

RESEARCH ARTICLE

Mean platelet volume is a significant biomarker in the differential diagnosis of acute appendicitis

Recep Aktimur¹, Suleyman Cetinkunar², Kadir Yildirim³, Sabri Ozdas⁴, Sude Hatun Aktimur⁵, Ali Kagan Gokakin⁶

¹Samsun International Medicana Hospital, Department of General Surgery, Samsun, Turkey

²Adana Numune Training and Research Hospital, Department of General Surgery, Adana, Turkey

³Samsun Training and Research Hospital, Department of General Surgery, Samsun, Turkey

⁴Adiyaman Training and Research Hospital, Department of General Surgery, Adiyaman, Turkey

⁵Ondokuz Mayıs University, Faculty of Medicine, Department of Internal Medicine, Hematology, Samsun, Turkey

⁶Denizli Pamukkale University, Faculty of Medicine, Department of General Surgery, Denizli, Turkey

Correspondence: Recep Aktimur

E-mail: recepaktimur@gmail.com

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In order to reduce negative appendectomy (NA) rate, red cell distribution width (RDW), neutrophil-to-lymphocyte ratio (NLR) and mean platelet volume (MPV) were investigated. But, their combined role on the differential diagnosis of acute appendicitis (AA) with a control group of NA have not been established. A total of 530 patients who underwent appendectomy with the pre-diagnosis of AA were retrospectively analyzed and divided into two groups: 1) 469 AA, and 2) 61 NA. Diagnostic value of statistically significant parameters, white blood cell (WBC) and MPV were analyzed with ROC analysis. Median WBC and mean MPV values were found to be significantly higher in AA group (12.9 / μ L, range: 3.4-83.7 vs. 11 / μ L, range: 3.4-39.9; and 9.6 \pm 1.5 fL vs. 9.1 \pm 1.5 fL) ($P=0.002$ and 0.018). Mean RDW and median NLR were found to be similar. Combined sensitivity, specificity, positive predictive value and negative predictive value of WBC and MPV for recommended cut-off values were 67.4%, 72.7%, 96.1% and 17.9%, respectively. Among other inflammation related CBC parameters, increased MPV and its combination with WBC may be used as a valuable tool for the differential diagnosis of AA.

Keywords: Mean platelet volume; MPV; red cell distribution width; RDW; neutrophil-to-lymphocyte ratio; NLR; acute appendicitis; diagnosis; differential diagnosis

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Introduction

Acute appendicitis (AA) is one of the most common causes of acute abdomen, with nearly 7% lifetime occurrence [1], and 5% to 42% negative appendectomy (histopathologically normal appendix in pathological specimen) rates [2-4]. Timely diagnosis is crucial since diagnostic delay is associated with increased risk of perforation and consequently potential peritonitis, sepsis and

death [3]. On the other hand, negative appendectomy is associated with unnecessary risks and costs [5].

Although advanced diagnostic tests and imaging modalities have been developed, false diagnosis rate is still high [6]. To reduce negative appendectomy rate, a variety of diagnostic markers have been studied including procalcitonin [7], lactoferrin [8], calprotectin [8], serum amyloid A [9], red cell distribution width (RDW) [10], neutrophil-to-lymphocyte ratio (NLR) [11] and mean platelet volume (MPV) [12].

Table 1. Demographic characteristics and WBC, RDW, NLR and MPV values of the groups

| | AA group (n=469) | NA group (n=61) | P values |
|---------------------------|------------------|-----------------|----------|
| Age, (years) mean±SD | 29 (16-86) | 26 (16-73) | 0.381 |
| Gender, n(%) | | | 0.562 |
| Male | 272 (58) | 33 (54.1) | |
| Female | 197 (42) | 28 (45.9) | |
| WBC (/μL), median (range) | 12.9 (3.4-83.7) | 11 (3.4-39.9) | 0.002 |
| RDW (%) mean±SD | 12.3±1 | 12.2±1.2 | 0.292 |
| NLR median (range) | 4.8 (0.7-52.4) | 3.9 (0.5-30.1) | 0.058 |
| MPV (fL) mean±SD | 9.6±1.5 | 9.1±1.5 | 0.018 |

AA: Acute apendicitis, NA: Normal appendix, WBC: White blood cells, RDW: Red cell distribution width, NLR: Neutrophil-to-lymphocyte ratio, MPV: Mean platelet volume

Table 2. The diagnostic value of the recommended cutoff values of WBC and MPV in the diagnosis of AA and area under the curve

| Recommended cutoff values | Sensitivity (%) | Specificity (%) | AUC | 95% CI | P values |
|---------------------------|-----------------|-----------------|-------|-------------|----------|
| WBC value (/μL) = 12.1 | 57.4 | 60.7 | 0.619 | 0.548-0.690 | 0.002 |
| MPV (fL) = 9.6 | 57.1 | 60.7 | 0.595 | 0.523-0.667 | 0.016 |

WBC: White blood cells, MPV: Mean platelet volume, AA: Acute appendicitis, AUC: Area under the curve, CI: Confidence interval

The diagnostic role of RDW, NLR and MPV in AA, which have been suggested as a predictor of inflammation, were investigated separately or with different combinations [12-17]. However, their roles in the differential diagnosis of AA with a control group of normal appendix (NA) have not been established yet. To our knowledge, this is the first study to investigate the predictive power of RDW, NLR and MPV in the differential diagnosis of AA.

Material and Methods

Patient selection

The study was approved by the local ethics committee. Between January 2009 and March 2014, a total of 530 patients who underwent open or laparoscopic appendectomy with the pre-diagnosis of AA in two institutions were retrospectively analyzed. Patients who were younger than 15 years old, pregnant women, patients with perforated appendicitis and patients with appendix malignancies were excluded. According to histopathological assessment of the specimens, two groups were designed: the patients who have histopathologically confirmed diagnosis of acute appendicitis (AA group), and those with histopathological diagnosis of normal appendix (NA group).

The results of CBCs on admission were obtained from patient records. In addition to the demographic characteristics, WBC count, RDW, NLR and MPV values were recorded in all patients. The normal reference range for RDW and MPV values in our institution are: 11.7-14.6% and 6.5-11.6 fL, respectively.

Outcome variables of the study were determined as diagnostic accuracy of WBC, RDW, NLR and MPV and their combined role in the differential diagnosis of AA.

Statistical Analysis

Normally distributed continuous data were presented as mean ± standard deviation (SD) and not-normally distributed continuous data were presented as median and the range (minimum-maximum). Normally distributed continuous data were assessed with Student *t*-test. If the data were not normally distributed, continuous data were assessed with Mann-Whitney *U* test. The Chi square test and Fisher's exact test were used to compare categorical variables. WBC and MPV were found to be statistically different between groups, and they were analyzed for their diagnostic value in acute appendicitis with using ROC analysis. Recommended cut-off value of the parameters were determined for optimum sensitivity and specificity ratios of the diagnostic tests. And positive and negative predictive value (PPV and NPV) were calculated using recommended cut-off values. A two-tailed *P* value <0.05 was considered statistically significant. Statistical analyses were performed with the SPSS, version 16.00 (Chicago, IL, USA).

Results

A total of 530 patients who underwent open or laparoscopic appendectomies with a pre-diagnosis of AA were included the study. There were 469 (88.4%) patients in AA group and 61 (11.6%) patients in NA group. The median age and the gender distribution of the groups were similar. Demographic characteristics and WBC, RDW, NLR and MPV values of the groups were presented in Table 1.

The median WBC and the mean MPV values were found to be significantly higher in AA group. The differences in mean RDW and the median NLR were found to be non-significant between the groups (Table 1).

The cut-off values of WBC and MPV for the diagnosis of AA were determined using receiver operating characteristic (ROC) analysis. At each value, the sensitivity and specificity for each outcome under study were plotted. Recommended cut-off value of the parameters were determined for optimum sensitivity and specificity ratios of the diagnostic tests. The diagnostic value of the recommended cut-off values of WBC and MPV and area under the curve were presented in Table II. ROC curves of WBC and MPV were shown in Figure 1.

Combined sensitivity, specificity, positive predictive value and negative predictive value of WBC and MPV for recommended cut-off values were 67.4%, 72.7%, 96.1% and 17.9%, respectively.

A multivariate logistic regression analysis was used to assess the association between age, gender, WBC, RDW, NLR and MPV values and AA. Only MPV was found to be independently associated with AA: odds ratio (OR) and 95% CI were; 0.815 (0.685-0.970), $P=0.021$.

Discussion

In spite of the common occurrence of the disease, advanced diagnostic tests, and imaging modalities, negative appendectomy rates are still high [2-4]. Although, a lot of biomarkers have been suggested in the diagnosis of AA, most of them are expensive and unavailable in most of the emergency departments [7-9]. Therefore, as a cheap and commonly available diagnostic marker, inflammation-related CBC parameters have been used. The alteration in RDW was reported in various conditions. Despite the unknown pathophysiologic routes, RDW was found to be associated with unfavorable clinical outcomes and even mortality in chronic and acute inflammatory or infectious diseases [18-19]. NLR was suggested as a predictor of inflammation, also it have been found useful in the diagnosis of acute appendicitis [14]. Detected value of MPV has been shown to be affected in many inflammatory disorders and it was shown that it could be used as a diagnostic marker for acute appendicitis [13, 20]. In addition to traditionally used WBC, up to date, RDW, NLR and MPV have been studied separately or with different combination in the diagnosis of AA. But their roles in the differential diagnosis of AA with a control group of NA have not been established before.

This study demonstrates a diagnostic value of MPV in the differential diagnosis of AA. It was also found to have higher

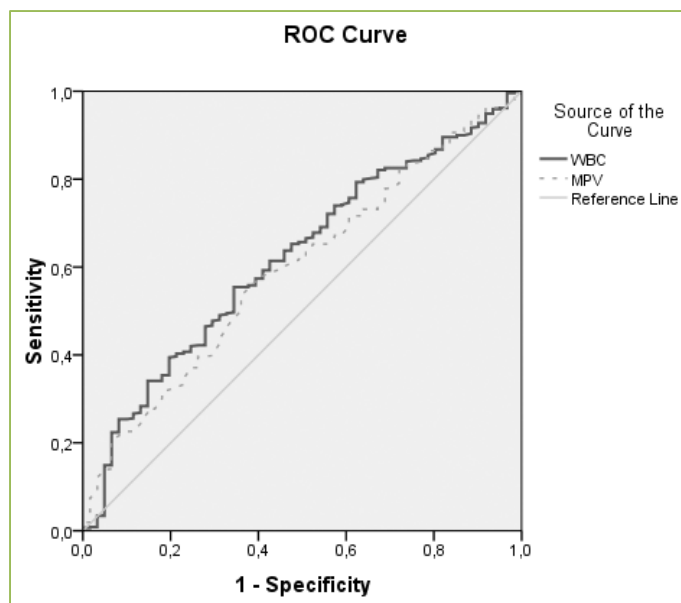


Figure 1. ROC curves of WBC and MPV

sensitivity and specificity ratios in its combined use with WBC. WBC count is one of the most commonly used first-line diagnostic tool for AA [21, 22]. Although the sensitivity of WBC in the diagnosis of AA are high, generally considered as an insufficient tool for the differential diagnosis due to lower specificity [23-26]. In AA group we found significantly higher WBC and MPV values. For recommended cut-off value of $12.1/\mu\text{L}$, we have calculated 57.4% sensitivity and 60.7% specificity with WBC. On the other hand, other inflammation-related CBC parameters have failed to show any diagnostic value but MPV. Platelet activation is reflected from the diseases which were prone to thrombosis and inflammation [27-30]. Previous studies have shown that, MPV values increases in cardio- and cerebrovascular disorders and low-grade inflammatory conditions which are prone to thrombosis [27, 29]. On the contrary, in high-grade inflammatory diseases including rheumatoid arthritis (RA) [30] and Crohn's disease (CD) [28] lower MPV values are present. Also, subsequent MPV increase is detected in the stable phase of chronic obstructive pulmonary disease (COPD), according to decreased level in acute exacerbation [31]. Tanrikulu *et al.* [17] demonstrated increased WBC and decreased MPV in AA patients. Albayrak *et al.* [12] and Bilici *et al.* [13] showed lower MPV values in AA patients with the comparison of healthy adults and pediatric individuals. On the other hand, Uyanık *et al.* [32] reported no statistically significant difference in MPV between AA and control group of healthy children. They commented that this difference could have resulted from a possible statistical error, due to frequent occurrence of clinically occult inflammation in pediatric age group. To the best of our knowledge, increase in MPV in AA were reported

in only one study conducted by Narci *et al.* [33]. They suggested that higher MPV values might guide the diagnosis of acute appendicitis, with 66% sensitivity and 51% specificity. In the present study, we have found higher MPV values in AA group, for recommended cut-off value of 9.6 fL, the sensitivity and the specificity for MPV were calculated as 57.1% and 60.7%. Although, calculated diagnostic value of WBC and MPV were lower, combined sensitivity and specificity for recommended cut-off values were found to be relatively superior; 67.4% and 72.7%.

Assessing the diagnostic role of a biomarker in AA and comparing it with healthy individuals are associated with serious limitations because of the major diagnostic challenge is whether or not to perform an emergent surgery. All of these studies were compared healthy individuals with AA patients. In a study of Narci *et al.* [33], which have the biggest sample size (503 AA and 121 healthy individual), higher MPV values were reported in AA patients. In the present study, we aimed to overcome this potential bias in control group selection, therefore compared AA (n=469) with NA (n=61) and to assess all inflammation-related parameters of CBC.

Narci *et al.* [10] reported WBC increase and RDW decrease in AA patients when they compared AA patients with the control group of healthy adults. In the comparison of AA and NA patients, Kahramanca *et al.* [15] demonstrated higher NLR values in AA patients, but they did not reported other relevant CBC parameters. NLR was suggested as a valuable predictor of gangrenous appendicitis in patients undergoing surgery for AA [11]. However, we have not found any significant diagnostic value of RDW and NLR, similar with the study of Tanrikulu *et al.* [17] which showed no difference in RDW in the diagnosis of AA.

As a result of our study, among other inflammatory related CBC parameters, increased MPV values may be used as a valuable diagnostic tool, and its combination with increased WBC may help clinicians in the differential diagnosis of AA.

Conflict of interest

The authors declare that there are no financial and non-financial conflicts of interest.

Author contributions

RA and SC were contributed the conception and design, analysis and interpretation of data and drafted the article KY, SO, AKG and SA were contributed the acquisition of data and analysis and interpretation of data. RA, SC, KY, SO, AKG and SA revised the article critically for important

intellectual content and gave final approval of the version to be published. All authors read and approved the final manuscript.

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