Original Article

Evaluation of the Performance of Simple Laboratory Parameters used in the Diagnosis of Acute Appendicitis

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Abstract

Background: Acute appendicitis (AA) is one of the most common emergency surgery. **Aim:** To evaluate the performance of laboratory parameters used in the diagnosis of AA. **Subjects and Methods:** There were two groups. In both groups, leukocyte (WBC), neutrophil, lymphocyte count, neutrophil/lymphocyte ratio (NLR), mean platelet volume (MPV), red cell distribution width (RDW), and platelet distribution width (PDW) values were examined in complete blood count (CBC). In addition, serum bilirubin (total bilirubin and direct bilirubin) values were examined. All laboratory parameters studied were compared to evaluate their diagnostic performance. **Results:** A total of 128 people were in the AA group and 122 people were in the healthy group (control). WBC count, neutrophil count, NLR, total bilirubin, direct bilirubin, and PDW values were significantly higher in the AA group than in the control group (*P* value <0.05). Lymphocyte counts and MPV values in the AA group were significantly lower than in the control group (*P* value <0.05). The sensitivity and selectivity of the WBC and neutrophil counts in AA were 95.13%, 89.34%, 94.53%, and 93.44%, respectively. The sensitivity and selectivity of the total bilirubin values were 59.38% and 73.77%, respectively. Area under the ROC curve (AUC) values within 95% confidence interval were over 0.900 for neutrophil count, WBC count, direct bilirubin, NLR, and PDW values. AUC values for total bilirubin, lymphocyte count, RDW, and MPV values were below 0.700. **Conclusions:** Diagnostic performances of the laboratory parameters were determined as follows: neutrophil count > WBC count > direct bilirubin = NLR = PDW > total bilirubin = lymphocyte count = RDW = MPV.

Keywords: *Acute appendicitis, leukocyte, neutrophil, total bilirubin, sensitivity, specificity*

Introduction

Acute appendicitis (AA) is one of the most common emergency surgeries in the abdomen, and its lifetime risk is approximately 7%.[1]

AA affects 1.5–1.9 individuals in a population of 100,000, and its perforation rates are between 17 and 20%.[2] The mortality risk of this condition is less than 1% in the general population but can rise to 50% among the elderly population.[3]

Diagnosing AA is a challenging task because many clinicians rely on the signs and symptoms presented by the patient. In appendectomies performed to reduce morbidity and mortality due to appendicitis perforation, the rate of negative laparotomy is globally between 15 and 30%.[4] Negative appendectomy rates can be reduced with accurate and rapid diagnosis. In the diagnosis of AA, physical examination and laboratory tests, scoring systems (Alvarado and Raja Isteri

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Pengiran Anak Saleha Appendicitis (RIPASA) score), and imaging methods (ultrasonography and computed tomography) are used. In particular, radiological examinations are widely and successfully used in the diagnosis of AA; however, sufficient equipment and experienced radiologists are required for this. This increases diagnostic costs and affects the diagnostic process. Surgeons have sought simpler and more accurate methods to reach a definitive diagnosis in a short time and at low cost.[2]

In recent years, easy-to-access, cheap, high-accuracy, and reliable laboratory parameters have been investigated in the diagnosis of AA. A complete blood count (CBC) is one of the first laboratory tests to diagnose AA. Some simple and routine preoperative tests, such as leukocyte (WBC) count, neutrophil percentage, neutrophil/ratio (NLR), mean platelet volume (MPV), red cell distribution width (RDW), platelet distribution width (PDW), and serum bilirubin, were used in the diagnosis of AA. Many studies have been performed on these laboratory parameters used in the diagnosis of AA, and the performances of some parameters have been compared.[4-8]

We planned this study to compare the performances of many laboratory parameters used recently to reach diagnosis in patients with AA.

Subjects and Methods

Our prospective study was initiated after obtaining ethics approval (protocol code no: 2018-80). The procedures followed in this study complied with the ethical standards of the committee responsible for human experiments and the 1975 Declaration of Helsinki as revised in 2000. Power analysis was performed to increase the effectiveness of the study and to find a sufficient number of patients. The study was started in February 2018 and was completed in January 2019. Two groups were formed: the patient group (AA group) and the control group.

The AA group consisted of patients with AA (simple appendicitis).

Patients who are given medical treatment and have complicated (gangrenous and perforated appendicitis, and periappendicular abscess) appendicitis and tumors were not included in this group.

People who applied to the outpatient clinic for different reasons other than acute abdomen were included in the control group. The participants in the control group did not have infections, blood, liver–biliary tract diseases, and malignant diseases.

Blood samples were taken from both groups for CBC and serum bilirubin. WBC count, neutrophil count, lymphocyte count, NLR, MPV, RDW, and PDW values were examined in CBC. In addition, serum bilirubin (total bilirubin and direct bilirubin) values were examined.

The demographic status and blood test results of the participants were recorded. The blood parameters of the two groups were compared. In addition, these parameters were compared among themselves to evaluate their diagnostic performance in AA disease.

Statistical method

Laboratory values of the patient group and the control group were statistically analyzed, and a P value <0.05 was considered significant in the analyses. Receiver operating characteristic (ROC) curve analysis was used to determine the diagnostic performance of laboratory measurements. Sensitivity, selectivity, and area under the ROC curve for the best cut points determined for each variable were obtained. To determine the performance differences among laboratory measurements, Z-test and AUC comparison were performed. IBM SPSS Statistics 22.0 for the Windows package program was used for statistical analysis. In the analysis, the level of significance was accepted as P value <0.05.

Results

During the study, 164 patients were hospitalized with a preliminary diagnosis of AA. Nonoperative treatment was applied to six of these patients, and surgical treatment was applied to 158 of them. Complicated appendicitis was found in 29 patients, and a mass in the caecum was also detected in one patient. One hundred and twenty-eight patients with simple appendicitis who met the criteria of our study constituted the AA group. One hundred twenty-two participants who applied to outpatient clinics for different reasons and met the criteria were also included in the control group. There were 89 men and 39 women in the AA group and 38 men and 84 women in the control group. The mean age of the AA group was 31 years (age range 16–60) and that of the control group was 36 years (age range 18–67). Mean WBC count, neutrophil count, NLR, total bilirubin, direct bilirubin, and PDW values were significantly higher in the AA group than in the control group (P value < 0.05). Lymphocyte counts and MPV values in the AA group were significantly lower than in the control group (P value < 0.05). There was no significant difference between the groups in terms of mean RDW values (P value > 0.05) [Table 1].

In univariate analysis, there was a significant difference between the AA group and the control

group in terms of WBC, neutrophil and lymphocyte counts, NLR, total bilirubin, direct bilirubin, MPV, and PDW values (P value < 0.05) [Table 1]. The comparison between AA and control groups is detailed in Table 1.

The values of cutoff, sensitivity, selectivity, and performance characteristics of the parameters used in the diagnosis of AA are given in Table 2.

ROC curve analysis was used to determine the diagnostic performance of laboratory parameters. In the ROC curve analysis of these independent variables, AUC values within 95% confidence interval were over 0.900 for neutrophil count, WBC count, direct bilirubin NLR, and PDW values [Table 2]. AUC values for total bilirubin, lymphocyte count, RDW, and MPV values were below 0.700 [Table 2].

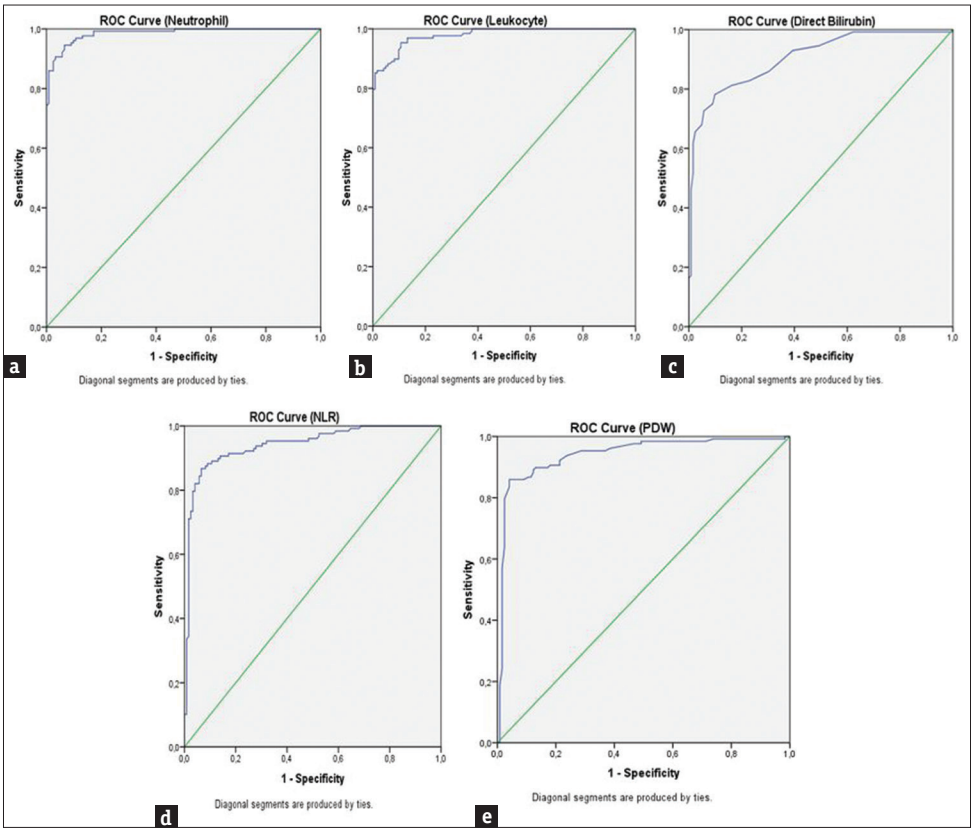

Figure 1: (a) ROC curve of neutrophil count. (b) ROC curve of WBC (leukocyte) count. (c) ROC curve of direct bilirubin. (d) ROC curve of NLR. (e) ROC curve of PDW

Table 1: Comparison of acute appendicitis (AA) and control groups

Variables	AA group	Control group	*P*	Univariate OR (95% CI)	OR, *P*
Age (year)	31 (16–60)	36 (18–67)			
Gender					
Male	89 (% 69.5)	38 (% 31.1)			
Female	39 (% 30.5)	84 (% 68.9)			
WBC (×10³/mm³)	14,7 (7.6–24.3)	7.05 (4.2–11.05)	<0.001	4.036 (2.630–6.195)	<0.001
Neutrophil (×10³/mm³)	11.98 (4.06–22.72)	3.91 (2.02–8.95)	<0.001	4.715 (2.883–7.711)	<0.001
Lymphocyte (×10³/mm³)	1.825 (0.38–5.21)	2.285 (0.42–2.52)	<0.001	0.597 (0.421–0.846)	0.004
NLR	6.155 (1.5–55.13)	1.815 (0.87–15.7)	<0.001	3.020 (2.229–4.091)	<0.001
Total bilirubin (mg/dL)	0.715 (0.16–3.41)	0.5 (0.17–1.2)	<0.001	10.148 (3.959–26.016)	<0.001
*Direct bilirubin (mg/dL)	0.26 (0.01–0.92)	0.1 (0.05–0.45)	<0.001	11.770 (6.091–22.743)	<0.001
MPV (fL)	9.55 (6.95–12.8)	9.7 (8–13.1)	0.004	0.693 (0.538–0.892)	0.004
PDW (%)	15.9 (9–17.6)	11.5 (8.8–20.2)	<0.001	2.834 (2.280–3.522)	<0.001
RDW (%)	13 (11.9–18.2)	13.35 (11–16.9)	0.010	0.848 (0.667–1.079)	0.180

*Only for direct bilirubin, odds ratio is given for 0.1 unit increment, OR: odds ratio, CI: confidence interval, WBC: white blood cell, NLR: neutrophil-to-lymphocyte ratio, MPV: mean platelet volume, PDW: platelet distribution width, RDW: red blood cell distribution width

Table 2: Diagnostic performance of laboratory parameters

Variables	Cutoff value	Sensitivity (%)	Specificity (%)	AUC (95% CI)	AUC, *P*
WBC count (×10³/mm³)	>9.26	95.13	89.34	0.979 (0.953–0.993)	<0.001
Neutrophil count (×10³/mm³)	>6.15	94.53	93.44	0.986 (0.962–0.996)	<0.001
Lymphocyte count (×10³/mm³)	≤1.79	49.22	78.69	0.635 (0.572–0.695)	<0.001
NLR	>2.93	86.72	93.44	0.942 (0.905–0.968)	<0.001
Total bilirubin (mg/dL)	>0.63	59.38	73.77	0.671 (0.609–0.728)	<0.001
Direct bilirubin (mg/dL)	>0.16	78.12	90.16	0.906 (0.862–0.939)	<0.001
MPV (fL)	≤9	40.63	86.89	0.606 (0.542–0.667)	0.004
PDW (%)	>15.1	85.94	95.90	0.941 (0.904–0.967)	<0.001
RDW (%)	≤13.4	75.00	45.08	0.594 (0.531–0.656)	0.009

AUC: area under the ROC curve, CI: confidence interval, WBC: white blood cell, NLR: neutrophil-to-lymphocyte ratio, MPV: mean platelet volume, PDW : platelet distribution width, RDW: red blood cell distribution width

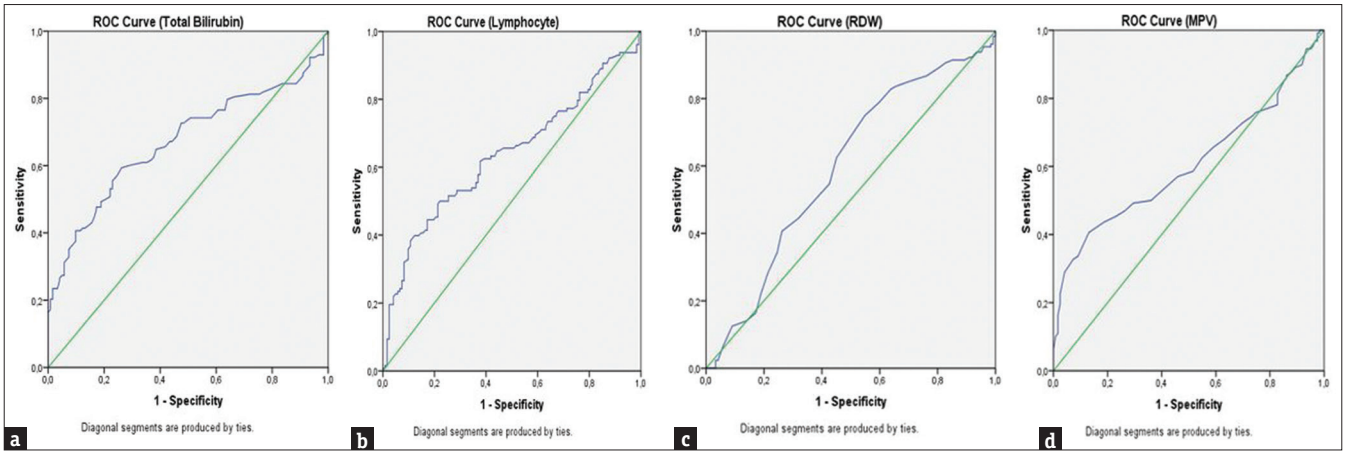

Figure 2: (a) ROC curve of direct bilirubin. (b) ROC curve of lymphocyte count. (c) ROC curve of RDW. (d) ROC curve of MPV

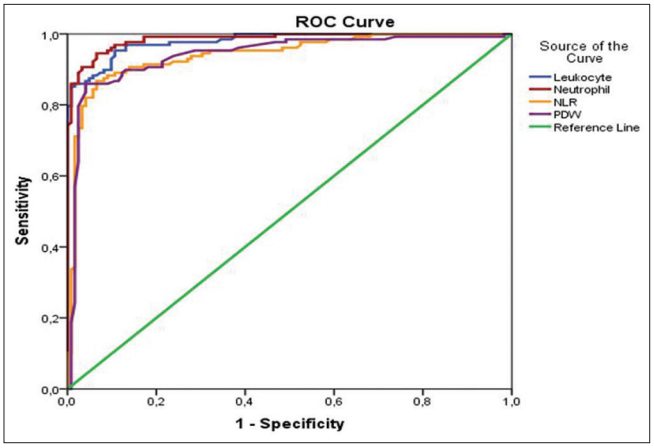

Figure 3: Comparison of ROC curves of neutrophil, WBC (leukocyte), NLR, and PDW values

ROC curves of neutrophil count, WBC count, direct bilirubin, NLR, and PDW are given in Figure 1a-e, respectively. In addition, ROC curves of total bilirubin, lymphocyte count, RDW, and MPV are given in Figure 2a-d, respectively.

The areas under the ROC curve are compared; while there was no difference among total bilirubin, lymphocyte count, RDW, and MPV (P value > 0.05), their performance was found to be low compared with other parameters (P value < 0.05). In field comparisons made under the curve among other parameters with high diagnostic performance, the performance of neutrophil count was found higher than all other parameters. The second best diagnostic parameter was determined as the WBC count. In the third row, direct bilirubin, NLR, and PDW values were next. The parameters with the lowest diagnostic performance were total bilirubin, lymphocyte count, RDW, and MPV values, respectively.

In Figure 3, ROC curves of WBC (Leukocyte) count, neutrophil count, NLR and PDW values are compared. While there was no difference between NLR and PDW values, they were found to have lower performance than neutrophil and WBC count.

The diagnostic performance of the laboratory parameters used in the diagnosis of AA was determined as follows: neutrophil count > WBC count > direct bilirubin = NLR = PDW > total bilirubin = lymphocyte count = RDW = MPV.

Discussion

AA is a disease caused by inflammation of the vermiform appendix. AA is one of the most common causes of acute abdomen and is more common in males and the young population. The lifetime risk of developing AA is 8.6% in males and 6.7% in females.[9] In a study, it was reported that 71.4% of the patients with AA were males and 28.62% were female.[1] Consistent with the literature, in our study, the ratio of males was higher in the AA group.

It is necessary to be meticulous in the diagnosis of acute abdominal pain, to reduce the incidence of negative appendectomy and complicated appendicitis. Many diagnostic methods are used in the diagnosis of AA. The effectiveness, time efficiency, and cost of these methods are very important. For example, imaging methods used in the diagnosis of AA are not easily accessible because most of them are expensive or are not available in small hospitals. Therefore, many studies have been carried out by researchers to find a simple laboratory parameter with high accuracy and efficiency and low cost in the diagnosis of AA.[2]

Acar *et al*.[10] reported that the mean WBC count, neutrophil count, and NLR in AA increased significantly, lymphocyte count decreased significantly, RDW increased insignificantly, and PDW and MPV decreased insignificantly. In the other study, in univariate analyses, WBC, MPV, serum bilirubin, and NLR values were found to be significantly different between the appendicitis and control groups. In the same study, the mean WBC count, NLR, and bilirubin values in AA increased significantly and MPV values decreased significantly.[2] In the literature, while MPV values decreased significantly in AA, bilirubin values increased.[11,12] In our study, WBC count, neutrophil count, NLR, total bilirubin, direct bilirubin, and PDW values were significantly higher in the AA group than in the control group (P value < 0.001). Lymphocyte count, MPV, and RDW values were significantly lower in the AA group than in the control group (P value < 0.05).

Moderate leukocytosis is an expected laboratory finding in AA cases.[13] Sevinc *et al*.[2] found WBC cutoff value as 11900/mm^3, sensitivity as 71%, and specificity as 68%. Rafiq *et al*.[3] found sensitivity as 87% and specificity as 92%. In our study, the WBC count increased significantly in the AA group. We found the cutoff value, sensitivity, and specificity of the WBC count as >9.26 × 10^3/mm^3, 95.13%, and 89.34%, respectively. As can be seen, the sensitivity of the WBC count in our study in AA was found to be quite higher than the studies in the literature. The sensitivity and specificity values of the WBC count we obtained show that it is an effective parameter in the diagnosis of AA.

Neutrophil values also increase in AA cases. The sensitivity of elevated neutrophil count in AA has been shown to be 60–87% in previous studies.[14] In the study of Acar *et al*.,[10] the neutrophil cutoff value in AA was 7.050, sensitivity was 80.9%, and specificity was 85.3%. In our study, neutrophil levels increased significantly in the AA group and our cutoff value was >6.15 × 10^3/mm^3. We found that the sensitivity (94.53%) and specificity (93.44%) of the neutrophil count in the AA group were higher than the values in the literature. Based on this finding, we can state that the neutrophil count is a very effective blood parameter in the diagnosis of AA.

Pehlivanli *et al*.[15] reported that lymphocyte count values were significantly lower in both the AA group and perforated appendicitis group compared with the control group (normal appendix) (P <0.001). In parallel with the literature, we observed that lymphocyte counts were significantly lower in the AA group.

The effectiveness of NLR in the diagnosis of AA in the preoperative period has been investigated in many studies. In one study, the median value, sensitivity, and specificity of NLR in AA were found to be 5.25, 75.23%, and 68.70%, respectively. In the same study, the cutoff value of the NLR and the AUC value in the 95% confidence interval were found to be ≥3.1 and 0.76, respectively.[16] Ahmed *et al*.[17] reported that, in diagnosing AA, the cutoff value of the NLR was 4.2, while the sensitivity, specificity, positive predictive value, and negative predictive value were 79.5%, 67.0%, 89.8%, and 47.5%, respectively. In this study, the cutoff value of NLR (>2.93) was found to be lower, and the sensitivity (86.72%), specificity (93.44%), and AUC value (0.942) were found to be higher than in the above studies.

Nevler *et al*.[18] reported that serum bilirubin levels, alone or combined with other markers, may be considered as a clinical marker for AA correlating with disease existence, severity, and length of hospital stay. In the study of Ambre *et al*.,[12] bilirubin values were reported to provide the highest diagnostic accuracy for AA cases. Besides, Kanlioz *et al*.[19] reported that direct bilirubin increased more than total bilirubin in perforated appendicitis. In the study by Zosimas *et al*.,[20] total serum bilirubin was found to have specificity (0.88), sensitivity (0.26), and diagnostic accuracy (0.40) for AA. In another study, the sensitivity of serum bilirubin levels was 84.1% and specificity was 83.3% in the diagnosis of AA.[21] Our total bilirubin

specificity (73.77%) was lower than the literature values. While the sensitivity value of total bilirubin (59.38%) was between the values quoted in the literature, the AUC value (0.671) was higher. In the diagnosis of AA, sensitivity (78.12%), specificity (90.16%), and AUC values (0.906) of direct bilirubin were found to be higher than values of total bilirubin. We found that the direct bilirubin level, which supports the severity of appendicitis disease, the presence of complicated appendicitis, and the length of hospital stay, is a more valuable laboratory parameter than serum total bilirubin value in the diagnosis of AA.

MPV is a parameter that shows platelet production and function, and it is also stated to reflect inflammation. Considering that an inflammatory condition can change the MPV value, MPV is thought to be used for the diagnosis of AA as a biomarker.[22] In the meta-analysis by Tullavardhana *et al*.,[23] MPV was found to be significantly lower in the AA group compared with the control group, and it was stated that a lower MVP value could be used as a marker in the diagnosis of AA. Likewise, in another study, a statistically significant decrease was noted in MPV values in AA patients compared with controls (P value <0.01). The best MPV cutoff value for AA was 7.6 fL, and sensitivity, specificity, positive predictive value, and negative predictive values were 73%, 84%, 84%, and 74%, respectively.[24] In this study, MPV values were significantly lower in the AA group compared with the control group. We found MPV cutoff value (≤9 fL) and specificity (86.89%) higher than the literature data and lower sensitivity (40.63%). The cutoff and sensitivity data of MPV we obtained are seen as contrary to the literature data given above. These results regarding MPV in our study support that the MPV is not an effective parameter in the diagnosis of AA. What is the probable reason?

PDW and MPV are platelet-derived parameters found in CBC. The reduction in MPV and PDW parameters can be used to show the burden of inflammation and disease severity in various diseases.[25] Dinç *et al*.[26] stated that PDW analysis can be used in the diagnosis of AA without requiring additional tests, thus reducing cost and time loss. They reported the PDW cutoff value as 32.15%, sensitivity as 97.1%, specificity as 93%, and average AUC value as 0.95. PDW values increased significantly in the AA group in this study. Our data, such as PDW cutoff value (>15.1%), sensitivity (85.94%), and AUC value (0.941), were lower than the literature data, and specificity (95.90) was higher. Contrary to the study of Dinç *et al*.[26] and our study, Espinosa-Campos *et al*.[27] reported that there was no difference between the PDW values of patients with AA and healthy patients. However, based on our findings, we think that PDW is a parameter that can be used in the diagnosis of AA.

RDW is a measure of red blood cell size variability. In the literature, it is mentioned that RDW can be used in the diagnosis of many inflammatory diseases, including AA. Narci *et al*.[28] reported that RDW levels were significantly low in patients with AA compared with the control, even in the normal range. However, Tanrikulu *et al*.[29] and Aktimur *et al*.,[30] in AA, did not find a significant diagnostic value for RDW. We found that there was no significant difference between the AA group and the control group in terms of RDW. As in the study of Tanrıkulu and Aktimur, we found that RDW did not have a significant diagnostic value for AA. Boshnak *et al*.[31] stated that PDW, which increases with high WBC and neutrophil counts, can be used as diagnostic tests in AA cases, but MPV and RDW levels are not useful diagnostic markers. In another study, it was suggested that increased WBC count, neutrophil count, MPV, and NLR values might be helpful in the diagnosis of AA.[9] We observed that neutrophil and WBC count, direct bilirubin, NLR, and PDW are important parameters in the diagnosis of AA, while total bilirubin, lymphocyte count, MPV, and RDW are not useful parameters.

Conclusion

The parameter with the highest performance in the diagnosis of AA was determined as the neutrophil count. WBC count is in the second place; direct bilirubin, NLR, and PDW are in the third place; and total bilirubin, lymphocyte count, RDW, and MPV are in the fourth place.

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Conflicts of interest

There are no conflicts of interest.

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