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Research Article

# The Importance of Evaluating Hematologic Parameters in the Diagnosis of Acute Appendicitis Among Pregnant Patients

**Ilkay Guler,[1] Umit Ozdemir,[2] Bulent Comcali,[3] Izzet Ozgurluk,[4] Nurgul Balci[1]**

[1]Republic of Türkiye, Ministry of Health, General Directorate of Public Hospitals, Ankara, Türkiye
[2]Department of General Surgery, Ankara Etlik City Hospital, Ankara, Türkiye
[3]Department of General Surgery, Ankara Bilkent City Hospital, Ankara, Türkiye
[4]Department of Gynecology and Obstetrics, Ankara Etlik City Hospital, Ankara, Türkiye

## Abstract

**Objectives:** The most frequently occurring non-obstetric surgical issue during pregnancy is acute appendicitis (AA). The aim of this study was to examine the diagnostic accuracy of hematological parameters such as neutrophil-lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), red cell distribution width (RDW) and systemic inflammatory index (SII) in the diagnosis of AA among pregnant women.

**Methods:** In this retrospective study, patients were examined in two groups: 52 pregnant patients who underwent appendectomy (appendectomy group) and 156 healthy pregnant women (control group). The diagnostic accuracy of hematology parameters was evaluated by receiver operating characteristic (ROC) curve and logistic regression analysis.

**Results:** According to ROC analysis, the sensitivity and specificity values of WBC, NLR, PLR, RDW and SII were found as follows, respectively: 69.2%, 91.03%; 78.4%, 82.1%; 62.7%, 59.0%; 67.2%, 52.6%; 73.1%, 85.9%. According to the logistic regression model in AA cases in pregnant women, an accuracy rate of 87.9% was determined by using WBC, NLR, PLR and RDW and SII values.

**Conclusion:** Combined evaluation of easily accessible tests such as NLR, PLR, RDW, and SII together with physical examination, anamnesis and imaging methods is useful in the diagnosis of AA in pregnant women.

**Keywords:** Acute appendicitis, hematologic parameters, pregnancy

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Acute appendicitis (AA) is one of the surgical pathologies that can occur in any age group.[1,2] The most frequently occurring non-obstetric surgical issue during pregnancy is AA. It is seen in approximately 1 in 1000 to 1500 pregnancies and 40% in the second trimester.[3,4] In addition to symptoms such as nausea and vomiting associated with pregnancy, changes in anatomical and laboratory parameters cause difficulties in the diagnosis process of AA that may develop.

Upward migration of the appendix with the enlargement of the uterus during pregnancy makes it difficult to visualize with ultrasonography (US) due to changes in pain localization and anatomical changes when AA develops.[5] In laboratory evaluation, there is an increase in physiological leukocytosis and C-reactive Protein (CRP) in parallel with the progression of the gestational week, but as in many inflammatory conditions, acute phase reactants such as white blood cell (WBC) and CRP increase in AA.[6]

**Address for correspondence:** Ilkay Guler, MD. Türkiye Cumhuriyeti Sağlık Bakanlığı Kamu Hastaneleri Genel Müdürlüğü, Ankara, Türkiye
**Phone:** +90 532 216 50 38 **E-mail:** drilkayguler@gmail.com

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In the event of inflammation, the first cell group to increase among leukocytes is neutrophil, which plays an active role in the response to inflammation.[7] Platelets are important regulators of inflammation. Red cell distribution width (RDW) is a parameter that shows the distribution of erythrocyte size and provides information about the cause of anemia.[8] Due to these difficulties in diagnosing AA during pregnancy, additional parameters that can help the clinician are required. As inflammatory biomarkers, neutrophil-lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR) and Red cell distribution width (RDW) obtained from complete blood count are seen as important inflammatory parameters used in the diagnosis and follow-up of many diseases.[9] Another parameter used in the evaluation of systemic inflammation is the Systemic Inflammatory Index (SII), and it is also an important index used in the follow-up of many diseases.[10,11]

Considering that the delay in the diagnosis of AA may have a mortal course for both the fetus and the mother, the importance of correct diagnosis and timely intervention becomes even more evident. However, it is also important to avoid unnecessary or delayed surgery of AA in pregnant women. By making use of the hemogram examination, which is available in almost all health facilities, the study of parameters such as NLR, PLR, RDW and SII, which are emphasized in other inflammatory conditions, in pregnant appendicitis may contribute to facilitating the diagnosis. The aim of this study is to conduct research on the importance of parameters such as NLR, PLR, RDW and SII in the diagnosis of AA among pregnant patients.

## Methods

Between January 2018 and December 2022, 52 pregnant patients (appendectomy group) who underwent appendectomy in general surgery clinic and did not meet the exclusion criteria were included in the this cross-sectional and retrospective study. In the same period, 156 healthy pregnant women (control group) who did not meet the exclusion criteria for routine pregnancy follow-up to the obstetrics and gynecology outpatient clinic were included in the study. Pulmonary, renal, cardiac, chronic liver diseases, autoimmune diseases, infectious diseases, cancers and addictions were evaluated as exclusion criteria. Patients under the age of 18 and over the age of 45 and patients with missing data were also excluded from the study. Appendectomy was performed laparoscopically or openly with Mc-Burney incision under emergency conditions. Patients' age, gestational week and length of stay data were collected from the hospital information management system. Preoperative lymphocyte, neutrophil, platelet, WBC, RDW values were recorded. NLR calculated by dividing the neutrophil count by the lymphocyte count. PLR calculated by dividing the platelet count by the lymphocyte count. SII calculated by multiplying the neutrophil count by the platelet count and dividing the result by the lymphocyte count.

### Ethical Statement

This study was conducted in accordance with the principles of the Helsinki Declaration and all applicable national regulations and institutional policies. This study was reviewed and approved by Ankara Bilkent City Hospital Clinical Research Ethics Committee (ethics committee ruling number: E1/3493/2023, date: 26.04.2023). Due to the retrospective nature of the study, informed consent forms from patients were not required.

### Statistical Analysis

SPSS v. 25.0 software (SPSS Inc., Chicago, IL, USA) and MedCalc v. 20,218 (MedCalc Software, Ostend, Belgium) were utilized for statistical analysis. The numerical variables' distributions were assessed through visual methods (histogram and probability graphs) as well as analytical approaches (Kolmogorov-Smirnov/Shapiro-Wilk tests). Descriptive statistics included the mean±standard deviation (SD) or median, minimum-maximum (min-max) values for continuous variables, and the number of patients (n) and percentage (%) for categorical variables. Parametric methods, such as Student's t-test, were applied to normally distributed data, while non-parametric methods, like the Kruskal-Wallis test, were used for non-normally distributed data. The correlation between patient groups, categorized by cut-off values, was determined based on the variables. The accuracy of the classification was evaluated by examining sensitivity, specificity, and receiver operating characteristic (ROC) curve analysis. Additionally, a multivariate logistic regression analysis model was developed to identify the independent predictive impact of laboratory variables in the diagnosis of AA. A p-value of less than 0.05 was considered statistically significant. 95% confidence interval analysis of the data was performed.

## Results

Comparison of clinical features and laboratory values is shown in Table 1. There was no significant difference between the appendectomy group and the control group in terms of mean age (p=0.54). When the weeks of gestation were compared, the median of the appendectomy group was higher (p=0.004). The length of hospital stay data is only available in the appendectomy group, with a median length of stay of 1.00 days. The mean lymphocyte count in the appendectomy group was significantly lower than in

**Table 1.** Comparison of Patients' Clinical Features and Laboratory Values

| | Appendectomy group n=52 (%25) | Control group n=156 (%75) | p |
|---|---|---|---|
| Age[a] | 27.63±5.29 | 28.14±5.26 | 0.54 (-2.172 to 1.159)[b] |
| Gestation week[c] | 20.50 (2–37) | 12.00 (4–37) | 0.004 |
| Lenght of stay[c] | 1.00 (1-7) | | |
| Lymphocyte[a] | 1.58±0.54 | 1.80±0.53 | 0.013 (-0.385 to -0.045)[b] |
| Neutrophil[c] | 12.05 (4.39-26.16) | 5.85 (2.37–14.38) | <0.001 |
| platelet[c] | 254.50 (152.00–435.00) | 256.00 (151.00–503.00) | 0.917 |
| RDW[c] | 14.17 (12.30–21.40) | 13.90 (11.80–22.20) | 0.041 |
| WBC[c] | 13960,00 (6300–29180) | 8325 (3800–19680) | <0.001 |
| NLR | 7.54 (2.05–64.28) | 3.53 (1.44–14.88) | <0.001 |
| PLR[c] | 164.04 (73.98–1163.33) | 144.82 (66.49–400.00) | 0.009 |
| SII[c] | 1997.26 (495.47–5719.13) | 891.67 (354.44–3444.05) | <0.001 |

[a]mean±standart deviation; [b]95% confidence interval of difference; [c]median (min–max); RDW: red cell distribution width; WBC: white blood cell; NLR: neutrophil lymphocyte ratio; PLR: platelet lymphocyte ratio; SII: systemic inflammatory index.

the control group (p=0.013). The median neutrophil count and WBC value were significantly higher in the appendectomy group, p<0.001 and p<0.001, respectively. There was no difference between the groups in terms of median platelet values (p=0.917). The median RDW value was significantly higher in the appendectomy group (p=0.041). Median NLR and PLR values were significantly higher in the appendectomy group, p<0.001 and p=0.009, respectively. The median SII value was also significantly higher in the appendectomy group (p<0.001).

Cut-off values, sensitivity, specificity, accuracy rate and area under the curve were calculated in the analysis performed by drawing receiver operating characteristic (ROC) curves, and are shown in Table 2. According to ROC analysis, the sensitivity and specificity values of WBC, NLR, PLR, RDW and SII were found as follows, respectively: 69.2%, 91.03%; 78.4%, 82.1%; 62.7%, 59.0%; 67.2%, 52.6%; 73.1%, 85.9% (Fig. 1).

A logistic regression model was created with WBC, NLR, PLR, RDW and SII to search for independent predictors of AA in pregnant women (Table 3). The strength of the model (Nagelkerke $R^2$) is 55.8%. Using this cut-off value, acute appendicitis can be diagnosed in pregnant women with an accuracy rate of 87.9%. WBC and NLR were found to be independent predictors (p<0.001, odds ratio=6.509; p=0.004, odds ratio=4.739, respectively). Although RDW was not an independent predictive factor, it was found to have a high predictive power and increased the probability of AA diagnosis by 2.092 times (odds ratio) (p=0.110). At the same time, although there was no independent predictive factor in Level II, it was found that its predictive power was very high and it increased the probability of diagnosis of appendicitis by 3.692 times (odds ratio) (p=0.057). PLR is not an independent predictive factor in the diagnosis of appendicitis in pregnancy (p=0.616).

## Discussion

WBC, NLR, PLR, RDW and SII are used by many clinicians in practice as inflammation markers in the diagnosis and/or treatment process of many diseases. In this study, we observed that the increase in the values of WBC, NLR, and SII was significantly correlated with the appendectomy group when compared with the healthy pregnants.

**Table 2.** Sensitivity, Spesificity and Cut-off Values Based on the Area Under the Receiver Operating Curve

| | Cut-off value | p | AUC±SE | %95 Confidence interval of AUC | Sensitivity (%) | Spesificity (%) | Accuracy Rate |
|---|---|---|---|---|---|---|---|
| WBC | >11790 | <0.001 | 0.861±0.032 | 0.798 to 0. 0.924 | 69.2 | 91.03 | 0.855 |
| Neutrophil | >9.17 | <0.001 | 0.874±0.03 | 0.821 to 0.916 | 68.63 | 92.95 | 0.860 |
| NLR | >4.97 | <0.001 | 0.847±0.035 | 0.778 to 0.916 | 78.4 | 82.10 | 0.811 |
| PLR | >153.79 | 0.006 | 0.622±0.044 | 0.552 to 0.688 | 62.7 | 59.0 | 0.599 |
| RDW | >13.9 | 0.040 | 0.595±0.046 | 0.525 to 0.662 | 67.2 | 52.6 | 0.562 |
| SII | >1382.68 | <0.001 | 0.837±0.035 | 0.769 to 0.906 | 73.1 | 85.9 | 0.828 |

AUC: area under the curve; SE: standart error.

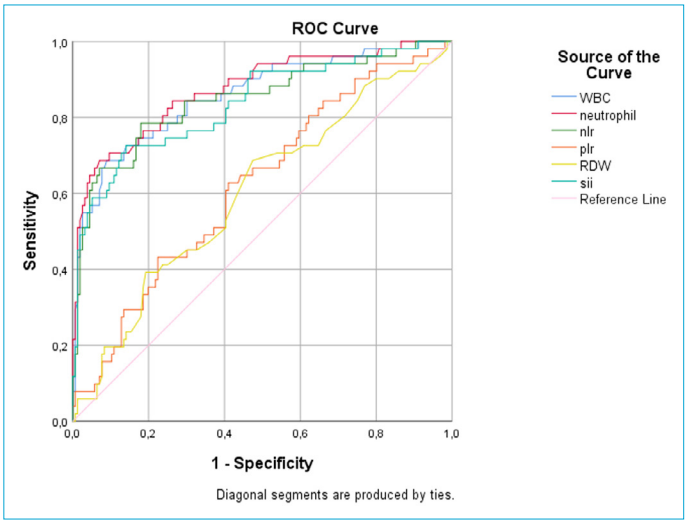


**Figure 1.** ROC Curve of the Parameters.

**Table 3.** Multipl Logistic Regression Analysis for İndependent Predictive Factors of Acute Appendicitis in Pregnant Women

| Variables | P | Odds ratio | 95% C.I. for Odds ratio |
|---|---|---|---|
| WBC | <0.001 | 6.509 | 2.361 to 17.942 |
| NLR | 0.004 | 4.739 | 1.627 to 13.802 |
| PLR | 0.616 | 0.728 | 0.210 to 2.525 |
| RDW | 0.110 | 2.092 | 0.845 to 5.175 |
| SII | 0.057 | 3.692 | 0.964 to 14.143 |
| Logistic regression analysis | <0.001 | Prediction: %87.9 | Nagelkerke $R^2$: 0.558 |

WBC: white blood cell; NLR: neutrophil lymphocyte ratio; PLR: platelet lymphocyte ratio; RDW: red cell distribution width; SII: systemic inflammatory index.

Physiological leukocytosis is present during pregnancy and peaks towards delivery.[6] Furthermore, including this study, many studies in the literature have demonstrated that an increase in leukocyte count is significant in diagnosing AA in pregnant patients.[10-12] However, WBC is not an appendicitis-specific parameter and is elevated in many inflammatory conditions.

Neutrophils and lymphocytes are important modulators of inflammation. Neutrophils increase in number in the early period and migrate to the site of inflammation. They activate mast cells, epithelial cells and macrophages and participate in the inflammatory response. The lymphocyte count, on the other hand, decreases in the early phase of inflammation, in contrast to the neutrophil count.[7] In previous studies, these two biomarkers were found to be useful in the diagnosis of pregnant AA in parallel with our study, but there are also contradictory opinions in a small number of studies.[12,13,15,16] There is increasing information that the ratio of these two biomarkers (NLR), which varies numerically in contrast to each other in the case of inflammation, is a stronger marker of inflammation.[17,18] The significance of NLR in diagnosing AA in pregnant patients was first demonstrated in the study by Yazar and colleagues, with 78.6% sensitivity and 80% specificity.[12,19] In our study, its contribution to the diagnosis is supported with 78.4% sensitivity and 82.10% specificity which is consistent with previous studies.

Platelets act as immunomodulators in inflammation. The mean platelet count may differ significantly in some inflammatory conditions. However, in cases where even the normal limits of laboratory markers change, as in AA pathologies in pregnant patients, its contribution to the diagnosis is limited, as demonstrated in our study.[12,16] Controversy continues regarding the contribution of platelet lymphocyte ratio (PLR) to the diagnosis of AA among pregnant patients.[12,15,16] In our study, it was significantly higher in the appendectomy group. There was a remarkable result of 62.7% sensitivity and 59.0% specificity in the ROC analysis.

RDW is a measure of the change in size of circulating erythrocytes and is included in the standard hemogram panel.[8] It has previously been shown to increase in pathological conditions such as inflammatory bowel disease, celiac disease, and coronary artery disease.[20] Therefore, it is reasonable to investigate it for the diagnosis of AA among pregnant patients. In terms of being a biomarker in the diagnosis of AA, there is no consensus in the literature and there are also opinions that it is not useful.[20,23] It has been shown to increase in pediatric appendicitis cases.[24] A limited number of studies in the literature have shown that RDW can be used for the diagnosis of AA in pregnant patients.[13,16,25] In our study, it was significantly higher in the appendectomy group.

SII is used as a new prognostic indicator because it is easily applicable in many acute and chronic inflammatory diseases.[26] It was used in the evaluation of pathologies such as placental anomalies, hyperemesis gravidarum, and peripartum cardiomyopathy during pregnancy and it was found to be significantly higher.[27-29] There is no study in the literature examining the relationship between SII and AA. In their study, Telaferli and colleagues found that the increase in SII level was more pronounced in patients with complicated AA than in patients with uncomplicated AA who were not pregnant.[30] In our study, SII was significantly higher in the appendectomy group.

Although the diagnostic value of RDW or SII is low in the case group where diagnostic tools such as AA in pregnant women are limited and complex, its use in combination with other laboratory tests and imaging methods contributes to a rapid and accurate diagnosis. As a matter of fact,

in our study, the accurate diagnosis was reached with a rate of 87.9% by using easily accessible biomarkers such as WBC, NLR, PLR, RDW, and SII together in the diagnosis of AA among pregnant patients.

Limitations of this study include its single-centered and retrospective design. These factors restrict the applicability of the results and enhance the likelihood of selection bias.

## Conclusion

Studies on inflammation markers in the literature have increased in recent years. This study is the first to evaluate the contribution of the combined use of NLR, PLR, RDW, and SII biomarkers to the correct diagnosis of AA among pregnant patients, whose information load on their importance in inflammation has recently increased. A good team with a multidisciplinary approach is needed, starting with the decision of surgery, which method will be used in the surgery and for follow-up afterward. It should also be kept in mind that the decisions to be taken to protect the life of the fetus should not put the mother's life at risk. In order to achieve this, the combined evaluation of easily accessible tests such as NLR, PLR, RDW and SII, together with history, physical examination and imaging methods, may contribute to the diagnosis.

### Disclosures

**Ethics Committee Approval:** This study was reviewed and approved by Ankara Bilkent City Hospital Clinical Research Ethics Committee (Ethics Committee ruling number: E1/3493/2023, Date: 26.04.2023).

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

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