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Role of mean platelet volume in differential diagnosis of adult-onset Still's disease and sepsis

Liyan Luo[1], Litao Zhang[2], Jiahong Jiang[2], Xiaoxia Ding[3]*

SUMMARY

OBJECTIVES: Mean platelet volume is a simple biomarker for inflammatory disease. The purpose of this study is to evaluate the role of mean platelet volume in distinguishing adult-onset Still's disease from sepsis.

METHODS: We retrospectively selected 68 patients with adult-onset Still's disease and 55 patients with sepsis between January 2015 and December 2019. Related laboratory data were collected and analyzed.

RESULTS: There were no significant differences in white blood cell counts, neutrophils, lymphocytes, and C-reactive protein between adult-onset Still's disease group and sepsis group. However, patients in adult-onset Still's disease group showed higher ferritin and platelets and lower mean platelet volume and platelet distribution width than those in sepsis group ($p<0.01$ for both). Receiver operating characteristic curve analysis was performed to distinguish adult-onset Still's disease and sepsis. The area under the curve of mean platelet volume was 0.761 (95%CI 0.673–0.849), with a sensitivity of 79.1%, a specificity of 63.3%, and a cutoff value of 10.9 fL. In contrast, the area under the curve of combined ferritin and mean platelet volume was 0.90l (95%CI 0.837–0.965), with higher sensitivity (82.8%) and specificity (96.2%). Therefore, mean platelet volume could be used as a supplementary indicator to distinguish adult-onset Still's disease from sepsis.

CONCLUSION: We suggest that mean platelet volume could be used as a supplementary biomarker for differential diagnosis of adult-onset Still's disease and sepsis in addition to ferritin.

KEYWORDS: Mean platelet volume. Still's disease, adult-onset. Sepsis.

INTRODUCTION

Adult-onset Still's disease (AOSD) is a rare condition characterized by leukocytosis, fever, arthralgia, and rash[1]. Due to the lack of specific biomarkers, it is difficult to differentiate AOSD from common diseases, such as malignancy, rheumatic diseases, and infections[1-3]. Sepsis, a dangerous and fatal disease, is difficult to be distinguished from AOSD[4]. Several studies show that signs, ferritin, and interleukin-18 (IL-18) could be used to identify AOSD and sepsis; however, none of them are specific[5]. Therefore, complementary indexes that can distinguish between these two diseases are needed.

Mean platelet volume (MPV) is a traditional biomarker of inflammation that can be measured in routine hematological examination[6,7]. Previous studies demonstrated low level of MPV in patients with rheumatoid arthritis and systemic lupus erythematosus[8,9]; however, MPV in AOSD and sepsis remains unclear. This study aimed to investigate the role of MPV in differential diagnosis of AOSD and sepsis and compare the role of MPV, C-reactive protein (CRP), and ferritin.

[1]Nanjing Gulou Yi Yuan: Nanjing University Medical School Affiliated Nanjing Drum Tower Hospital, Intensive care unit Affiliated – Nanjing, China.
[2]The First Affiliated Hospital of Nanjing Medical University, Department of Laboratory Medicine – Jiangsu, China.
[3]Taixing People's Hospital, Department of Laboratory Medicine – Jiangsu, China.
*Corresponding author: 842278953@qq.com
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METHODS

Subjects

A retrospective study was performed between January 2015 and December 2019. The study participants were patients admitted to the First Affiliated Hospital of Nanjing Medical University. The patients were divided into two groups: AOSD group (n=68) and sepsis group (n=55). Patients who met the Yamaguchi criteria[1] (meeting at least five criteria with two or more major criteria, no exclusion criteria); age ≥18 years; first diagnosed in our hospital without hematological disease, glucocorticoids, and other autoimmune diseases; and received no chemotherapy were included in AOSD group. The major inclusion criteria are (1) fever >39°C for at least 1 week, (2) joint pain or arthritis that lasts 2 weeks or more, (3) typical skin rash, and (4) leukocytosis ≥10×10^9/L with at least 80% granulocytes. The minor inclusion criteria are

(1) sore throat,
(2) splenomegaly/lymphadenopathy,
(3) the absence of rheumatoid factor or antinuclear antibodies, and
(4) impaired liver function. Patients diagnosed with sepsis (meeting the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference criteria[10]) were assigned in the sepsis group.

Patients were excluded if they have diseases that affect platelet parameters. This study was approved by the Ethics Committee of the local hospital and was in accordance with the guidelines of the Declaration of Helsinki.

VARIABLES

All variables (i.e., demographics, clinical features, and laboratory values) were obtained from electronic medical records. Complete blood count (before any treatment) was detected using a Sysmex XE 2100 analyzer (Sysmex, Hyogo, Japan), C-reactive protein (before any treatment) was measured by a BN II nephelometer (Dade Behring, Marburg, Germany), and ferritin (before any treatment) was evaluated on a Unicel DXI 800 (Beckman Coulter, Brea, CA, USA).

Statistical analysis

The parametric quantitative data were expressed as mean and standard deviation and evaluated by chi-square test. Nonparametric quantitative data were displayed as median (interquartile range) and estimated with Wilcoxon test. Qualitative data were represented as number (percentages). The Student's *t* test and Mann-Whitey U test were used to compare the difference between the groups. Spearman's correlation analysis was used to evaluate the correlation between variables. The best cutoff value was confirmed with receiver operating characteristics (ROC) curve analysis. All analyses were conducted with SPSS (SPSS 21 Inc., Chicago, IL, USA). A $p<0.05$ was considered statistically significant.

RESULTS

Characteristics

Table 1 summarizes the characteristics of the study patients. The median ages of AOSD group (male-to-female ratio: 23:45) and sepsis group (male-to-female ratio: 27:28) were 40 and 33 years, respectively. The main clinical characteristics and signs of AOSD group and sepsis group are displayed in Table 1.

Comparison of variables between the two groups

A comparison was made to find the difference between the two independent groups. The levels of ferritin, platelets, MPV, and platelet distribution width (PDW) were found to be 2206.6 (31.2–15000) µg/L, 261.51×10^9/L, 10.08 fL, and 11.85% for AOSD group and 404.65 (14.2–1507) µg/L, 163.44×10^9/L, 11.14 fL, and 14.00% for sepsis group, respectively, which showed significant difference between the groups ($p<0.001$ for both) (Table 2). Also, the levels of ferritin and platelets were higher and those of MPV and PDW were lower in AOSD group compared to sepsis group. In addition, there was no difference in white blood cell (WBC) count, neutrophils, lymphocytes, and CRP values between the two groups ($p>0.05$ for both) (Table 2).

Table 1. Clinical features of the study patients.

	Patients with sepsis n=55	Patients with AOSD n=68
Fever, n (%)	43 (93.5)	62 (91.2)
Arthralgia/arthritis, n (%)	2 (4.3)	32 (47.1)
Myalgia, n (%)	10 (21.7)	21 (30.9)
Typical skin rash, n (%)	–	26 (47.2)
Sore throat, n (%)	3 (6.5)	31 (45.6)
Lymphadenopathy, n (%)	5 (10.9)	7 (10.3)
Hepatomegaly/splenomegaly, n (%)	3 (6.5)	3 (4.4)

AOSD: adult-onset Still's disease.

Correlations between MPV and other variables

The correlation between MPV and clinically relevant variables in AOSD group and sepsis group was assessed. The results showed that MPV was positively correlated with PDW (r=0.830, p<0.001) and inversely correlated with WBC count, lymphocytes, neutrophils, platelets, CRP, and ferritin (r=0.060, p=0.524; r=0.158, p=0.090; r=0.047, p=0.619; r=0.509, p<0.001; r=0.003, p=0.976; r=0.076, p=0.473, respectively). However, only the correlation between MPV and platelets or PDW was significant (Table 3).

Table 2. Clinical data of patients with adult-onset Still's disease or sepsis.

	Patients with sepsis n=55	Patients with AOSD n=68	p-value
Age, years	40 (18–68)	33 (18–74)	0.239
Sex, male/female	27/28	23/45	0.088
WBC ($\times10^9$/L)	15.27±8.58	15.17±8.63	0.948
Lymphocyte ($\times10^9$/L)	1.17±1.17	1.38±0.71	0.223
Neutrophil ($\times10^9$/L)	9.45±7.15	13.51±8.12	0.870
Platelet ($\times10^9$/L)	163.44±96.58	261.51±118.47	<0.001
MPV (fL)	11.14±1.09	10.08±1.11	<0.001
PDW (%)	14.00±2.93	11.85±2.48	<0.001
CRP (mg/L)	92.39±73.32	99.95±63.51	0.553
Ferritin (µg/L)	404.65 (14.2–1507)	2206.6 (31.2–15000)	<0.001

AOSD: adult-onset Still's disease; WBC: white blood cell; MPV: mean platelet volume; PDW: platelet distribution width; CRP: C-reactive protein.

Comparison of roles of MPV, CRP, and ferritin in AOSD group and sepsis group

We identified the optimal cutoff value of variables (including CRP, platelets, MPV, PDW, and ferritin using ROC curve) in predicting AOSD and found that the variables were significantly different between AOSD and sepsis groups. The area under the curve (AUC) of ferritin (AUC 0.872, 95%CI 0.814–0.949, sensitivity 73.8%, specificity 90.0%) gave the best result, followed by MPV (AUC 0.761, 95%CI 0.673–0.849, sensitivity 79.1%, specificity 63.3%) (Table 4). Then, the performance of the combined MPV and ferritin was analyzed and gave a better result with the highest AUC (AUC 0.901, 95%CI 0.837–0.965, sensitivity 82.8%, specificity 96.2%), which could be helpful to distinguish AOSD from sepsis (Figure 1).

Table 3. Correlations between Mean platelet volume and variables.

	Correlation coefficient (r)	p-value
WBC ($\times10^9$/L)	-0.060	0.524
Lymphocytes ($\times10^9$/L)	-0.158	0.090
Neutrophils ($\times10^9$/L)	-0.047	0.619
RDW (%)	0.173	0.063
Platelets ($\times10^9$/L)	-0.509	<0.001
PCT	-0.325	<0.001
PDW	0.830	<0.001
CRP (mg/L)	-0.003	0.976
Ferritin (µg/L)	-0.076	0.473

CRP: C-reactive protein; WBC: white blood cell; RDW: red cell distribution width; PCT: plateletcrit; MPV: mean platelet volume; PDW: platelet distribution width.

Table 4. The performance for each tested markers.

	Cutoff	AUC	95%CI	Sensitivity	Specificity	p-value
CRP(mg/L)	84.0	0.558	0.452–0.664	58.5	49.0	0.282
Ferritin(µg/L)	1086.4	0.872	0.814–0.949	73.8	90.0	<0.001
PLT(fL)	190.0	0.739	0.652–0.827	69.1	63.6	<0.001
PCT(mg/L)	0.25	0.711	0.615–0.807	50.7	75.5	<0.001
MPV(fL)	10.9	0.761	0.673–0.849	79.1	63.3	<0.001
PDW(fL)	12.5	0.737	0.644–0.829	65.3	70.1	<0.001
Ferritin+MPV	–	0.901	0.837–0.965	82.8	96.2	<0.001

CRP: C-reactive protein; PLT: platelet count test; PCT: plateletcrit; MPV: mean platelet volume; PDW: platelet distribution width; AUC: area under the curve.

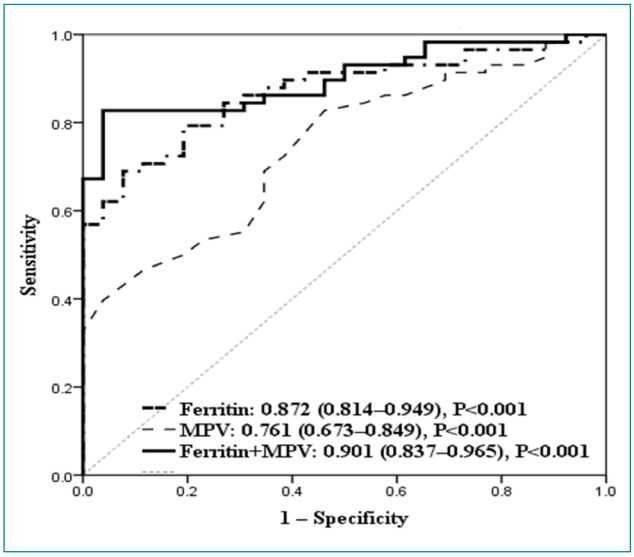

Figure 1. Comparison of AUC between ferritin, MPV, and combined ferritin and MPV.

DISCUSSION

The clinical manifestations and characteristics of AOSD are nonspecific; therefore, it is difficult to distinguish AOSD from infectious diseases, especially sepsis. AOSD is difficult to cure and easy to relapse, with 9–10% mortality rate when combined with complications such as pneumonia[11,12]. Timely and accurate diagnosis could relieve mental and physical pain in patients. Thus, the sooner AOSD is diagnosed, the better the prognosis will be. Previous literature showed that signs, ferritin, and IL-18 could distinguish AOSD from sepsis; however, none of them were specific.

MPV has been considered a predictive biomarker for sepsis[6,7,13,14]. One study showed that the baseline MPV of patients with culturally- proven sepsis was comparatively higher than that of patients in control group[6]. Furthermore, high cord blood and day-3 MPV can be used as a surrogate marker of predicting early-onset sepsis and associated mortality in preterm neonates[13]. However, few studies addressed the benefit of MPV in patients with AOSD. In this study, we found that MPVs in AOSD group were remarkably lower than those in sepsis group (10.08 fL *versus* 11.14 fL, p=0.001), while ferritin in AOSD group was considerably higher than that in sepsis group (2206.6 [31.2–15000] µg/L *versus* 404.65 [14.2, 1507] µg/L). ROC curve showed ferritin had better performance than MPV in differentiating AOSD from sepsis (AUC 0.872 *versus* 0.761), and the AUC of the combined MPV and ferritin was 0.901. MPV is a sensitive biomarker of platelet morphology that is related to the increased production of platelets, despite its destruction or consumption. Ferritin is a useful marker for diagnosis, disease activity assessment, and prognosis. This means that if a patient (sepsis or AOSD) has high ferritin and low MPV, then the patient is considered primarily to have AOSD or sepsis. MPV in AOSD group was strongly correlated with the levels of platelets and PDW, which had been reported as inflammation biomarkers[15]. Meanwhile, consistent with other reports, we found CRP is the most commonly used reaction protein that is neither different between patients with AOSD and sepsis [15,16] nor correlated with MPV. Therefore, we speculated that serum MPV could represent a complementary marker to ferritin for differential diagnosis between AOSD and sepsis (sensitivity 79.1%, specificity 63.3%) in febrile patients with indistinguishable or similar clinical and laboratory features. The mechanism of elevated MPV in inflammatory conditions remains unclear. Numerous studies demonstrated that MPV increased in patients with sepsis and hypothesized that activated platelets altered in terms of shapes and sizes[17].

MPV was used to describe the average size of platelets in the blood and was routinely measured as part of an automated full blood count request. Given that no objective laboratory results can help physicians discriminate AOSD and sepsis at admission, MPV might be useful for the differential diagnosis of AOSD and sepsis, which is more rapid and more cost-effective than other markers (although the performance of MPV did not surpass that of ferritin).

The research had some limitations due to its retrospective nature. First, limited data of patients were included. Second, no validation group validates the conclusion. Third, we did not validate different MPV measurement methods in individual laboratories. Therefore, a multicenter study with more patients with AOSD is needed.

CONCLUSIONS

MPV might be a rapid, cost-effective, and helpful marker for the differential diagnosis between AOSD and sepsis in regard to indistinguishable disease patterns.

AUTHORS' CONTRIBUTIONS

LL: Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft. **LZ:** Conceptualization, Data curation, Formal analysis, Writing – review & editing. **JJ:** Conceptualization, Data curation, Formal analysis, Writing – review & editing. **XD:** Conceptualization, Data curation, Formal analysis, Writing – review & editing. All authors contributed equally to this work.

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