

# The Role of Immature Granulocyte in Patients with Complex Appendicitis

✉ Utku Murat Kalafat<sup>1</sup>, ✉ Bilal Yeniurt<sup>1</sup>, ✉ Melih Uçan<sup>1</sup>, ✉ Bahadır Kartal<sup>2</sup>, ✉ Salih Fettahoğlu<sup>1</sup>,  
✉ Ayşe Fethiye Basa Kalafat<sup>1</sup>, ✉ Serkan Doğan<sup>1</sup>

<sup>1</sup>Department of Emergency Medicine, İstanbul University of Health Sciences, Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Türkiye

<sup>2</sup>Department of General Surgery, Hitit University Çorum Erol Olçok Training and Research Hospital, Çorum, Türkiye

## ABSTRACT

**Objective:** The most frequent cause of emergency abdominal surgeries is acute appendicitis (AA). Biomarkers are utilized by clinicians to aid in predicting acute or perforated appendicitis, which may influence treatment decisions. This study aims to examine the potential of immature granulocyte (IG), a robust marker of inflammatory response, in anticipating the occurrence of complications in patients with AA.

**Materials and Methods:** This retrospective study covering 1 year was performed with patients who were operated on by general surgery with a preliminary diagnosis of AA. The study was conducted with a total of 470 patients, 303 of whom were uncomplicated and 167 were complicated, whose diagnosis was confirmed by pathology reports and met the inclusion criteria. White blood cell (WBC), C-reactive protein, neutrophil, platelet, red cell distribution width, IG numbers, and percentages of the patients were recorded in the study form.

**Results:** Area under the curve values of WBC, neutrophil, and IG numbers were 0.590, 0.588, and 0.559, respectively, and we found that they were statistically significant. Each unit increase in the number of IG increases the probability of complication in appendicitis cases approximately 3333 times.

**Conclusion:** In this study, we have demonstrated that the probability of having a complicated appendicitis (CA) is higher in AA patients with higher IG levels when distinguishing between complicated and in CA. Together with physical examination, imaging studies, and other laboratory tests, IG values can assist clinicians in identifying high-risk AA patients in the emergency department.

**Keywords:** Acute abdomen diagnosis, appendicitis, complicated appendicitis, immature granulocytes

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## INTRODUCTION

Diagnostic causes of an acute abdomen range from a relatively mild illness to a serious life-threatening illness. The most common causes of surgical acute abdomen in the emergency department are acute appendicitis (AA) with or without perforation, intestinal obstruction, intestinal perforation, intestinal ischemia, diverticulitis, and hepatobiliary diseases, including acute cholecystitis and cholangitis.

[1] AA is one of the most common causes of presenting with acute abdominal pain and one of the most common diseases requiring surgical treatment. [2] Complicated appendicitis (CA) refers to a state where the inflammation has

progressed to a point where the appendix has perforated, or an abscess or phlegmon has formed. In clinical practice, it is important to differentiate between uncomplicated and CA because the management and treatment strategies differ significantly. [3-5] Patients with CA can often be managed with antibiotics alone or undergo a laparoscopic appendectomy, while patients with CA may require a more extensive surgical intervention such as an open appendectomy or drainage of the abscess. [3-5] The diagnosis of AA is difficult because the symptoms are not specific and there are no specific biomarkers. [6,7] For these reasons, early diagnosis and treatment of CA are critical. [8]



**Address for Correspondence:** Ayşe Fethiye Basa Kalafat, Department of Emergency Medicine, İstanbul University of Health Sciences, Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Türkiye  
**E-mail:** aysebasa@yahoo.com **ORCID ID:** 0000-0002-2139-2061

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Many articles have focused on imaging modalities as well as preoperative laboratory parameters that can improve diagnostic accuracy in differentiating acute and perforated appendicitis. C-reactive protein (CRP) levels and white blood cell (WBC) counts are commonly checked in patients with suspected appendicitis. CRP has been shown to increase markedly after appendiceal perforation or abscess formation, making it a potential indicator for perforated appendicitis; however, the WBC count is an early marker of appendiceal inflammation, but cannot reliably distinguish between acute and perforated appendicitis.<sup>[9]</sup>

Immature granulocytes (IG) in peripheral blood are an indicator of increased bone marrow activation.<sup>[10]</sup> Due to technical advances in automated hematological analyzers, the amount of IG can be easily measured during routine complete blood count (CBC) and presented as a new biomarker of inflammation.<sup>[10,11]</sup> Studies have shown that the number (IGC) and percentage (IG%) of IG are significantly increased in sepsis and infections compared to healthy individuals.<sup>[11]</sup>

The aim of this study is to determine whether the IGC and IG% of CBC parameters add additional discrimination ability in the preoperative differentiation of un CA (UCA) and CA cases admitted to an emergency department, in conjunction with the traditionally used laboratory values.

## MATERIALS and METHODS

### Study Design

This study was started after the study approval was obtained from the ethics committee of our hospital (Ethics committee decision no: KAEK/2022.03.76). Our study was designed as a retrospective and single-center study.

Between January 01, 2021, and January 01, 2022, 477 patients who applied to the emergency department with abdominal pain and were operated on with the diagnosis of AA, meeting the inclusion criteria were evaluated. WBC, platelet count, neutrophil count, hemoglobin, mean platelet volume, red cell distribution width (RDW), IG number and percentage, CRP, and pathology results of AA cases were recorded in the case form from the Hospital Information Management System. AA cases were divided into two groups CA (Phlegmonous, suppurative, perforated, and abscess) and UCA according to their pathology reports. A total of 470 patients, including 303 UCA and 167 CA confirmed in pathology reports, were included in the study.

It was excluded from the study because of diverticulitis in 6 patients and neuroendocrine tumor in 1 patient in pathology reports. The patients whose disease history could not be

obtained by examining the epicrisis reports, those with a history of hematological disease, malignancy, those under 18 years of age or pregnant, and those using anti-inflammatory or immunosuppressive drugs were excluded from the study.

### Statistical Analysis

Categorical data are expressed as numbers and percentages. Normality analysis of continuous variables was performed using Kolmogorov–Smirnov and Shapiro–Wilk tests and skewness and kurtosis values. The t-test was used in the analysis of data with normal distribution, and the Mann–Whitney U test was used for those that did not, and the data were shown as mean+Standard Deviation (SD) and median [IQR], respectively. The cut-off values were determined by performing receiver operating characteristic (ROC) analysis of the variables that were found to be significant between the groups. Binary logistic regression analysis was performed to determine the effect of IGC in the diagnosis of CA.  $P < 0.05$  and 95% CI were used for statistical significance.

## RESULTS

While 160 (34%) of the 470 patients included in the study were female, 310 (66%) were male, with a mean age of  $35.13 \pm 0.95$  and  $32.48 \pm 0.68$ , respectively ( $p = 0.023$ ). While pathology findings consistent with UCA were detected in 303 (64.5%) of the patients, we found that there were findings consistent with CA in 167 (35.5%) patients. We found that 34% of UCA cases were female and 34.1% of CA cases were female, and we found that there was no significant relationship between gender and pathological diagnosis ( $p = 0.976$ ). The distribution of laboratory parameters of the groups of patients according to their pathological diagnosis is shown in Table 1.

The ROC analysis of the independent variables, which were found to be significant in the analysis performed between the groups, was performed (Fig. 1).

In the analysis of statistically significant independent variables between the groups; area under the curve values of WBC, neutrophil, and IG counts were 0.590, 0.588, and 0.559, respectively, and we found that they were statistically significant (Table 2).

Binary logistic regression analysis data of IGC for the diagnosis of CA in appendicitis cases are shown in Table 3. Each unit increase in the number of IG increases the probability of complication in appendicitis cases approximately 3333 times.

## DISCUSSION

Biomarkers, such as WBC, CRP, and procalcitonin, have been studied extensively in the context of appendicitis di-

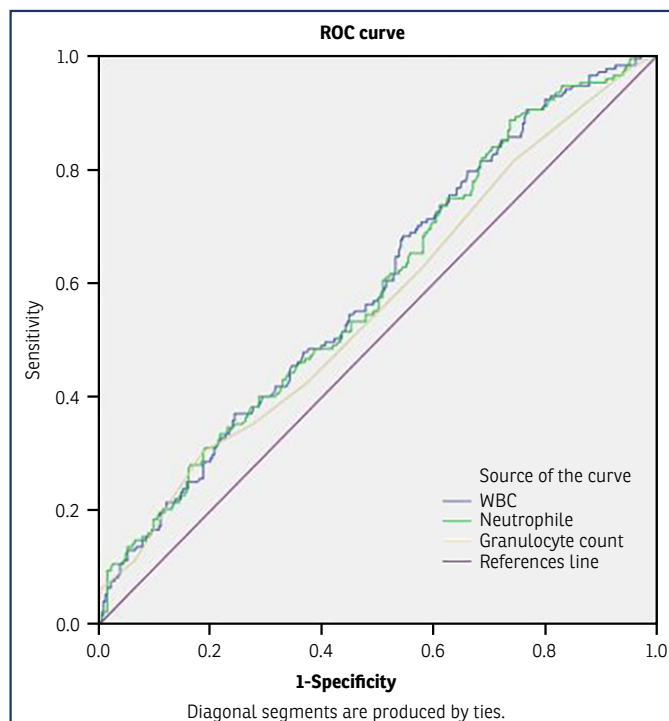
**Table 1. Comparison of laboratory values of UCA and CA groups**

Parameters	UCA (303)	CA (167)	p
WBC, 10 <sup>3</sup> /μL	12.76±0.25	14.23±0.37	<0.01
Hgb, g/dl	13.77±0.11	14.02±0.16	0.078
Platelet, 10 <sup>3</sup> /μL	236000 (84000)	242000 (67500)	0.319*
MPV, fL	10.1 (1.6)	10.2 (1.6)	0.695*
RDW, %	13.1 (1)	13.1 (1)	0.826*
Neutrophil, 10 <sup>3</sup> /μL	9.94±0.25	11.98±0.37	<0.01
Lymphocyte, 10 <sup>3</sup> /μL	1.9 (0.9)	1.8 (1.1)	0.604*
IG percentage	0.2 (0.39)	0.2 (0.4)	0.077*
IG count, 10 <sup>3</sup> /μL	0.03 (0.05)	0.04 (0.05)	0.031*
CRP, mg/L	21.3 (56.74)	27.99 (87.55)	0.075*

Data with normal distribution are shown as mean±SD, and data not in accordance with the normal distribution are shown as median (IQR). Student t test, \*: Mann Whitney U test. UCA: Un CA; CA: Complicated appendicitis; WBC: White blood cell; Hgb: Hemoglobin; MPV: Mean platelet volume; RDW: Red cell distribution width; IG: Immature granulocytes; CRP: C-reactive protein

agnosis. They may be particularly useful in cases where imaging is inconclusive, such as when the appendix is not clearly visualized. In these cases, biomarkers can provide additional information to support a diagnosis of appendicitis.<sup>[12,13]</sup> In our study, we investigated the role of IG in recognizing CA cases in patients who were grouped as CA and UCA according to the pathology reports who underwent surgery with the diagnosis of AA.

Multiple biomarkers used together may further increase the accuracy of the diagnosis. However, it is important to note that biomarkers should never be used in isolation, as they are not definitive in diagnosing appendicitis. Rather,

**Figure 1.** Receiver operating characteristic analysis

ROC: Receiver operating characteristics; WBC: White blood cell

they should be used as a complementary tool to aid in diagnosis.<sup>[14]</sup> There are very few studies in the literature on the use of IG measurements in the diagnosis of AA and the distinction between UCA and CA. In studies, many parameters such as WBC, CRP, delta neutrophil index (DNI), neutrophils, and NLR were compared with each other and evaluated in the distinction of CA and UCA.<sup>[15–19]</sup> A higher inflammatory response in CA cases causes higher inflamma-

**Table 2. ROC analysis results**

Test result variables	Area	Sensitivity	Specificity	NLR	PLR	p	95% CI
WBC >11.78 10 <sup>3</sup> /μL	0.590	68.3	45.5	0.80	1.44	0.001	0.537–0.643
Neutrophile >6.32 10 <sup>3</sup> /μL	0.588	89.2	25.4	0.42	1.20	0.002	0.534–0.641
IG Count >0.065 10 <sup>3</sup> /μL	0.559	30.5	81.2	0.86	1.62	0.033	0.505–0.614

ROC: Receiver operating characteristic; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; CI: Confidence interval; WBC: White blood cell; IG: Immature granulocytes

**Table 3. Binary logistic regression analysis results**

Variable	β	S.E.	Wald	df	p	OR	%95 CI
IG count, 10 <sup>3</sup> /μL	8.112	2.738	8.779	1	0.003	3333.175	15.578–713172.642

S.E.: Standard error; df: Degree of freedom; OR: Odds ratio; CI: Confidence interval

tory biomarkers to be detected in CA cases. The increase in circulating IG is a reaction of the blood marrow to bacterial infection.<sup>[10]</sup> Mathews et al.<sup>[15]</sup> found that increased IG% was significant in the differentiation of UCA and CA in the pediatric age group, but increased CRP level and left shift were more significantly significant for the diagnosis of CA, and when compared, IG% did not provide any additional benefit in this distinction. Soh and Lim found that DNI, which is the circulating IG fraction, is a valuable prognostic marker in patients presenting to the emergency department with a complaint of acute abdominal pain. They stated that DNI can help in selecting high-risk patients and deciding on therapeutic modalities such as emergency surgery or intensive care unit treatment.<sup>[18]</sup> Kubat and Şengül reported that WBC, CRP, neutrophil, IGC, NLR, and PLR values in AA patients were statistically significant in differentiating CA and UCA cases.<sup>[19]</sup> We obtained similar results with the literature in our study.

Beltrán et al.<sup>[20]</sup> evaluated the predictive value of WBC count and CRP in children with appendicitis. They found that not only the CRP levels but also the WBC count can help in the differentiation of acute and perforated appendicitis. Williams et al.<sup>[21]</sup> developed a scoring system to potentially improve the accuracy of preoperative identification of perforated appendicitis. The only laboratory value that created a score in the scoring systems was WBC >19,400. Although WBC counts are frequently requested in patients with suspected appendicitis, the results are nonspecific and insensitive. One study found that leukocytosis had a sensitivity of 18% for AA patients whose symptom onset lasted <24 h, and 90% for those lasting more than 48 h.<sup>[22]</sup> In another study, WBC values were not found to be significant in the comparison of CA-UCA patients, while CRP values were found to be significant.<sup>[23]</sup> The specific biomarker(s) used and the thresholds for abnormal values may vary depending on the patient population being studied and the specific clinical scenario. For example, some studies have found that procalcitonin is more useful in diagnosing CA, while others have found that it is more useful in UCA.<sup>[24,25]</sup> We think that the fact that the time from symptom onset to the application was not included in the evaluation of the studies caused this difference.

In our study, there was a statistically significant difference between patients with CA and UCA in WBC, IGC, and neutrophil values. Selig et al.<sup>[26]</sup> found a significantly higher number of IG in patients with bacterial infections compared with healthy controls. Another study found that

the percentage of IG had a stronger correlation between infection and positive blood culture results than the WBC count.<sup>[11]</sup> In our study, we have identified that the number of IG is elevated in CA cases due to the more severe inflammatory response. Each unit increase in the number of IG increases the probability of complication in appendicitis cases approximately 3333 times. The most accepted diagnostic method for AA is still clinical evaluation and routine laboratory tests. However, it is insufficient to determine the severity of AA. This situation causes prolonged treatment, increased treatment costs, unnecessary risks and increased morbidity.<sup>[27]</sup>

### Limitations

We acknowledge that this study has some limitations. First, as it was a retrospective study, the available data were limited. The time from the onset of symptoms to admission to the hospital could not be evaluated. This time is likely to affect the values of inflammatory markers. In addition, our study group was selected from a tertiary hospital and is not representative of the entire population.

### CONCLUSION

Early diagnosis and treatment of acute CA are very important as it reduces postoperative morbidity rates and medical costs. IG is a new inflammatory marker that can be easily detected with a routine CBC without any additional time or cost. Based on the results of this study, it can be said that IGC is a more important predictor of CA than other hematological parameters in suspected AA cases.

### Disclosures

**Ethics Committee Approval:** The study was approved by the Istanbul University of Health Sciences, Kanuni Sultan Süleyman Training and Research Hospital Clinical Research Ethics Committee (No: 2022.03.76, Date: 23/03/2022).

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