In the present prospective study, a total of 141 pediatric patients with IM and 146 healthy subjects were enrolled. The white blood cell count (WBC), red blood cell count (RBC), hemoglobin (HB), platelet count (PLT), mean platelet volume (MPV), platelet distribution width (PDW), alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ -glutamyl transferase (GGT), uric acid (UA), urea, creatinine, total cholesterol (TC) and triglycerides (TG) in peripheral blood were evaluated. WBC, ALT, AST, GGT, UA, TG, MPV and the MPV/PLT ratio in the patients were significantly higher compared with those in the controls ($P < 0.01$), while RBC, HB, urea, TC, PLT and PDW were significantly lower in the patients ($P < 0.05$ for PDW and $P < 0.01$ for others). Regression analysis under stepwise adjustment indicated that PLT and MPV/PLT were significantly associated with IM ($P < 0.01$). Furthermore, MPV/PLT was positively correlated with ALT, AST, GGT, UA and TC ($P \leq 0.01$). In the receiver operating characteristic analysis, a sensitivity of 83.7% and specificity of 76.0% regarding the prediction of IM in pediatric patients using the MPV/PLT ratio was achieved at the cutoff of MPV/PLT(%)=3.42. In conclusion, the MPV/PLT ratio may be a novel diagnostic indicator for pediatric IM and indirectly predict damage to liver function.

Introduction

Epstein-Barr virus (EBV), which is carried in >95% of the population worldwide, is a human γ -1 herpes virus (1). This virus is the cause of a range of lymphoid and epithelial malignancies and autoimmune diseases (2,3). EBV usually infects B cells in oropharyngeal lymphoid tissues and then establishes a persistent infection in the circulating memory B cells (4,5). EBV infection may lead to downregulation of the expression of most of the viral genes with the ability to evade the host's immune response (6).

Infectious mononucleosis (IM) is a typical form of primary EBV infection. It usually affects pediatric, adolescent and young adult patients. It is characterized by fever, pharyngitis, lymphadenopathy and hepatosplenomegaly. Local or generalized rash usually occurs during the onset or end of the disease and lasts for 1-6 days (7,8). IM frequently manifests as hepatosplenomegaly and the enlargement of the spleen is highly correlated with the platelet count (PLT) in the peripheral blood. The mean platelet volume (MPV), as an indicator of platelets, is a simple biomarker of inflammation and is increased in cardiovascular diseases, peripheral diseases and diabetes mellitus (9-11). Hepatic dysfunction is common in IM patients. Numerous studies have indicated that elevation of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and γ -glutamyl transferase (GGT) was more common than elevation of bilirubin (12).

Although the MPV/PLT ratio is known to be a useful index for the diagnosis of numerous diseases in adult patients (13,14), its utility in pediatric patients with IM has remained elusive. The aim of the present study was to investigate the ability of MPV/PLT to detect IM in pediatric patients. The correlation between MPV/PLT and liver function indices was also determined. To the best of our knowledge, the present study was the first to perform this assessment.

Materials and methods

Patients. The present prospective study was performed at the Children's Hospital of Zhejiang University School of Medicine (Hangzhou, China). A total of 141 patients (sex, 54 males and 83 females; mean age, 4.9 ± 3.0 years; age range, 0.8-16.6 years)

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with a confirmed diagnosis of IM and a normal control cohort consisting of 146 healthy participants (sex, 69 males and 77 females; mean age, 5.2 ± 3.0 years; age range, 0.3-16.3 years) were enrolled. In Western developed countries, the diagnostic criteria are as follows (15): i) Clinical triad: Fever, angina, lymphadenopathy; ii) peripheral blood lymphocyte ratio ≥ 0.50 and atypical lymphocyte ratio ≥ 0.10 ; iii) serum heterophilic agglutination antibody-positive. However, the diagnostic criteria for the aforementioned standard adaptation population was composed of IM cases of 10-30 years of age. China is a developing country and the peak age of IM is during childhood (<18 years old) (16). Referring to previous studies (17,18), the following criteria were used to diagnose IM in the present study: i) 3 of the following clinical symptoms: Fever, angina, large cervical lymph nodes, hepatomegaly, splenomegaly; ii) serological evidence of primary EBV infection, meeting any of the following two standards: a) Positivity for anti-EBV-capsid antigen (CA)-IgM and anti-EBV-CA-IgG antibodies; b) negativity for anti-EBV-CA-IgM but positivity for anti-EBV-CA-IgG antibody, which is a low-affinity antibody. Those patients meeting the two criteria described above were diagnosed with IM. The participants selected for the present study met the diagnostic criteria aforementioned. Healthy participants were those who visited the hospital for a general health examination and with excluded inflammatory diseases based on WBC and hypersensitive C-reactive protein measurements. The present study was approved by the medical ethics committee of the Children's Hospital of Zhejiang University School of Medicine (Hangzhou, China). Written informed consent was obtained from the guardians on behalf of the participants of the study.

Blood and liver function examination. Routine complete blood count (CBC) of peripheral blood from all participants was performed using the BC-5380 instrument (Mindray Medical International Ltd) and liver function parameters were detected on an AU5800 (Beckman Coulter). All reagents for testing were the original reagents of the instruments.

Statistical analysis. The Kolmogorov-Smirnov normality test was used to determine if the data is normally distributed. The Mann-Whitney U-test was used to compare differences in non-parametric variables (non-normally distributed data). Categorical variables were presented as a proportion and analyzed with the Chi-squared test. Continuous data were analyzed using Student's t-test. Values were expressed as n (%), the mean \pm standard deviation or median (interquartile range). Spearman correlation analysis was used for grading variable data, whereas Pearson correlation analysis was used for continuous variable data. For the prediction of IM based on platelet indices, logistic regression analysis was used to determine odds ratios (OR) with 95% CI. Receiver operating characteristic (ROC) curve analysis was used to assess the diagnostic accuracy of MPV/PLT for IM. All statistical analyses were performed using SPSS version 22.0 (IBM Corp.). $P < 0.05$ was considered to indicate statistical significance.

Results

Characteristics of IM patients and controls. In the IM group, a total of 91.5% of the 141 pediatric patients had fever, 85.8%

had angina, 92.9% had cervical lymphadenopathy, 71.6% had liver enlargement and 65.2% had splenomegaly. Furthermore, 61.7% were positive for EBV-CA-IgM antibody and 97.9% were positive for EBV-CA-IgG antibody.

Apart from age and gender for which no statistical significance were found between the IM and control groups, it was observed that WBC, ALT, AST, GGT, uric acid (UA) and triglycerides (TG) were significantly higher in the IM patients compared with in the healthy controls ($P < 0.001$; Table I). However, RBC, hemoglobin (HB), urea and total cholesterol (TC) were significantly reduced ($P < 0.001$; Table I). The four platelet indices, PLT, platelet distribution width (PDW), MPV and MPV/PLT, exhibited statistically significant differences between the two groups (PLT, $P < 0.001$; PDW, $P = 0.035$; MPV, $P < 0.001$; MPV/PLT, $P < 0.001$; Table I).

Predictive value of platelet indices in IM patients. Regression analysis was used to analyze the predictive value of the four indices of platelets in the disease group. For regression analysis, three models were built (Table II). Using Model 1 without any correction factors, all four indices were statistically significant predictors of IM within the 95% CI ($P < 0.05$). Following adjustment for age and gender in Model 2, the four indices remained statistically significant in the 95% CI ($P < 0.05$). However, based on Model 2, after WBC, RBC, HB, ALT, AST, GGT, UA, urea, creatinine (CREA), TC and TG were adjusted in Model 3, MPV and PDW were no longer statistically significant (PDW, $P = 0.350$; MPV, $P = 0.353$), while PLT and MPV/PLT remained significant predictors of IM ($P = 0.005$ and 0.006 , respectively; Table II).

Correlation of MPV/PLT with laboratory parameters in IM and healthy control groups. In the IM group, age, WBC, ALT, AST, GGT, CREA and UA were positively correlated with MPV/PLT, while RBC, HB, urea, TC and TG were negatively correlated with MPV/PLT. The correlation of MPV/PLT with ALT, AST, GGT, CREA, UA and TC was statistically significant ($P \leq 0.01$). Regarding the correlation between MPV/PLT (%) and other variables in healthy controls, only age, creatinine and WBC were statistically significant ($P < 0.05$). Of note, the correlation between MPV/PLT and liver function indices in the IM patients was statistically significant (ALT, $P = 0.005$; AST, $P = 0.010$; GGT, $P = 0.004$). The details are provided in Table III.

Diagnostic accuracy of MPV/PLT in IM. As indicated above, it was possible to distinguish pediatric patients with IM from healthy controls based on the MPV/PLT. ROC curve analysis was therefore used to evaluate the diagnostic sensitivity and specificity of MPV/PLT for pediatric IM (Fig. 1). When the cut-off value for MPV/PLT was set at 3.42%, the sensitivity was 83.7%, the specificity was 76% with an area under the curve calculated to be 0.862.

Discussion

EBV has a high prevalence worldwide (19). In industrialized countries, it is estimated that >50% of the population under the age of 5 years have been infected with EBV (20). Most individuals infected with EBV are either asymptomatic or have mild symptoms; however, certain patients develop IM, particularly during childhood.

Table I. Baseline characteristics of pediatric patients with IM and controls.

Characteristic	IM group (n=141)	Normal range	Control group (n=146)	P-value
Male gender	54 (38.3)	-	69 (47.3)	0.125
Age (years)	4.9±3.0 (0.8-16.6)	-	5.2±3.0 (0.3-16.3)	0.334
WBC (10 ⁹ /l)	15.06±6.40	4.0-12.0	7.19±1.47	0.000
RBC (10 ¹² /l)	4.37±0.33	3.50-5.50	4.52±0.36	<0.001
HB (g/l)	119.7±9.2	110-155	125.0±8.4	<0.001
ALT (U/l)	79.0 (36.0-178.5)	<50	13.0 (11.0-16.0)	<0.001
AST (U/l)	69.5 (45.0-116.3)	15-60	31.0 (27.0-35.3)	<0.001
GGT (U/l)	52.5 (16.0-106.3)	8-57	11.0 (10.0-13.0)	<0.001
CREA (μmol/l)	46.0 (41.0-51.0)	15-77	46.0 (40.0-52.3)	0.922
Urea (μmol/l)	2.95 (2.47-3.55)	1.79-6.43	4.14 (3.64-4.90)	<0.001
UA (μmol/l)	304 (254-364)	155-357	257 (228-296)	<0.001
TC (mmol/l)	3.19±0.72	3.00-5.70	4.28±0.95	<0.001
TG (mmol/l)	1.87±0.84	<1.70	1.07±0.86	<0.001
PLT (10 ⁹ /l)	208.4±73.0	100-400	308.4±81.2	<0.001
MPV (fl)	9.73±1.25	6.5-11.5	8.39±1.00	<0.001
PDW (%)	15.37±1.44	0.0-20.0	15.65±0.64	0.035
MPV/PLT (%)	5.43±2.66	-	2.95±1.06	<0.001

Values are expressed as n (%), mean ± standard deviation or median (interquartile range). IM, infectious mononucleosis; PLT, platelet count; MPV, mean platelet volume; WBC, white blood cell count; RBC, red blood cell count; HB, hemoglobin; PDW, platelet distribution width; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transferase; UA, uric acid; CREA, creatinine; TC, total cholesterol; TG, triglycerides.

Table II. Logistic regression analysis for platelet indices to distinguish pediatric patients with infectious mononucleosis from healthy controls.

Variable	Model 1		Model 2		Model 3	
	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value
PLT (10 ⁹ /l)	0.982 (0.977-0.986)	<0.001	0.981 (0.976-0.985)	<0.001	0.976 (0.959-0.993)	0.005
MPV (fl)	2.938 (2.212-3.902)	<0.001	3.225 (2.381-4.368)	<0.001	1.425 (0.675-3.006)	0.353
PDW (%)	0.782 (0.617-0.989)	0.040	0.778 (0.614-0.984)	0.036	0.693 (0.322-1.493)	0.350
MPV/PLT (%)	2.997 (2.268-3.961)	<0.001	3.297 (2.448-4.442)	<0.001	3.224 (1.396-7.447)	0.006

Model 1 was not adjusted. Model 2 was adjusted for age and gender. Model 3 was adjusted as Model 2 + white blood cell count, hemoglobin, red blood cell count, aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transferase, uric acid, urea, creatinine, total cholesterol and triglycerides. OR, odds ratio; PLT, platelet count; MPV, mean platelet volume; PDW, platelet distribution width.

Numerous studies have investigated the association between certain diseases and readily available parameters from CBC data, including the neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, PLT-to-lymphocyte ratio and MPV/PLT (15,16,21,22). MPV, PDW and PLT are three general indicators of platelets. Studies have suggested that a high MPV may be associated with an increased risk of vascular complications (23,24).

MPV mainly reflects the proliferation, metabolism and platelet production of megakaryocytes in the bone marrow. In addition, it reflects the survival time of platelets in the circulation. When the function of myeloproliferation is normal,

the decrease in the number of platelets stimulates the production of large-volume platelets by megakaryocytes, resulting in an increase in MPV (25). Thrombocytopenia in aplastic anemia or acute leukemia is caused by bone marrow damage and as a result, the MPV is reduced. Idiopathic thrombocytopenic purpura (ITP), also known as primary or immune thrombocytopenic purpura, is an autoimmune disease, and most pediatric patients affected have a history of viral infections (e.g., viral upper respiratory tract infection, rubella or chickenpox) (26). Thrombocytopenia occurs 1-3 weeks after viral infection, indicating that it is not a virus that directly destroys platelets. Intravascular platelet destruction may

Table III. Correlation between mean platelet volume-to-platelets ratio (%) and other variables in pediatric patients with IM and controls.

Variable	IM group (n=141)		Control group (n=146)	
	r	P-value	r	P-value
Age (years)	0.125	0.140	0.247	0.003
WBC ($10^9/l$)	0.013	0.877	-0.174	0.036
RBC ($10^{12}/l$)	-0.137	0.106	-0.047	0.574
HB (g/l)	-0.109	0.200	0.054	0.517
ALT (U/l) ^a	0.235	0.005	-0.048	0.574
AST (U/l) ^a	0.216	0.010	-0.152	0.071
GGT (U/l) ^a	0.244	0.004	-0.133	0.114
CREA ($\mu\text{mol/l}$) ^a	0.292	<0.001	0.202	0.016
Urea ($\mu\text{mol/l}$) ^a	-0.039	0.653	0.113	0.182
UA ($\mu\text{mol/l}$) ^a	0.271	0.001	0.100	0.237
TC (mmol/l)	-0.300	<0.001	-0.095	0.261
TG (mmol/l)	-0.131	0.123	-0.048	0.570

^aSpearman correlation analysis was used. Pearson correlation analysis was used for continuous variable data. IM, infectious mononucleosis; WBC, white blood cell count; RBC, red blood cell count; HB, hemoglobin; PDW, platelet distribution width; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ -glutamyl transferase; UA, uric acid; CREA, creatinine; TC, total cholesterol; TG, triglycerides.

be another mechanism for thrombocytopenia in pediatric patients with ITP (26).

The present study indicated that in pediatric patients with IM, the MPV was higher than that in the control group and the difference was statistically significant ($P < 0.01$). IM patients frequently have splenomegaly, while the spleen has a close association with platelets in peripheral blood. Thus, PDW and PLT were examined in the present study. Of note, the disease group had a higher MPV and a lower PDW ($P < 0.01$). As the MPV was relatively higher and the PLT was lower in IM patients, the MPV/PLT ratio was introduced to observe the difference between the two groups. As expected, the MPV/PLT ratio in IM patients was significantly higher than that in the controls ($P < 0.01$). ITP has a good bone marrow compensatory function and PLT feedback activates megakaryocytes, resulting in an increase in platelet volume. Increased MPV and thrombocytopenia lead to an increase in MPV/PLT; however, this occurs one to three weeks after viral infection.

IM usually unfolds as a benign clinical process but serious complications may occur. Hepatic failure has been reported in patients with IM (27,28). ALT, AST and GGT are the three transferases with the highest clinical relevance and primary indices of liver function. GGT is widely used as a marker of excessive alcohol intake in patients with alcoholic liver disease (29). In addition, serum GGT levels are frequently increased in patients with non-alcoholic fatty liver disease (30). As GGT is a manifestation of liver injury, the present study aimed to predict liver damage in the early stage of IM.

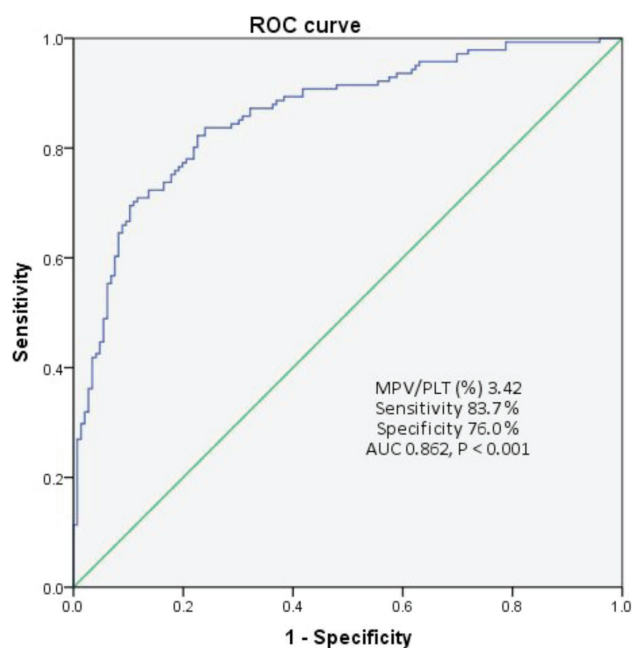


Figure 1. ROC curve for the prediction of infectious mononucleosis in pediatric patients based on the MPV/PLT ratio. ROC, receiver operating characteristic; AUC, area under curve; PLT, platelet count; MPV, mean platelet volume.

In the clinic, anti-viral therapy is generally applied in pediatric IM complicated with liver function damage. Early prediction and intervention of liver function damage in children is necessary. In order to study the diagnostic value of each indicator, regression analysis was used in the present study to assess various indicators. After adjustment for other variables, only PLT and MPV/PLT were obtained as diagnostic indices independent of other clinical indices ($P < 0.01$). It was indicated that MPV/PLT had a higher predictive value for IM than PLT alone (MPV/PLT, 95% CI=1.396-7.447 and OR=3.224; PLT alone, 95% CI=0.959-0.993 and OR=0.976). Although 0.976 appears to be an insufficient OR, MPV/PLT was significantly superior in predicting disease compared with PLT.

The present study indicated that the liver function indices of pediatric patients with IM were significantly higher than those of the control group. Sampling of liver biopsies from patients with IM may explain the cause of the increased transferase levels (31). Of note, liver biopsy places high emotional and physical burden on children. In the present study, MPV/PLT was indicated to be an independent diagnostic factor for IM, which also had a significant positive correlation with liver function indicators. Although MPV/PLT had a significantly correlated with creatinine ($P < 0.001$) in a positive manner, it is a renal index which can be investigated further in future research. At the same time, the ROC curve analysis for MPV/PLT to predict IM had high sensitivity and specificity (sensitivity, 83.7%; specificity, 76%).

CBC is an examination that is routinely performed for almost all diseases. The present study indicated that the MPV/PLT ratio has a certain diagnostic value for pediatric IM. At the same time, it was revealed that if the MPV/PLT ratio is increased, liver function damage is more likely to occur. MPV/PLT may be a novel indicator for the diagnosis of pediatric IM and indirectly predict damage of liver function.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

XCH and PFX designed the current study and were major contributors in writing the manuscript. XZD, YXL and JFZ were responsible for the collection and analysis of data. HX performed the statistics of the data and gave final approval of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the medical ethics committee of the Children's Hospital of Zhejiang University School of Medicine (Hangzhou, China). Written informed consent was obtained from the guardians on behalf of the participants of the present study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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