ORIGINAL ARTICLE

Case Control Study

New parameter in diagnosis of acute appendicitis: Platelet distribution width

Bulent Dinc, Alten Oskay, Selcan Enver Dinc, Bilge Bas, Sabri Tekin

Bulent Dinc, Department of General Surgery, Ataturk State Hospital, Antalya 07040, Turkey
Alten Oskay, Department of Emergency, Denizli State Hospital, Denizli 20010, Turkey
Selcan Enver Dinc, Department of Emergency, Isparta State Hospital, Isparta 32100, Turkey
Bilge Bas, Department of Gastroenterology, Ataturk State Hospital, Antalya 07040, Turkey
Sabri Tekin, Department of Surgery, Medical Park Hospitals, Antalya 07160, Turkey

Correspondence to: Bulent Dinc, MD, Department of General Surgery, Ataturk State Hospital, Gulluk Street, Antalya 07040, Turkey. bulent1999@yahoo.com
Telephone: +90-242-3454550
Fax: +90-242-3343373

Abstract

AIM: To investigate the diagnostic accuracy of the mean platelet volume and platelet distribution width in acute appendicitis.

METHODS: This retrospective, case-controlled study compared 295 patients with acute appendicitis (Group Ⅰ), 100 patients with other intra-abdominal infections (Group Ⅱ), and 100 healthy individuals (Group Ⅲ) between January 2012 and January 2013. The age, gender, and white blood cell count, neutrophil percentage, mean platelet volume, and platelet distribution width values from blood samples were compared among the groups. Statistical analyses were performed using SPSS for Windows 21.0 software. In addition, the sensitivity, specificity, positive and negative predictive values and likelihood ratios, and diagnostic accuracy were calculated.

RESULTS: The mean ages of patients were 29.9 ± 12.0 years for Group Ⅰ, 31.5 ± 14.0 years for Group Ⅱ, and 30.4 ± 13.0 years for Group Ⅲ. Demographic features such as age and gender were not significantly different among the groups. White blood cell count, neutrophil percentage and platelet distribution width were significantly higher in Group Ⅰ compared to groups Ⅱ and Ⅲ ($P < 0.05$). Diagnostically, the sensitivity, specificity and diagnostic accuracy were 73.1%, 94.0%, and 78% for white blood cell count, 70.0%, 96.0%, and 76.0% for neutrophil percentage, 29.5%, 49.0%, and 34.0% for mean platelet volume, and 97.1%, 93.0%, and 96.0% for platelet distribution width, respectively. The highest diagnostic accuracy detected was for platelet distribution width between Group Ⅰ and Group Ⅲ ($P < 0.01$).

CONCLUSION: Platelet distribution width analysis can be used for diagnosis of acute appendicitis without requiring additional tests, thus reducing the cost and loss of time.

Key words: Appendicitis; Diagnosis; Platelet function test; Platelet distribution width

Core tip: The diagnosis of acute appendicitis can be difficult and confusing. A rapid and accurate diagnosis is important because of potential complications, therefore, new biomarkers for diagnosis are needed. This study investigated the diagnostic accuracy of indicators of platelet activation, namely mean platelet volume and platelet distribution width, in acute appendicitis patients. Results shows that platelet distribution width analysis can be used for diagnosis of acute appendicitis without requiring additional tests. Therefore, it reduces the cost and loss of time.

INTRODUCTION

Acute appendicitis (AA) is among the most common urgent abdominal surgical conditions worldwide[1,2]. The people in Western society have an approximately 8% possibility of having AA during their lifetime[3]. Whereas the diagnosis of AA is usually established clinically, the symptoms and findings may not always typical, in which case the establishment of diagnosis becomes difficult[4,5]. Rapid and accurate diagnosis is important because extension of the period between the initiation of the symptoms and start of the surgical procedure increases the risk for appendiceal perforation, thereby potentially resulting in sepsis and even death[6]. In addition, the ratio of patients undergoing appendectomy with a normal histopathologic investigation result (negative appendectomy) ranges between 5% and 42%. The morbidity of these patients who are operated on despite the absence of AA is thus increased[7,8]. The rate of clinical diagnosis of AA is approximately 85%[1]. Although current advanced imaging methods such as ultrasonography, computed tomography and magnetic resonance imaging are promising, they are not adequate. Therefore, novel methods that differentiate AA from nonspecific abdominal pain and reduce the rate of negative appendectomy are needed. Such methods should be inexpensive and convenient, with results obtained in a short time.

Recent studies have investigated the diagnostic accuracy of inflammatory markers[9,10]. Mean platelet volume (MPV) and platelet distribution width (PDW) are presented in the complete blood cell count, which is routinely used in emergency departments. They are the indicators of platelet activation. The size of the platelet is correlated with the activity and the function of the platelet; larger platelets are more active than small ones. Thus, MPV may be used as a biomarker in myocardial infarction, diabetes mellitus, inflammatory

disorders, sepsis-like conditions, myeloproliferative diseases, massive hemorrhage, leukemia, vasculitis and post-splenectomy conditions[11,12]. Platelet distribution width is an indicator of variation in platelet size, which can be a sign of active platelet release. Studies have demonstrated that in addition to MPV, PDW is also altered compared to healthy subjects in several conditions[13,14].

There are very few studies investigating the diagnostic accuracy of platelet function parameters in cases of AA. We present the first case-controlled study investigating the diagnostic significance of platelet parameters, including MPV and PDW, in AA.

MATERIALS AND METHODS

Participants

The records of 295 adult patients, aged between 16 and 94 years, who underwent appendectomy (Group I), 100 patients with other intra-abdominal infections (Group II), and 100 healthy individuals (Group III) were retrospectively investigated between January 2012 and January 2013. The groups were compared by age, gender and routine tests of complete blood count. Group I was comprised of patients diagnosed with AA based on the analysis of at least two samples performed by the pathologist.

Patients were excluded from the study for: < 15 years of age, having acute or chronic infectious disease, comorbid conditions (cardiac, respiratory, renal, endocrinal, and vascular disease, cancer, *etc*.), hematologic disease and blood transfusion within the last year for any reason, using ongoing medication (analgesics, oral contraceptives, antimetabolites, *etc*.), having a histopathologically normal appendix following appendectomy.

There were two control groups. The first of these, Group II did not have AA but they had intra-abdominal infections that depended on causes such as acute cholecystitis, pelvic inflammatory disease, and mesenteric lymphadenitis. Group III was comprised of healthy individuals, including people who came for health control and they did not have acute or chronic disease. The control groups were selected from among people of similar age and gender to AA patients. There was no history of drug use or blood transfusion in any of the patients.

Test methods

All blood samples were obtained from the venous system and stored in tubes containing EDTA and assayed automatically using internationally certified devices. The reference values were $4.5 \times 10^9/\mu L$-$10.8 \times 10^9/\mu L$ for white blood cell count (WBC), 40%-70% for neutrophils, 7.2-11.0 fL for MPV and 10%-18% for PDW. All results were approved by an independent biochemistry expert who was blind to the patients' histories. Extreme results were repeated again. The

Table 1 Comparison of the laboratory values between the groups

Variable	Group I	Group II	Group III	P values			
	(*n* = 295)	(*n* = 100)	(*n* = 100)	I *vs* II	I *vs* III	II *vs* III	Overall
White blood cell count, × 10^9/μL	12.9 (3.1-25.7)	11.5 (5.2-20.0)	7.5 (3.5-13.6)	0.032	< 0.001	< 0.001	< 0.001
Neutrophil, %	73.9 (18.0-93.0)	67.9 (45.0-87.9)	57.6 (21.0-76.0)	0.031	< 0.001	< 0.001	< 0.001
Mean platelet volume, fL	8.5 (6.1-14.2)	8.9 (6.0-13.0)	8.9 (6.9-14.5)	NS	0.001	NS	0.003
Platelet distribution width, %	49.0 (10.6-86.5)	40.8 (12.8-87.9)	18.4 (10.3-62.5)	< 0.001	< 0.001	< 0.001	< 0.001

Data are presented as mean (range). NS: Not significant.

Table 2 Diagnostic comparison of blood parameters

Parameter	Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	PLR	NLR	DA
		(95%CI)	(%)	(%)	(%)	(%)			(%)
White blood cell count	10.6 × 10^9/μL	0.87 (0.84-0.91)	73.1	94	97.1	56.0	12.1	0.3	78
Neutrophil	69.85%	0.87 (0.84-0.91)	70.0	96	97.9	54.2	23.0	0.3	76
Mean platelet volume	8.98 fL	0.62 (0.55-0.68)	29.5	49	61.1	20.1	0.5	4.5	34
Platelet distribution width	32.15%	0.95 (0.92-0.98)	97.1	93	97.4	92.1	13.8	0.0	96

AUC: Area under the receiver operating characteristic curve; DA: Diagnostic accuracy; NLR: Negative likelihood ratio; NPV: Negative predictive value; PLR: Positive likelihood ratio; PPV: Positive predictive value.

results of blood samples were approved in < 10 min.

Statistical analysis

Statistical analyses were performed using SPSS for Windows 21.0 software (IBM Corp., Armonk, NY, United States). The demographic and clinical properties of patients are expressed using mean ± SD, median (range), and percentage values. Parametric parameters were investigated with a Student's *t*-test and one-way analysis of variance, and non-parametric parameters were investigated using the Mann-Whitney *U*, χ^2 and Kruskal-Wallis tests. The association between the numeric data was compared using a correlation analysis. The parameters in the AA and control groups were described using a receiver operating characteristic (ROC) curve analysis. In addition, the sensitivity, specificity, positive and negative predictive values and likelihood ratios, and diagnostic accuracy were calculated by the area under the ROC curve. Results were evaluated within the 95%CI, and a *P* < 0.05 was considered as statistically significant.

RESULTS

The mean ages of patients were 29.9 ± 12.0 (range: 16-94 years), 31.5 ± 14.0 (range: 16-85 years) and 30.4 ± 13.0 years (range: 16-70 years) in Group I, Group II and Group III, respectively. Group I was comprised of 60.7% (179/295) men and 39.3% (116/295) women; Group II was comprised of 50.0% (50/100) men and 50.0% (50/100) women; and Group III was comprised of 60.0% (60/100) men and 40.0% (40/100) women. There were no demographic differences among the groups.

The comparisons of the laboratory values among the groups are given in Table 1. For all parameters,

there were statistical differences between Group I and the two control groups (*P*s < 0.05). MPV was lower in Group I, whereas PDW, WBC (Figures 1 and 2) and neutrophil percentage were higher compared to the control groups.

The diagnostic comparisons of the blood value evaluations are given in Table 2. PDW was the most important diagnostic parameter, followed by WBC, neutrophil percentage and MPV. PDW showed high positive and low negative likelihood ratios. As a result, the diagnostic accuracy for PDW is higher than WBC and neutrophil percentage. In contrast, MPV has the lowest diagnostic accuracy, with a significant difference between Group I and Group III. The ROC curves for these parameters are shown in Figure 3. The high positive accuracy of PDW can also be seen here. As the MPV accuracy shows a reduction in Group I, it is located on the negative side of the reference line as a weak positive. The ROC curve analysis is presented for MPV without correction; smaller test results used in SPSS indicate a more positive test.

DISCUSSION

AA is the most common cause of "acute abdomen" in all age groups. Although the classical symptomatology and the examination findings of AA are well known, the diagnosis remains quite difficult to make among the causes of abdominal pain[15]. It is important to make a rapid and accurate diagnosis before the complications develop[1]. As AA is an inflammatory process, many authors consider using biomarkers for diagnosis. Among these, WBC is the one most commonly used. Many studies support that WBC is the first indicator to be elevated in appendix inflammation[16]. Among patients with AA, the sensitivity and specificity of WBC is
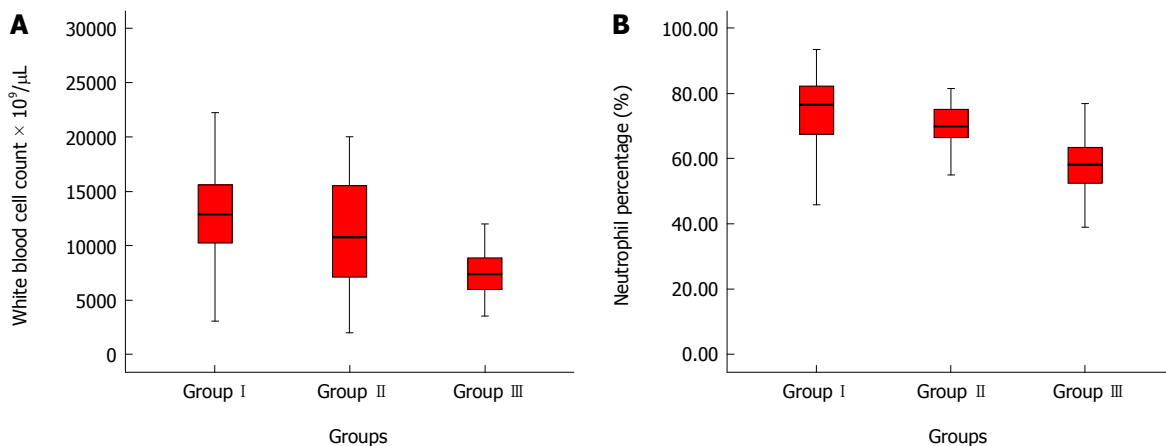
Figure 1 Blood cell counts. A: White blood cell count; B: Neutrophil percentage count variation.
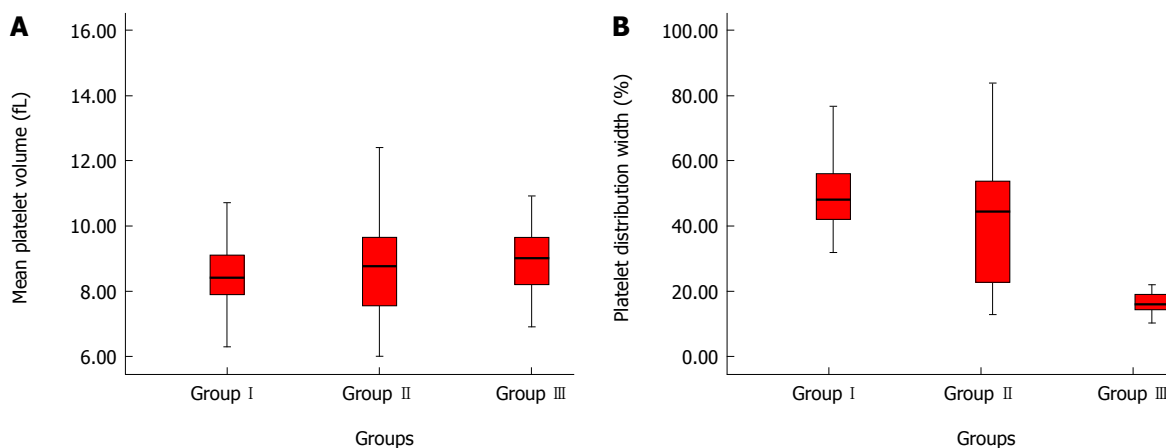

Figure 2 Platelet analyses. A: Mean platelet volume; B: Platelet distribution width variation.
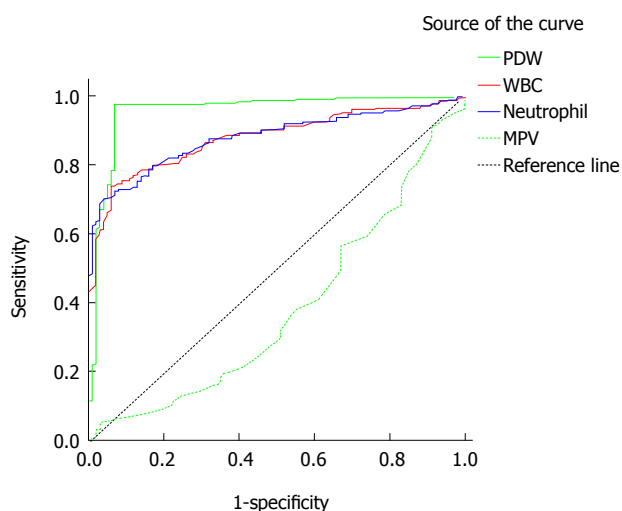

Figure 3 Receiver operating characteristic curves. MPV: Mean platelet volume; PDW: Platelet distribution width count; WBC: White blood cell count.

60%-87% and 53%-100%, respectively[15], with cut-off values of 11×10^9/L in the study by Bilic *et al*[9], and 10.4×10^3/mm^3 in the study by Narci *et al*[6], which are consistent with our findings. In addition, the

78% diagnostic accuracy enhances the significance of WBC diagnostically.

There are several studies investigating the diagnostic accuracy of neutrophils in AA. Al-Gaithy[17] reported a sensitivity and a specificity of 70.9% and 65.5%, respectively, for neutrophil detection in patients undergoing surgery for suspected appendicitis that were classified according to pathology as AA or normal. In a case-controlled study by Bilici *et al*[9] in children, the sensitivity was 77% and the specificity was 91%. In the current study, we found a sensitivity of 70% and a specificity of 96%, which is similar to the literature. The differences in ratios were potentially attributed to the variability of the individuals (adult, child, *etc.*) and the type of the designed study.

Platelet activation is related to pathophysiology of disorders with a tendency for inflammation and thrombosis. MPV, a marker of platelet activation, is being investigated for its correlation with both inflammation and thrombosis. High MPV values are associated with cardio- and cerebrovascular disorders, and low-grade inflammatory conditions prone to arterial and venous thrombosis. Low MPV values may occur in high-grade inflammatory diseases, such as active rheumatoid

arthritis or attacks of familial Mediterranean fever. These results are from anti-inflammatory treatment. As a result, a decrease in MPV occurs in acute cases, whereas an increase occurs with chronic events[18].

The proinflammatory activities of platelets are maintained by bioactive molecules stored within their alpha and dense granules[19,20]. After activation, these molecules are rapidly secreted. However, the exact organelle activity that controls the thrombocyte volume has not yet been clearly identified[19]. Danese *et al*[20] speculated that the reduced MPV could be due to the consumption or sequestration of the large activated platelets in the intestinal vasculature.

In the current trial, we detected a lower MPV in patients with AA. The cause of this remains unclear. A small number of studies failed to clearly demonstrate the correlation between MPV and AA. In the studies by Albayrak *et al*[21], Bilici *et al*[9] and Aydogan *et al*[11], MPV was significantly lower in the AA group, and with a sensitivity and specificity of 73%-84% and 54%-84%, respectively. Uyanik *et al*[15] failed to detect a correlation between AA and MPV in their study in children. However, we detected a statistical difference between the groups, and MPV was lower in the infected group. While the pathophysiology of this decrease is not known, it may be similar to the mechanism suggested by Danese *et al*[20]. The values of sensitivity and specificity of MPV in our study, 25.9% and 49.0%, respectively, are low compared to the literature. This result may stem from the emergency surgery after the clinical history and physical examination.

Both MPV and PDW are markers of platelet immaturity, and an increase in both as compared to controls suggests that young platelets are entering peripheral circulation. PDW is a function of standard deviation of log volume and is also known as the volume change coefficient. PDW is an index of thrombocyte volume heterogeneity, similar to erythrocyte distribution. The heterogeneity of thrombocyte volume occurs due to heterogenic demarcation of megakaryocytes rather than the aging of circulating thrombocytes[11].

There are a small number of studies that evaluate PDW. In a trial by Liang *et al*[22] investigating vascular dementia and Alzheimer's disease, PDW was significantly lower in the patient group compared to the control group. In contrast, Mete Ural *et al*[23] detected high PDW values in patients with recurrent miscarriages. Cetin *et al*[24] reported a higher PDW value in patients with acute ST-segment elevation myocardial infarction compared to those with stable coronary artery disease. Yang *et al*[25] detected higher PDW values in patients with severe preeclampsia relative to those with mild preeclampsia. In the literature, there exists only one study that investigates the correlation between PDW and AA. In a 202-case study by Aydogan *et al*[11], patients were divided into groups as perforated and non-perforated. In this study with no control group, PDW values were significantly higher in the perforated

group. In conclusion, PDW was considered as a marker that could be used in early detection of the perforation risk in AA. In the current study, we detected high PDW values in patients with AA, for which the sensitivity, specificity and diagnostic accuracy suggest that it could help in early diagnosis of AA.

This is the first study in the literature to present the correlation between AA and PDW as a case-controlled clinical trial. Detection of higher PDW values in the AA group relative to the control groups, and the high values of sensitivity, specificity, and diagnostic accuracy detected for AA are promising for future studies in diagnosis and early prediction of potential complications. This may provide an opportunity for making a diagnosis of AA without requiring additional analysis, increased cost, or loss of time, and is practically applicable in the emergency department. Nevertheless, diagnosis of AA should always be combined with clinical, laboratory and radiologic evaluations. PDW could be an important laboratory evaluation, but should always be associated with additional signs (right lower quadrant tenderness, elevated temperature, rebound tenderness), symptoms (migration of pain, vomiting) and other laboratory tests (leukocytosis, C-reactive protein). Additional multi-center, prospective studies are needed involving a larger sample size to confirm the results of this study.

COMMENTS

Background
The diagnosis of acute appendicitis (AA) can be difficult and confusing. While the diagnosis of AA is usually established clinically, the symptoms and findings may not always be typical. Rapid and accurate diagnosis is important because of potential complications. Novel methods that differentiate AA from non-specific abdominal pain and reduce the rate of negative appendectomy are needed. Such methods should be inexpensive and convenient, with results obtained in a short time. Therefore, recent studies have been investigating the diagnostic accuracy of inflammatory markers.

Research frontiers
Mean platelet volume (MPV) and platelet distribution width (PDW) are presented in the complete blood cell count, which is routinely used in emergency departments. They are the indicators of platelet activation.

Innovations and breakthroughs
There are very few studies investigating the diagnostic accuracy of platelet function parameters in cases of AA. A diagnostic comparison of these blood values was conducted in this study. The most important parameter identified was PDW, followed by white blood cell count, neutrophil percentage and MPV. Among the laboratory evaluations for AA, PDW could be an important one, but it should always be in association with the signs (right lower quadrant tenderness, elevated temperature, rebound tenderness), symptoms (migration of pain, vomiting) and other laboratory tests (leukocytosis, C-reactive protein).

Applications
In the literature, there is no case-controlled study investigating MPV or PDW in cases with AA. This is the first study in the literature to investigate the diagnostic significance of platelet function parameters in AA.

Terminology
MPV and PDW are indicators of platelet activation and are inflammatory markers.

Peer-review
This manuscript is a well-designed, interesting, retrospective, case-controlled study. It defines a new parameter for diagnosis of AA, which is a universal problem. PDW can be an important test in the diagnosis of AA.

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