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Preoperative immature granulocyte count and percentage for complicated acute appendicitis and uncomplicated acute appendicitis (A retrospective cohort study)

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ABSTRACT

Aim: Complicated acute appendicitis causes prolonged hospitalisation and increased risk of complications. Preoperative differentiation of this case can help us to select appropriate treatment options (surgery or medical treatment). In this retrospective cohort study it is aimed to evaluate the preoperative immature granulocyte count (IGC) and percentage (IGP) in differentiation of complicated and uncomplicated acute appendicitis cases. *Methods:* 70 of 156 patients who were operated with the same surgical team for acute appendicitis between June 2018 – June 2019 included into this study. Demographic data (age, sex), white blood cell count (WBC), Neutrophil-Lymphocyte Ratio (NLR), IGC and IGP of complicated acute appendicitis (Group C) cases and uncomplicated acute appendicitis (Group UC) cases were evaluated retrospectively. *Results:* Male/Female rate was 40/30 (%57.1/%42.9). The count of cases for Group C and Group UC was 25/45 (%35.7/ %65.3). Between Group C and Group UC, there was no statistically significant difference for age and sex (p>0.05); there was statistically significant difference for WBC, NLR IGC and IGP (p<0.05). A multivariant analysis of the effective factors shows that both of the factors WBC, NLR, IGC and IGP are predictive for complicated acute appendicitis cases (p value <0.001 for both of the factors). *Conclusion:* The IGC and IGP obtained from the complete blood count test are sensitive predictive factors with the other inflammatory parameters to make a differential diagnosis between uncomplicated and complicated acute appendicitis. As a result IGC and IGP can be useful for guidance of nonoperative management of acute appendicitis.

Keywords: Acute Appendicitis, Complicated Acute Appendicitis, Emergent Surgery, Immature Granulocyte Count, Immature Granulocyte Percentage

1. INTRODUCTION

Complicated acute appendicitis accounts for 20 to 30% of the patients undergoing appendectomy. Complicated acute appendicitis cases lead to increased risk of postoperative complications, delayed recovery and longer hospital stay (Díaz-Barrientos et al., 2018; Khan et al., 2019; Park et al., 2018). Therefore, early diagnosis of complicated acute appendicitis is important; however, the most appropriate and inexpensive diagnostic method to make this diagnosis has not been established yet. Although the use of imaging methods is widespread, these methods are not accessible in many rural hospitals due to unavailability of specialists (Hakkoymaz et al., 2019). Thus, the need for an effective diagnostic technique allowing to make a differential diagnosis has not been met yet. For this purpose, several easily accessible blood parameter tests have been proposed; including the white blood cell count, C-reactive protein levels or the neutrophil-to-lymphocyte ratio (Barut et al., 2020; Bozan et al., 2021; Hakkoymaz et al., 2019; Khan et al., 2019; Yazar et al., 2018).

An increase in the immature granulocyte count means that the bone marrow is active (Barut et al., 2021; van der Geest et al., 2014). This parameter has been used as a prognostic factor in many diseases including sepsis, acute pancreatitis, and acute myocardial infarction (Sauneuf et al., 2014; van der Geest et al., 2014). The immature granulocyte count (IGC) and percentage (IGP) have become an easy-to-use method, especially with the introduction of technological advances, as it can be easily determined using the results of a routine complete blood count.

The aim of this study was to evaluate whether IGC and IGP in the complete blood count would be helpful for differentiation of complicated and uncomplicated acute appendicitis patients in the preoperative period especially in rural areas without enough imaging modalities.

2. METHOD

The data of 156 patients elder than 18 years, who admitted to the Kahramanmaras Sutcu Imam University, Faculty of Medicine, Department of Emergency Medicine and Department of General Surgery outpatient clinic with the complaint of abdominal pain diagnosed with acute appendicitis and who were operated by the same surgical team between June 2018 and June 2019 were evaluated retrospectively after the approval of the local ethics committee (Kahramanmaras Sutcu Imam University, Faculty of Medicine, Ethical Committee of Human Studies, session no. 2019/11, decision no. 5 for the study number 180, on 19.06.2019). Before the surgical procedure, informed consent was provided from the patients. Patient data were retrieved by reviewing the patient charts and the electronic database of the hospital. Twenty-two patients were excluded because their patient charts were unavailable, there were missing data, or the pathological diagnosis did not confirm acute appendicitis (negative appendectomies and appendiceal mucinous cystadenomas). The patients were assigned to the complicated acute appendicitis group (Group C) based on intraoperative exploration findings (presence of gangrenous appendicitis, perforation or abscess formation), and pathological examination findings (acute phlegmonous appendicitis, acute gangrenous appendicitis or acute perforated appendicitis). The patients were assigned to the uncomplicated acute appendicitis group (Group UC) based on the presence of edema and the absence of gangrene, perforation or abscess in the exploratory surgery of appendix, and confirmation of the diagnosis of acute appendicitis by the pathological examination findings (Jha et al., 2019; Kim et al., 2019; Rawolle et al., 2019; Ünal, 2018; Xu et al., 2017).

White blood cell count (WBC), neutrophil count, lymphocyte count, IGC and IGP were measured using an automated hematological analyzer (XN 3000; SysmexCorp, Kobe, Japan) from blood samples obtained at the preoperative period of the patients. The neutrophil-to-lymphocyte ratio (NLR) was manually calculated from the CBC results. The immature granulocyte (IG) fraction included promyelocytes, myelocytes and metamyelocytes but not band neutrophils or myeloblasts. Moreover, the IGP was the ratio of the IGC to the WBC (Bozan et al., 2021). The demographic data (age, sex) of the patients, and the preoperative CBC values of WBC, NLR, IGC and IGP were evaluated retrospectively.

Statistical Analysis

Statistical analyses were performed with IBM Statistical Package for Social Sciences (SPSS) version 20.0 software. For evaluating distribution of normality, Shapiro Wilk test was used. The student t-test and the Mann-Whitney U test were used for analyzing the quantitative values according to normality test. The chi-square test was used for analyzing the categorical data. Univariate and multivariate analysis of the factors was done to detect the predictive factors for complicated acute appendicitis cases. Data were presented in percentages and mean ± standard deviation (minimum - maximum values) or median (%25 - %75). A p-value of <0.05 was considered statistically significant.

For this study, which has a retrospective character, the potency calculated by the G Power 3.0.10 program was 0.5, while the α value was 0.05, while the expected power for 70 patients was 0.98.

3. RESULTS

Of the 156 patients, 70 patients met the inclusion criteria. The male/female ratio of the study patients was 40/30 (57.1%/42.9%). The Group C/Group UC ratio was 25/45 (35.7%/65.3%). There was not a significant difference in the age of the patients and the gender distribution between Group C and Group UC (*p*-values; 0.801 and 0.249, respectively). However, there were statistically significant differences in the WBC, the NLR, IGP and IGC between Group C and Group UC ($p<0.05$) (Table 1).

Table 1 Demographic data and the preoperative blood sample results of the study

	Acute Appendicitis Cases		*p* value
	Group C (n=25)	Group UC (n=45)	
Age (year) [Median (%25 – %75)]	35 (25 – 51)	33 (28 – 44)	0.801
Gender (Male/female)	12/13	28/17	0.249
WBC (/mm^3)[Mean ± SD (Min – Max)	15215 ± 5053 (5690 – 25920)	12058 ± 3389 (5130 – 21180)	0.008*
NLR [Median (%25 – %75)]	7.55 (3.66 – 13.14)	4.18 (2.76 – 6.52)	0.015*
IGP (%)[Median (%25 – %75)]	0.4 (0.4 – 0.8)	0.3 (0.3 – 0.3)	<0.001*
IGC (n/mm^3) [Median (%25 – %75)]	70 (50 – 100)	30 (20 – 40)	<0.001*

*p<0.05

WBC: White Blood Cell Count; NLR: Neutrophil to lymphocyte ratio; IGP: Immature granulocyte percentage; IGC: Immature granulocyte count; Min: Minimum value; Max: Maximum value;

A univariate analysis of the factors was done for obtaining the affective factors to predict complicated cases. WBC, NLR, IGC and IGP were found to be affective factors (*p* values: 0.003; 0.032; <0.001; and <0.001, respectively). However age and sex were not found to be affective factors (*p* values: 0.333 and 0.256, respectively). A multivariant analysis of the effective factors shows that both of the factors are predictive factor for complicated acute appendicitis cases (*p* value; <0.001 for both of the factors) (Table 2).

Table 2 Multivariant analyses results of preoperative inflamatory markers for prediction complicated acute appendicitis cases

	Odds Ratio	B Value	*p* value	% 95 Coefficient Interval	
				Lower Bound	Upper Bound
WBC	0.854	12057,556	<0.001*	10851.267	13263.844
NLR	0.433	5.899	<0.001*	4.265	7.533
IGP	0.505	0.3	<0.001*	0.228	0.372
IGC	0.426	35.111	<0.001*	25.249	44.974

WBC: White Blood Cell Count; NLR: Neutrophil to lymphocyte ratio; IGP: Immature granulocyte percentage; IGC: Immature granulocyte count

ROC curve analysis of inflammatory markers for diagnosing Complicated Acute Appendicitis

The discriminatory power of the IGP for diagnosing complicated was moderate, with 76% sensitivity and 75.4% specificity at a cut-off value ≥ 0,35% (AUC, 0.800; 95% confidence interval [CI] 0.686–0.913) and the discriminatory power of the IGC84% sensitivity and 75.6% specificity at a cut-off value ≥ 45/mm^3 (AUC, 0.880; 95% CI 0.791–0.969) (Table 3 and Figure 1).

Table 3 The Receiver Operating Curve (ROC) analysis of inflammatory markers for diagnosing complicated acute appendicitis

	ARUC	PPV (%)	NPV (%)	Cut-off value	Sensitivity (%)	Specificity (%)	Asymptotic 95% Confidence Interval		*p* value
							Lower Bound	Upper Bound	
WBC (/mm^3)	0,700	50	81.2	≥12390	76	60	0.564	0.836	0.006
NLR	0,677	56.7	80	≥5.635	68	71.1	0.903	0.991	0.015
IGC (/mm^3)	0,880	65.6	89.5	≥45	84	75.6	0.791	0.969	<0.001*
IGP (%)	0,800	63.3	85	≥0.35	76	75.4	0.686	0.913	<0.001*

*p<0.005

ARUC: Area under curve; PPV: Positive predictive value; NPV: Negative predictive value; WBC: White blood cell count; NLR: Neutrophil to lymphocyte ratio; IGC: Immature granulocyte count; IGP: Immature granulocyte percentage

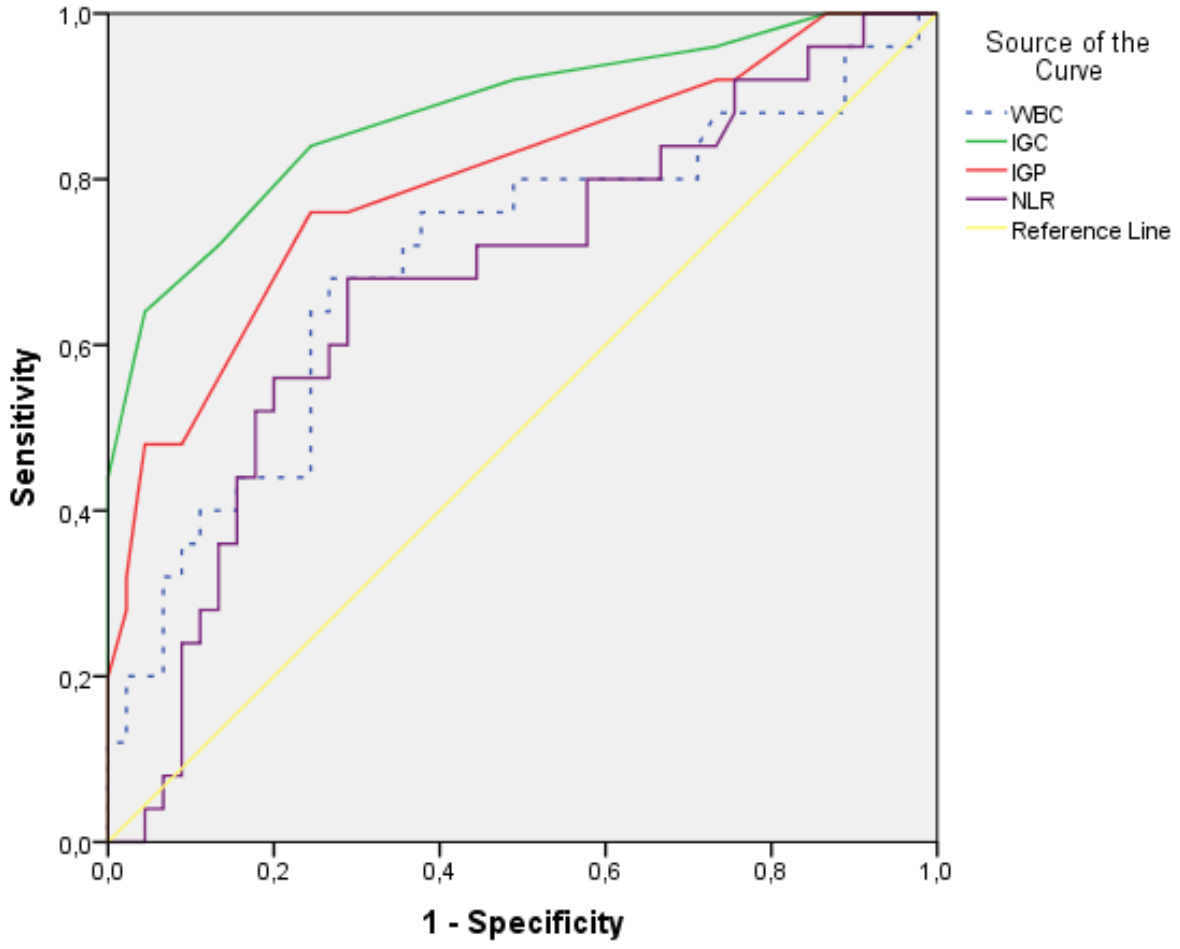

Figure 1 The Receiver Operating Curve (ROC) of Immature Granulocyte Count (IGC), Immature Granulocyte Percentage (IGP), White Blood Cell Count (WBC) and Neutrophyl/Lymphocyte Ratio (NLR)

4. DISCUSSION

Determining whether acute appendicitis is complicated or not in the preoperative period will help to choose the medical treatment option, which is among the treatment options of uncomplicated acute appendicitis and which is more prominent nowadays. In this way, unnecessary operations in uncomplicated acute appendicitis can be reduced and surgical complications can be prevented. In a meta-analysis by Yang et al., (2019), they stated that conservative treatment of acute appendicitis is beneficial in adult patients, and

the incidence of complications was significantly lower than appendectomy. Tingstedt et al., (2004) stated that re-hospitalizations increased after appendectomy, therefore unnecessary appendectomies should be avoided in order to prevent this situation caused by negative appendectomy. In their cohort study, Blomqvist et al., (2001) reported that the mortality risk increased 3.5-fold in patients without perforation in the first 30 days postoperatively, and 6.5-fold in complicated cases. However, they stated that these mortality rates increased 9.1 times after negative appendectomy. Another complication of appendectomies, postoperative small bowel obstruction rates were reported as 10.7% after open appendectomy in the study conducted by Zbar et al.,(1993).

The IGP/DNI, the ratio of the count of the precursor white blood cells (promyelocytes, myelocytes, andametamyelocytes) to total WBC, is an important indicator of bone marrow activity reacting against infectious agents before the formation of leukocytes (Karon et al., 2017; Park et al., 2018; Soh & Lim, 2019). It is possible to obtain the immature granulocyte ratio by counting the immature granulocytes under microscopy and proportioning them to the number of white cells. However, it is currently possible to measure it using automatic analyzers introduced along with technological advances (Sauneuf et al., 2014; van der Geest et al., 2014).

Nahm et al., (2008) studied 237 sepsis patients and reported that the DNI index is a valuable indicator to determine the severity and prognosis of sepsis. Cimenti et al., (2012) reported that the IGC obtained from automated measurement systems would be beneficial in making an early diagnosis of neonatal sepsis. Karon et al., (2017) prospectively investigated the significance of the neutrophil count, WBC, IGC, and the procalcitonin and lactate levels in following up the progression of sepsis, determining its severity, and making its early diagnosis. They reported that the IGC provided no additional benefits. Unal, (2019) compared acute edematous pancreatitis and acute necrotizing pancreatitis in a 94-patient retrospective study to determine the severity of acute pancreatitis. That study found a significant difference in the IGP along with the significant differences in the other laboratory parameters (WBC, NLR, etc.) between the acute edematous pancreatitis group and the acute necrotizing pancreatitis group (Ünal, 2019). In a 130-patient study, Saunef et al., (2014) demonstrated that the IG/total granulocyte ratio was a poor prognostic factor for mortality in the intensive care unit after cardiac arrest.

The use of IGC and IGP in acute appendicitis increasingly receives attention. Unal, (2018) compared the IGC and the IGP between the groups of patients with complicated and uncomplicated acute appendicitis. That study found out that the IGP and the IGC were significantly higher in the complicated acute appendicitis patients. Park et al., (2018) demonstrated that the IGP did not provide an additional benefit in making the diagnosis of acute appendicitis on 403 patients, who were admitted to the emergency department with suspicion of acute appendicitis. In a study evaluating the IGP in pediatric appendicitis patients, Mathew et al., (2014) observed that the increase in the percentage of IG in perforated acute appendicitis cases showed no additional benefits compared to the use of CRP levels and a left shift. In our study, the IGC and IGP were significantly higher in the Group C similar to the results of the Unal, (2018) study. The multivariant analysis results of our study showed us that the IGC and IGP were a useful parameter along with other inflammatory parameters in the preoperative differential diagnosis of complicated acute appendicitis with uncomplicated acute appendicitis. So with lower IGC and IGP showed uncomplicated acute appendicitis cases and helpful for choosing nonoperative management of acute appendicitis.

Limitations

Retrospective character of our study is the main limitation. Additionally being a third center hospital limits the count of our uncomplicated and total acute appendicitis cases, because the most of the acute appendicitis cases were operated in the second center state hospitals. With greater numbers of cases the importance of the IGC and IGP can be more discussable.

5. CONCLUSION

The IGC and IGP obtained from the CBC count test are sensitive predictive factors to make a differential diagnosis between uncomplicated and complicated acute appendicitis with the other inflammatory parameters. As a result preoperative IGC and IGP can be useful for guide for choosing uncomplicated cases for nonoperative management of acute appendicitis.

Funding

This study has not received any external funding.

Conflict of Interest

The authors declare that there are no conflicts of interests.

Informed Consent

Written & Oral informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this manuscript.

Ethical Approval

The study was approved by the KahramanmarasSutcu Imam University, Faculty of Medicine, Ethical Committee of Human Studies, session no. 2019/11, decision no. 5 for the study number 180, on 19.06.2019. Data and materials availability all data associated with this study are present in the paper.

Clinical Trial ID

NCT04440150

Author Contributions

Conception and design was planned by Mehmet Buğra Bozan, Fatih Mehmet Yazar, Özlem Güler and Ömer Faruk Boran.
Analysis an interpretation was done by Ayşe Azak Bozan, Özlem Güler, Mehmet Buğra Bozan, Fatih Mehmet Yazar
Data collection was done by Mehmet Buğra Bozan, Fatih Mehmet Yazar, Özlem Güler, and Ömer Faruk Boran
Writing the article was done by Mehmet Buğra Bozan, Fatih Mehmet Yazar, Ayşe Azak Bozan
Critical revision of the article was done by Mehmet Buğra Bozan, Fatih Mehmet Yazar, Ayşe Azak Bozan, and Ömer Faruk Boran
Approving the final version was performed by Mehmet Buğra Bozan, Fatih Mehmet Yazar, Ayşe Azak Bozan, and Ömer Faruk Boran

Informed consent

Informed consent was obtained from all participants included in the study.

Ethical Consideration

The study acquired the ethical approval from the ethical committee at the College of Medicine, University of Hail (letter number Nr. 20455/5/42- project number H-2020-218).

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Author Contributions

All the authors contributed evenly with regards to data collecting, analysis, drafting and proofreading the final draft.

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There are no conflicts of interest.

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All data associated with this study are present in the paper.

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