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Original Article

Mean platelet volume as a marker of Kawasaki disease in children

Soumya Roy, Sumit Datta Majumdar, Subroto Chakrabartty, Swati Chakravarti

From Department of Pediatrics, Institute of Child Health, Kolkata, West Bengal, India

Correspondence to: Soumya Roy, Department of Pediatrics, Institute of Child Health, Kolkata, West Bengal, India.
E-mail: dr.roy85@gmail.com

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ABSTRACT

Background: Kawasaki disease (KD) is a clinical diagnosis, with common confusion among other causes of febrile illnesses. There are no confirmatory laboratory parameters for diagnosing KD. **Objective:** To investigate whether low mean platelet volume (MPV) is associated more with fever due to KD than due to the other common causes. **Methods:** This retrospective case-control study was done on febrile children between 6 months and 6 years of age admitted from January 2015 to January 2017. The MPV values of 28 KD and 50 non-KD febrile children admitted to our hospital were obtained from the hospital records. The diagnosis of KD was accepted only when (1) two pediatricians had agreed upon the diagnosis independently based on the American Heart Association guidelines 2004, (2) no other cause of fever coexisted with KD in a particular patient, and (3) prompt clinical response within 48 h of administration of intravenous immunoglobulin. Using suitable statistical software, the range of MPV in KD fever and non-KD fevers was compared. **Results:** MPV was lower in the KD group (9.75±0.98 femtoliter) than in the non-KD fever group (11.14±1.53 femtoliter). From the receiver operating characteristic curve, it was found that at MPV ≤10.0 fl, KD can be diagnosed with 75% sensitivity and 80% specificity. This means that lower the value of MPV, lower is the probability that a non-KD patient will be wrongly diagnosed as KD. **Conclusion:** Our study shows that low MPV is associated with KD. Hence, a low MPV can raise the index of suspicion for KD in febrile children, especially in cases of incomplete KD. Further, prospective studies involving larger sample size are needed to ascertain its diagnostic utility.

Key words: *Kawasaki disease, Mean platelet volume, Pediatrics, Rheumatology, Vasculitis*

The mean platelet volume (MPV) is universally available free of any extra cost during performing routine blood counts by automated hemograms [1]. MPV, unlike mean corpuscular volume of erythrocytes, has been less put to clinical utility. There are a number of studies regarding the changes of MPV in different diseases including pyelonephritis [1], pneumonia [2], septicemia [3], bronchiolitis [4], rotaviral diarrhea [5], malaria [6], and infective endocarditis [7]. There is a potential role of MPV in evaluating patients of acute coronary syndromes [8], peripheral arterial diseases [8], deep vein thrombosis [8], pulmonary embolism [8], and other vascular diseases. However, the cutoff values of the platelet indices with regard to clinical scenarios have not been validated by rigorous studies [8].

There are only a very few studies on the changes of MPV in Kawasaki disease (KD). Most of them have investigated the changes of MPV in KD patients with coronary artery disease (CAD) versus those without CAD [9]. To the best of our knowledge, there are only two studies that have tried to apply MPV as a diagnostic marker of KD. Hu et al. had studied 23 KD patients and found the MPV to be significantly lower in KD patients than the controls [10]. In 2012, Liu et al. had a similar observation from a study based on 309 KD cases [11]. However, there has been no such study in the Indian subcontinent.

KD is essentially a clinical diagnosis with common confusion with other febrile illnesses. An overdiagnosis results in prescribing intravenous immunoglobulin which is both very expensive as well as has its own potential adverse effects whereas a hesitation in diagnosis results in antibiotic abuse and silent development of potentially lethal CAD later on in life. In fact, a previous study published by the author Chakrabartty et al. [12] also found that as much as 56% of KD patients, who present beyond the 2nd week, do not meet the criteria laid down by the American Heart Association guidelines for either complete or incomplete KD.

This retrospective study investigates the association of low MPV with fever due to KD and its role in differentiating KD from other common causes of fever in children.

METHODS

The values of MPV of 28 children admitted with KD to a pediatric hospital in Eastern India in January 2015 to January 2017 were collected retrospectively from the hospital records. In these patients, the diagnosis of KD was accepted only when the following criteria were met: (a) The diagnosis was agreed upon by at least two pediatricians independently according to the American Heart Association 2004 criteria for the diagnosis

of KD, (b) No other obvious cause of fever coexisted with KD in a particular patient, and (c) prompt clinical response within 48 h of administration of intravenous immunoglobulin. As the values were collected from the past hospital records, hence, the clinicians who had diagnosed these children as KD were absolutely unaware of the study, thereby eliminating any bias.

The MPV values of a second group of 50 children admitted during the same time in the same hospital with other etiologies of fever were randomly selected as controls by another person, who was also unaware of the objective of the study. All children were between the ages 6 months and 6 years. There were no significant differences between the baselines characteristics of the cases and controls such as age, sex distribution, and duration of fever at presentation (Table 1). Furthermore, the serum sodium, serum albumin, and the platelet counts of the KD patients were noted. The values of serum albumin were available for only 10 patients. The other causes of fever have also been investigated (both by history and laboratory tests, including inflammatory markers and blood culture), even after having clinically suspected KD.

Collection of Blood and Analysis

Blood was collected from a peripheral vein with minimal stasis and dipotassium edetic ethylenediaminetetraacetic acid (EDTA) was used as an anticoagulant while storage and transportation of the sample. All blood samples were tested within 2 h of collection to avoid distortion of the MPV values due to EDTA. The blood was tested using a quality-controlled automated hemogram machine. The values of MPV were obtained only from the first blood sample sent after the admission of the child. Being a retrospective study, authors did not have any active control on these blood collection or analysis methods. However, these are the protocols being universally followed at all times in our hospital for all the patients.

Statistical Analysis

Statistical analysis was done using statistical version 6 [Tulsa, Oklahoma: StatSoft Inc., 2001] and MedCalc version 11.6 [Mariakerke, Belgium: MedCalc Software 2011] software. All numerical variables are normally distributed by Kolmogorov-Smirnov goodness-of-fit test. The MPV values of the KD group and the non-KD group were compared by Student's unpaired t-test. The receiver operating characteristic (ROC) curve was obtained so as to find the cutoff value of MPV, at which KD can be suspected. The sensitivity and specificity of this cutoff value was also calculated from the ROC curve.

RESULTS

The mean MPV among the KD group was 9.75±0.98 femtoliter [fl] whereas it was 11.14±1.53 fl in the control group. Area under the ROC curve was 0.707 with a 95% confidence interval (CI) of 0.680-0.872 ($p<0.001$). From the ROC curve, it was found that at MPV of ≤10.0 fl, KD can be diagnosed with 75% sensitivity (CI: 55.1-89.3) and 80% specificity (CI: 66.3-90.0) (Fig. 1). At values MPV <10 fl, the specificity progressively increases.

Among the KD patients, mean serum sodium was 133.9±3.6 mEq/L (range: 128-140 mEq/L, median 133.5 mEq/L), mean serum albumin was 3.27±0.67 g/dl (range 2.2-3.9 g/dl, median 3.6 g/dl), and the mean platelet count was 496500±213267/cc (range 165000-904000, median 470000). Hyponatremia was observed in 17 patients (60.7%), hypoalbuminemia in 4 patients (40%), and thrombocytosis in 12 patients (42.9%). A MPV of ≤10 fl was seen in 21 patients (75%) (Fig. 2).

DISCUSSION

The mean MPV in the KD group was 9.75±0.98 fl whereas it was 11.14±1.53 fl in the control group. This is the only third [10,11] study which has shown that MPV values are lower in KD and this

Table 1: Baseline characteristics of the cases and controls

Baseline characteristics	KD cases	Controls
Age (in months)	26.9±15.2	28.1±19.1
Gender (male:female)	19:9	32:18
Duration of fever (in days)	8.2±1.9	9.2±3.1

KD: Kawasaki disease

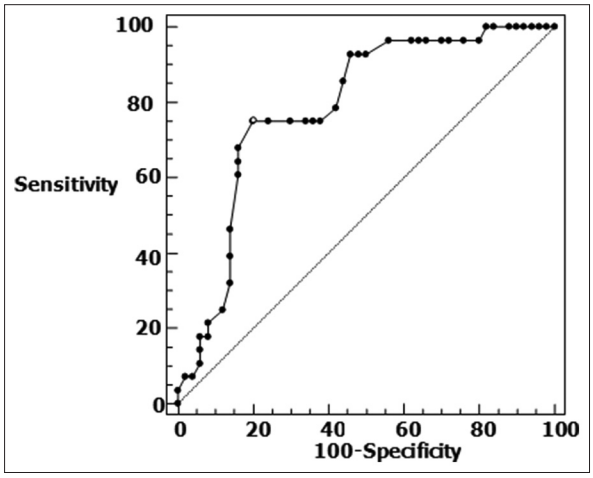

Figure 1: Receiver operating characteristic to identify mean platelet volume cutoff for diagnosing Kawasaki disease

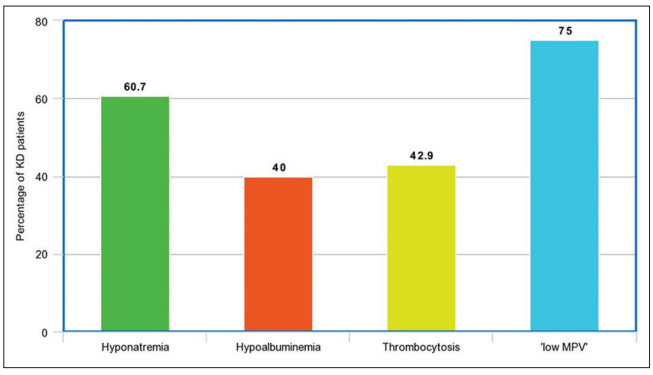

Figure 2: Frequency of occurrence of the established parameters of Kawasaki disease versus "low mean platelet volume"

fact can be used to clinch the diagnosis of KD with even more certainty. Furthermore, in incomplete KD, where the established features are even more lacking, low MPV can aptly serve as an important diagnostic tool. As mentioned previously, at values of MPV <10 fl, the specificity progressively increases. This means that lower the value of MPV, lower is the probability that a non-KD patient will be wrongly diagnosed as KD patient.

KD affects as much as 60-150/100,000 children worldwide [13]. With increasing awareness, more and more cases are being diagnosed every year. It has become the most common pediatric vasculitis and also the most common vasculitic disorder among all ages [13]. With the increasing control of infective diseases worldwide, KD has surpassed rheumatic heart disease as the most common cause of heart disease in the adolescents and young adults. Without treatment, coronary artery problems occur in 25% and about 1% die [14]. However, prompt diagnosis and treatment can reduce the mortality to 0.17% [14]. With this background, lower values of MPV, especially when available at no extra cost, may be valuable in differentiating KD from other common childhood fevers.

The accepted laboratory parameters for KD are hyponatremia, hypoalbuminemia, and thrombocytosis. However, we observed that a MPV ≤10 fl was present in much higher number of KD patients (75%), than hyponatremia (60.7%), hypoalbuminemia (40%), and thrombocytosis (42.9%). Hence, if the parameter of "low MPV" is taken into account, along with the established parameters, then, the probability of diagnosing KD more correctly increases.

As discussed earlier, the MPV has been found to be altered in various infective and inflammatory conditions [1-8], including various procoagulant states that involve reactive activation of platelets [8]. MPV has also been found to be decreased in rheumatological diseases such as rheumatoid arthritis and ankylosing spondylitis [15-17]. The cause of change of MPV in these diseases is unknown. Liu et al. [11] observed that the platelet volume, rather than platelet count, is a more effective marker of platelet function. Defective regulation as well as altered secretions of various cytokines such as interleukin-6 and Granulocyte-macrophage colony-stimulating factor (GM-CSF) during thrombopoiesis and megakaryocyte fragmentation may be the cause of altered MPV in various diseases [18-21]. Studies have suggested that interleukin-6 and GM-CSF increase during the acute phase of KD which might contribute to the decreased MPV in KD [22,23].

Andrews and Berndt reported that infective, inflammatory, and allergic conditions stimulate the bone marrow, leading to increased platelet production. A large number of young platelets with a bigger (higher MPV) size are released into the circulation [24]. Kisacik et al. published that MPV was lower in autoimmune vasculitis such as rheumatoid arthritis and ankylosing spondylitis in their study population [17]. Yüksel et al. had a similar observation of low MPV in inflammatory bowel disease (autoimmune disease) [25]. The question arises that although the inflammatory diseases are provoking the bone marrow to produce young platelets with larger sizes, still why many authors have found low MPV in these diseases? Ergül et al. explained the reason that: "Reduction in the MPV value may be related with migration of large young platelets to the site of inflammation and a relative decrease (of larger platelets) in the circulation [4]." Flad and Brandt reported that during inflammation, the microtubular structure of the platelets undergoes depolymerization, and there are also changes in the structure of actin polymerization. This causes the changes in the MPV during inflammation [26]. Tanju et al. opined that the inverse relationship between platelet count and MPV in some diseases (as also in KD) occurs in an effort to maintain a normal hemostasis by maintaining a constant platelet mass [27].

There is a lack of any international guideline or recommendation for the blood collection and transport pertaining to studies on platelet indices. However, the studies of platelet parameters as diagnostic and prognostic tools in different diseases is still a research subject and is yet to be accepted on daily clinical practice. This may be a limitation to our study as well as to a large number of other studies on platelet parameters. Hence, as more studies continue to accumulate in future, the awareness for more stringent protocols will be inspired for. We, however, observed that our method of blood collection and transport was exactly the same as the method described by Liu et al. (which, incidentally, is the largest study on this topic) [11].

The second major limitation was to decide whether to take healthy afebrile children as the controls or whether to take children suffering from other diagnosed causes of fevers as control? The only two studies done on this topic differ in opinion in this regard. While Liu et al. took healthy children as controls, Hu et al. took febrile (fever due to causes other than KD) as controls. Our study followed Hu et al. in this regard [10,11]. The third limitation was whether MPV measurement will be significantly affected by the day of illness when the blood is tested? However, most of the studies mentioned above have not tested the blood on a specific date from the onset of fever.

Lastly, this was a retrospective study and the sample size was also small. However, the largest study on this topic done by Liu et al. was also retrospective [11]. While Liu et al. had studied 309 participants, the only other study done by Hu et al. Studied only 23 participants [10,11]. Considering the paucity of data on this topic in the medical literature, our study may be quite important in paving for further larger and stringent studies in this regard.

CONCLUSION

Low MPV is strongly associated with KD, and a low MPV should raise the suspicion of KD in febrile children. Further, prospective studies involving larger sample size are needed to establish the pathophysiology as well as clinical significance of MPV to diagnose KD.

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