Cardiology in the Young

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Relationship between mean platelet volume-to-lymphocyte ratio and coronary artery abnormalities in Kawasaki disease

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Abstract

Objectives: Recently, mean platelet volume-to-lymphocyte ratio has emerged as a novel parameter of inflammation. No study has investigated the role of mean platelet volume-to-lymphocyte ratio in children with Kawasaki disease. We aimed to evaluate the relationship between mean platelet volume-to-lymphocyte ratio and coronary artery abnormalities in Kawasaki disease. *Methods:* Between January 2008 and January 2017, a total of 58 children with Kawasaki disease and 42 healthy subjects matched for sex and age were enrolled. Before the treatment, transthoracic echocardiography for all children was performed. Clinical and laboratory results including mean platelet volume, platelet distribution width, red blood cell distribution width, and counts of platelets, neutrophils, lymphocytes, and white blood cells, erythrocyte sedimentation rate, and C-reactive protein levels were measured. Mean platelet volume-to-lymphocyte ratio was calculated as mean platelet volume divided by lymphocyte count. *Results:* Compared with healthy controls, mean platelet volume-to-lymphocyte ratio was significantly lower in the children with Kawasaki disease ($p < 0.01$). A total of 14 patients (24.1%) had incomplete Kawasaki disease and 15 (25.8%) children with Kawasaki disease had coronary involvement. Mean platelet volume-to-lymphocyte ratio was significantly lower in patients with coronary artery abnormalities ($p < 0.01$). According to receiver operating characteristic curve analysis performed for the prediction of coronary artery abnormalities, the best cut-off point for mean platelet volume-to-lymphocyte ratio was 2.5 (area under curve = 0.593, sensitivity 53.3%, specificity 51.1%). *Conclusion:* It was first shown that the children with Kawasaki disease have lower mean platelet volume-to-lymphocyte ratio compared with control subjects. Mean platelet volume-to-lymphocyte ratio may be helpful in predicting coronary artery lesions in patients with Kawasaki disease.

Kawasaki disease is an acute, self-limited febrile illness of unknown aetiology that predominantly affects children <5 years of age.[1] The disease is markedly more prevalent in children in Japan, and its incidence is increasing over time in some countries.[1,2] The diagnosis is based on a series of symptoms including persistent fever, bilateral non-exudative conjunctivitis, oral mucosal changes, non-purulent cervical lymphadenopathy, polymorphous rash, and erythematous induration of the extremities.[1] Coronary artery abnormalities, which are present in 15–20% of the patients, are the most serious complications in Kawasaki disease.[2,3] Coronary artery abnormalities are critical problems of the disease, leading to myocardial ischaemia, infarction, and sudden death. Several studies have been attempted to predict the risk factors for developing coronary artery abnormalities in children with Kawasaki disease.[4–7] On the other hand, contradictory results have been reported in other contries.[8]

More recently, the mean platelet volume-to-lymphocyte ratio has emerged as a novel and readily available parameter of inflammation. There are only a few studies examining the relationship between mean platelet volume-to-lymphocyte ratio and coronary lesions and adverse cardiovascular events in adult patients.[9–11] However, no study has investigated the usefulness of mean platelet volume-to-lymphocyte ratio in children with Kawasaki disease. In the present study, we aimed to evaluate the relationship between mean platelet volume-to-lymphocyte ratio and coronary artery abnormalities in children with Kawasaki disease.

Materials and methods

Local Ethics Committee approval was obtained for the study protocol (2017/267). We retrospectively reviewed the medical records of 58 children with Kawasaki disease who were hospitalised at our institution between January 2008 and January 2017. The diagnosis of

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complete and incomplete Kawasaki disease was made according to the American Heart Association guidelines.[1] Briefly, Kawasaki disease was diagnosed when the children had prolonged fever for 5 or more days, and at least 4 of 5 principal findings. Patients with prolonged fever and fewer than four of the principal clinical findings were labelled as having incomplete Kawasaki disease, if no other disease process could explain the illness. All children with Kawasaki disease received a single infusion of intravenous immunoglobulin and aspirin, within 10 days. In addition, 42 healthy, age- and sex-matched children were included as healthy controls. Children with incomplete medical records, known liver disease, systemic haematological disease, allergic disease, malignant or inflammatory disease, or receiving drugs that can affect haematological parameters were excluded from the study.

Coronary arteries were assessed by transthoracic echocardiography on admission. It was performed via Vivid S5 Pro Ultrasound System (GE Medical Systems, Horten, Norway), using 3- and 6-MHz transducers in two-dimensional, M-mode, and colored Doppler visualising modes. Coronary artery abnormalities were diagnosed on the basis of the criteria proposed by the American Heart Association guidelines.[1] Coronary artery abnormalities were defined as a coronary artery z score ⩾2.5. Coronary aneurysms were defined according to internal lumen diameter of at least 3 mm in children <5 years of age or at least 4 mm in children ⩾5 years of age; internal diameter of a segment measuring ⩾1.5 times that of an adjacent segment; and lumen that is clearly irregular.

Before the treatment, routine complete blood count parameters including mean platelet volume, platelet distribution width, red blood cell distribution width, and counts of platelets, neutrophils, lymphocytes, and white blood cells, erythrocyte sedimentation rate, and C-reactive protein levels were measured. Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio were calculated. Mean platelet volume-to-lymphocyte ratio was calculated as mean platelet volume divided by lymphocyte count (10^3/mm^3).

Statistical analyses

All continuous variables are expressed as mean ± standard deviation. Data of patients and controls were compared. The t-test, analysis of variance, and receiver operating characteristic curve were used for statistical analysis. Multiple comparisons were made using one-way analysis of variance with posthoc Tukey's test. The receiver operating characteristic curve was used to examine the predictive value of mean platelet volume-to-lymphocyte ratio in patients with coronary artery abnormalities. The area under the curve was calculated. The appropriate cut-off value of mean platelet volume-to-lymphocyte ratio was determined using maximum sum of sensitivity and specificity. Multivariate logistic regression models was used to identify predictors of Kawasaki disease patients with coronary artery abnormalities. The results were considered statistically significant if p values were ˂0.05.

Results

The characteristics of the patients and control groups are shown in Table 1. There was no significant difference between the patient and control groups in terms of gender, age, mean platelet volume, and platelet distribution width ($p = 0.632$, $p = 0.824$, $p = 0.848$, and $p = 0.723$, respectively). Compared with healthy controls, the mean levels of white blood cells, platelets, red blood cell distribution width, erythrocyte sedimentation rate, and C-reactive protein were significantly higher and mean platelet volume-to-lymphocyte ratio was significantly lower in children with Kawasaki disease ($p < 0.01$, Table 1).

Table 1. Comparison of characteristics between patients with Kawasaki disease (KD) and controls.

	KD (n = 58)	Control (n = 42)	p
Age (month) (range)	52.56 ± 22.99 (20–97)	51.42 ± 19.44 (20–97)	0.824
Male/female (%)	35 (60.3)/23 (39.7)	25 (59.5)/17 (40.5)	0.632
WBC (×10^3/μl)	15.54 ± 5.86	8.15 ± 3.02	0.001
PLT (×10^3/μl)	481.33 ± 365.20	351.2 ± 118.8	0.01
MPV (fl)	9.23 ± 0.94	9.26 ± 0.79	0.848
PDW (%)	10.54 ± 2.18	10.40 ± 1.80	0.723
RDW (%)	14.66 ± 1.78	13.51 ± 0.99	0.01
MPVLR	3.32 ± 2.66	5.32 ± 4.83	0.01
CRP (mg/dl)	116.42 ± 87.41	3.06 ± 3.70	0.001
ESR (mm/hour)	48.24 ± 25.23	6.45 ± 4.41	0.001

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; MPV = mean platelet volume; MPVLR = mean platelet volume-to-lymphocyte ratio; PDW = platelet distribution width; PLT = platelet; RDW = red blood cell distribution width; WBC = white blood cell

A total of 14 patients (24.1%) had incomplete Kawasaki disease and 15 (25.8%) children with Kawasaki disease had coronary involvement. There was no significant difference between fever duration, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and the levels of white blood cells, platelets, red blood cell distribution width, erythrocyte sedimentation rate, and C-reactive protein in patients with complete and incomplete Kawasaki disease ($p > 0.05$, Table 2). Children with complete Kawasaki disease had lower mean platelet volume-to-lymphocyte ratio levels than those with incomplete Kawasaki disease, but it was not statistically significant ($p = 0.187$).

Mean ages of children with coronary artery abnormalities were significantly lower than those without coronary artery abnormalities − 41.06 ± 18.12 months and 56.58 ± 23.32 months, respectively, $p = 0.013$. Laboratory results in Kawasaki disease patients with and without coronary artery abnormalities are shown in Table 3. The children with coronary artery abnormalities had significantly lower levels of mean platelet volume-to-lymphocyte ratio than did those without coronary artery abnormalities ($p = 0.008$) (Fig 1). According to the receiver operating characteristic curve analysis, the best cut-off of mean platelet volume-to-lymphocyte ratio level on admission for predicting coronary artery abnormalities was 2.5 with a sensitivity of 53.3% and a specificity of 51.1% (area under curve = 0.593, Fig 2). According to multivariable logistic regression analysis, age, white blood cells, and lymphocyte count were independent predictors of coronary artery abnormalities in Kawasaki disease (Table 4).

Discussion

To the best our knowledge, this is the first study that has investigated the role of mean platelet volume-to-lymphocyte ratio in children with Kawasaki disease. The results of our study indicated

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Table 2. Comparison of characteristics between patients with complete and incomplete Kawasaki disease (KD).

	Complete KD (n = 44)	Incomplete KD (n = 14)	p
Age (months) (range)	53.22 ± 24.23 (20–97)	50.50 ± 19.21 (28–91)	0.703
Male/female (%)	24(54.5)/20 (45.5)	9(64.2)/5(35.8)	0.113
Fever duration (days)	7.26 ± 3.91	7.55 ± 4.08	0.687
WBC (×10^3/μl)	15.50 ± 6.11	15.68 ± 5.20	0.914
Neutrophils (×10^3/μl)	9.60 ± 5.84	9.80 ± 5.22	0.913
Lymphocytes (×10^3/μl)	4.25 ± 2.21	4.30 ± 3.06	0.941
PLT (×10^3/μl)	507.86 ± 398.56	397.93 ± 222.42	0.331
MPV (fl)	9.20 ± 0.95	9.31 ± 0.93	0.705
PDW (%)	10.50 ± 2.16	10.67 ± 2.35	0.819
RDW (%)	14.43 ± 1.69	15.40 ± 1.91	0.103
MPVLR	2.94 ± 1.95	4.50 ± 4.06	0.187
NLR	3.23 ± 2.77	3.55 ± 2.85	0.144
PLR	192.34 ± 125.78	157.28 ± 104.09	0.745
CRP (mg/dl)	111.05 ± 91.60	133.28 ± 73.13	0.361
ESR (mm/hour)	47.52 ± 25.98	50.50 ± 23.47	0.704

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; MPV = mean platelet volume; MPVLR = mean platelet volume-to-lymphocyte ratio; NLR = neutrophil-to-lymphocyte ratio; PDW = platelet distribution width; PLR = platelet-to-lymphocyte ratio; PLT = platelet; RDW = red blood cell distribution width; WBC = white blood cell

Table 3. Relationship between laboratory findings in Kawasaki disease (KD) patients with and without coronary artery abnormalities (CAAs).

	KD with CAAs (n = 15)	KD without CAAs (n = 43)	p
WBC (×10^3/μl)	15.61 ± 5.84	15.52 ± 5.94	0.920
Neutrophils (×10^3/μl)	10.22 ± 6.09	9.45 ± 5.55	0.654
Lymphocytes (×10^3/μl)	4.13 ± 2.52	4.31 ± 2.41	0.806
PLT (×10^3/μl)	430.60 ± 173.95	499.02 ± 380.92	0.288
MPV (fl)	9.25 ± 0.98	9.22 ± 0.93	0.749
PDW (%)	11.46 ± 2.09	10.22 ± 2.15	0.832
RDW (%)	14.14 ± 1.39	14.84 ± 1.87	0.241
MPVLR	2.29 ± 0.78	3.68 ± 2.98	0.008
NLR	2.99 ± 2.83	3.59 ± 3.41	0.453
PLR	110.85 ± 69.26	128.24 ± 98.82	0.348
CRP (mg/dl)	121.97 ± 94.54	100.50 ± 62.68	0.418
ESR (mm/hour)	46.33 ± 24.27	48.90 ± 25.80	0.737

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; MPV = mean platelet volume; MPVLR = mean platelet volume-to-lymphocyte ratio; NLR = neutrophil-to-lymphocyte ratio; PDW = platelet distribution width; PLR = platelet-to-lymphocyte ratio; PLT = platelet; RDW = red blood cell distribution width; WBC = white blood cell

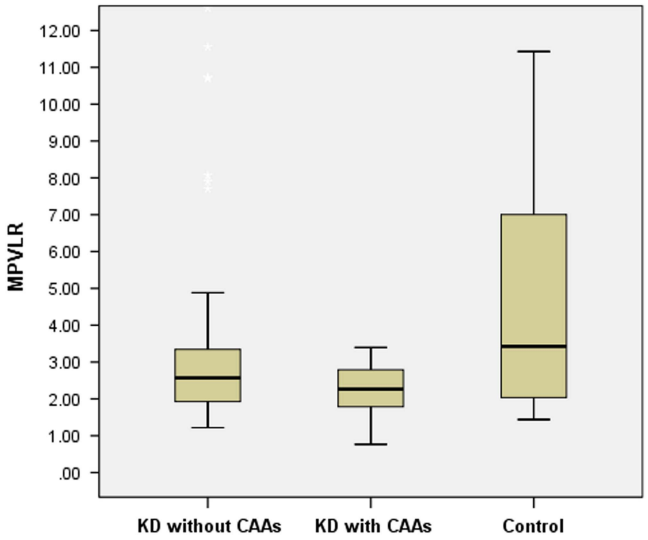

Figure 1. Mean platelet volume-to-lymphocyte ratio (MPVLR) levels in Kawasaki disease (KD) patients with and without coronary artery abnormalities (CAAs) and control subjects.

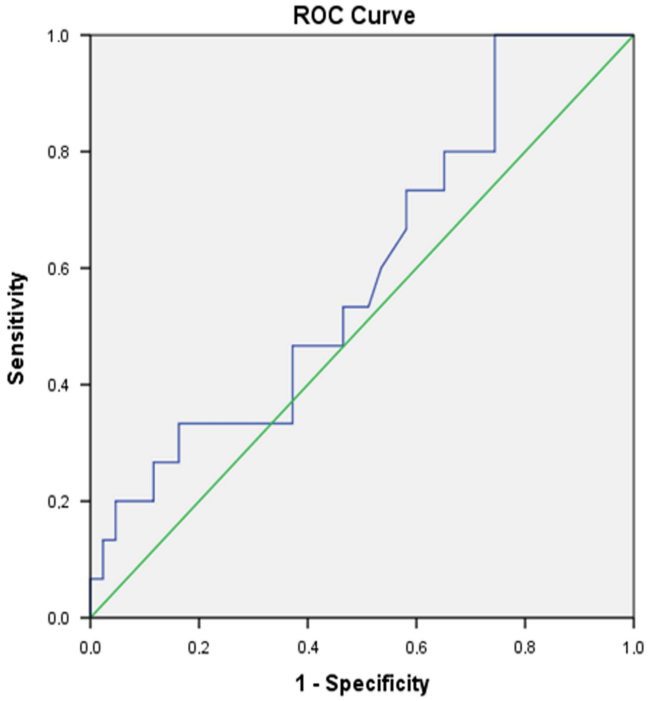

Figure 2. The receiver operating characteristic (ROC) curve analysis for mean platelet volume-to-lymphocyte ratio in the prediction of coronary artery abnormalities (area under curve = 0.593, p = 0.008).

that children with Kawasaki disease had significantly lower mean platelet volume-to-lymphocyte ratio compared with the control subjects. We also showed that mean platelet volume-to-lymphocyte ratio level was significantly lower in Kawasaki disease children with coronary artery abnormalities than in those without coronary artery abnormalities. Although it was not statistically significant, we found that complete Kawasaki disease patients had lower mean platelet volume-to-lymphocyte ratio levels compared with those with incomplete Kawasaki disease.

Inflammation of the coronary arteries results in serious clinical outcomes of Kawasaki disease.[1] One of the most important problems in Kawasaki disease is cardiac morbidity, including coronary aneurysms, myocardial infarctions, and giant coronary aneurysms.

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Table 4. Multivariate logistic regression analysis of patients with coronary artery abnormalities.

			95% CI for OR	
	p	OR	Lower	Upper
Age (⩽48 months)	0.017	43.85	1.971	975.685
Male/female	0.867	0.824	0.086	7.882
WBC	0.028	0.259	0.077	0.864
Neutrophils	0.060	1.001	1.000	1.003
Lymphocytes	0.041	1.002	1.000	1.003
PLT	0.495	1.008	0.985	1.031
MPV	0.730	0.826	0.279	2.446
PDW	0.154	1.522	0.854	2.713
RDW	0.076	0.459	0.194	1.084
MPVLR (⩽2.5)	0.650	0.510	0.028	9.331
NLR	0.682	1.491	0.221	10.070
PLR	0.558	0.976	0.898	1.060
CRP	0.338	0.991	0.973	1.009
ESR	0.400	1.027	0.966	1.091

CI = confidence interval; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; MPV = mean platelet volume; MPVLR = mean platelet volume-to-lymphocyte ratio; NLR = neutrophil-to-lymphocyte ratio; OR = odds ratio; PDW = platelet distribution width; PLR = platelet-to-lymphocyte ratio; PLT = platelet; RDW = red blood cell distribution width; WBC = white blood cell

Kawasaki disease is the leading cause of acquired heart disease among children in developed countries, and approximately 15–20% of the patients develop coronary artery abnormalities.[2,12] There are several biomarkers of inflammation and risk-scoring systems that use routine laboratory data to evaluate the outcomes of Kawasaki disease.[8,13] Recent studies have been reported that complete blood tests including neutrophils, lymphocytes, and platelets, and their combinations, such as neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio, play a central role in the inflammation associated with acute Kawasaki disease and coronary artery abnormalities.[14,15]

Mean platelet volume is a marker of platelet function and activation, and it can be easily measured in routine complete blood count test cycle. There has been rapidly growing interest in the association between mean platelet volume and inflammation, and the risk of cardiovascular events.[16] For this purpose, a study conducted by Liu et al[17] evaluated the role of mean platelet volume in children with Kawasaki disease. They found that Kawasaki disease patients have lower mean platelet volume, but it was not a useful marker for predicting coronary artery abnormalities. In the current study, we found that there was no statistically significant difference in mean platelet volume between children with Kawasaki disease and controls. However, we have shown that mean platelet volume was not valuable for predicting coronary artery abnormalities.

In recent years, mean platelet volume-to-lymphocyte ratio has emerged as a novel marker that can be a prognostic indicator of adverse cardiovascular events in adult patients.[9–11] Hudzik et al[9] first defined mean platelet volume-to-lymphocyte ratio in 2016, and they reported that mean platelet volume-to-lymphocyte ratio plays a povital role in developing intravascular thrombus in ST elevation myocardial infarction. The findings supported with the study conducted by Kurtul et al[10] and they demonstrated that mean platelet volume-to-lymphocyte ratio was a strong independent predictor for angiographic no-reflow and short-term mortality in adult patients with ST elevation myocardial infarction. In patients with coronary artery disease, coronary collateral circulation develops as an adaptation to ischaemia and reduces the cardiovascular events. More recently, Ornek et al[11] found that mean platelet volume-to-lymphocyte ratio was associated with impaired collateral circulation in patients with stable angina pectoris.

As the role of mean platelet volume-to-lymphocyte ratio has not been defined in Kawasaki disease previously, the studies mentioned above encourage us to assess whether mean platelet volume-to-lymphocyte ratio may have a value in children with Kawasaki disease. In contrast to the previous studies in adults, we found that the levels of mean platelet volume-to-lymphocyte ratio was significantly lower in children with Kawasaki disease and those with coronary artery abnormalities. The real mechanism of the decrease in mean platelet volume-to-lymphocyte ratio in children with Kawasaki disease is not clearly understood. The evidence suggests that that platelet volume is correlated with platelet function and may be a more sensitive index than platelet number as a marker of clinical interest in various disorders including systemic infection and inflammatory conditions.[9] Mean platelet volume was decreased in active rheumatological diseases.[16] It has been speculated that the reduced platelet volume could be because of the consumption or sequestration of the large activated platelets in the vasculature.[17]

Mean platelet volume-to-lymphocyte ratio has two parameters, and it is calculated by dividing the mean platelet volume value by the lymphocyte count. There is strong evidence that high-grade inflammatory diseases, such as active rheumatoid arthritis or attacks of familial Mediterranean fever, present with low levels of mean platelet volume.[16,18] During the acute stage of Kawasaki disease, lymphocyte predominance may be seen. Igarashi et al[19] found that macrophage colony-stimulating factor, granulocyte colony-stimulating factor, and interleukin-6, derived from monocytes as monokines or derived from vascular endothelial cells, might play an important role in the acute phase of Kawasaki disease. They have suggested that these markers increase during the acute phase of Kawasaki disease, which might contribute to the decreased platelet volume in Kawasaki disease. On the other hand, there were no statistically significant differences in mean platelet volume and lymphocyte counts between Kawasaki disease patients with and without coronary artery abnormalities in our study. Further studies are needed to clarify the exact mechanism of low levels of mean platelet volume-to-lymphocyte ratio in Kawasaki disease patients with coronary artery abnormalities.

Our study had several limitations. First, this study was designed as retrospective in nature. Second, the sample size was relatively small. Third, mean platelet volume-to-lymphocyte ratio was evaluated only on admission, and we did not evaluate fluctuations in mean platelet volume-to-lymphocyte ratio levels. As most of the children with Kawasaki disease had elevated inflammatory markers in the current study, we did not evaluate the role of mean platelet volume-to-lymphocyte ratio in patients with normal levels of white blood cells, platelets, red blood cell distribution width, erythrocyte sedimentation rate, and C-reactive protein. Hence, our findings may need to be confirmed in prospective studies. On the other hand, our study has several strengths as well. To our knowledge, this is the first study to

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examine the value of mean platelet volume-to-lymphocyte ratio in children with Kawasaki disease. The level of mean platelet volume-to-lymphocyte ratio may be affected with several conditions such as haematological diseases, allergic diseases, malignant and inflammatory diseases, and medications. In the current study, children with these conditions were excluded. We did not provide information regarding the value of mean platelet volume-to-lymphocyte ratio in children with fever and no Kawasaki disease. This issue may require further evaluation.

To date, there has been relatively little research on mean platelet volume-to-lymphocyte ratio. No study has assessed the role of mean platelet volume-to-lymphocyte ratio in children with Kawasaki disease. The results of this study show that mean platelet volume-to-lymphocyte ratio may be a novel marker to predict coronary artery abnormalities in children with Kawasaki disease. We believe that further studies with larger numbers of patients are needed to clarify the relationship between mean platelet volume-to-lymphocyte ratio and Kawasaki disease.

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Conflicts of Interest. None.

Ethical Standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation (Mersin University) and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the institutional committees of Mersin University.

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