

Role of Immature Granulocyte Count and Percentage in The Differential Diagnosis of Appendicitis

Apendisit Ayırıcı Tanısında İmmatür Granülosit Sayısının ve Yüzdesinin Rolü

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Özet

Amaç: Akut apandisit, çocuk cerrahisi pratiğinde en önemli ve yaygın olarak uygulanan acil cerrahilerden biridir. Çocuklarda apandisit tanısı yetişkinlere göre daha zordur. Olgunlaşmamış granülosit yüzdesi (%IG) son zamanlarda erişkin popülasyonda inflamasyon şiddetinin saptanması için laboratuvar parametresi olarak araştırılmaktadır. Çalışmanın amacı, pediatrik akut apandisit erken tanısında IG sayısı ve yüzde rolünün belirlenmesidir.

Gereç ve Yöntemler: Ocak 2021-Aralık 2022 tarihleri arasında karın ağrısı şikayeti ile Acil Servise başvuran ve preoperatif akut apandisit tanısı ile opere edilen hastaların verileri hastane kayıtlarından geriye dönük olarak incelendi. 18 yaş altı, akut apandisit ön tanısı ile ameliyat edilen ve hemogramı olan hastalar çalışmaya dahil edildi.

Bulgular: Çalışmaya 108 hasta dahil edildi. Akut apandisit grubunda 48 hasta, perforate apandisit grubunda 9 hasta ve kontrol grubunda 53 hasta vardı. Apandisit ve kontrol grubundaki hastalarda ortalama IG %'si sırasıyla 0.31 ± 0.37 ve 0.96 ± 5.1 idi. Apandisit hastaları ile kontrol grubu arasında IG sayısı ve yüzdesi açısından anlamlı fark bulunmadı. Akut ve perforate apandisit arasında IG sayısı ve IG % açısından istatistiksel olarak anlamlı fark bulunmadı.

Sonuç: IG sayısı ve IG%, herhangi bir ek fayda sağlamadı ve klinisyen için akut apandisit belirlemede kesin bir biyobelirteç değildir. Akut apandisit tanısı için anamnez, fizik muayene ve laboratuvar testinin bir kombinasyonu altın standart olmaya devam etmektedir.

Anahtar kelimeler: Akut apandisit, İmmatür granülosit, Pediatri

Abstract

Objective: Acute appendicitis is one of the most important and widely performed emergent surgery in pediatric surgery practice. Diagnosis of appendicitis in children is more challenging compared to adults. The immature granulocyte percentage (IG%) is recently investigated laboratory parameter for detection of inflammation severity in adult population. The aim of the study was determination of IG count and percentage role in early detection of pediatric acute appendicitis.

Materials and Methods: The data of patients who applied to Emergency Room with the complaint of abdominal pain and who were operated with a pre-operative diagnosis of acute appendicitis between January 2021 and December 2022 retrospectively reviewed from hospital records. Patients under 18 years, operated due pre-operative diagnosis of acute appendicitis and who have hemogram included in the study.

Results: One hundred eight patients included in the study. Forty-eight patients were in the acute appendicitis group, 9 patients were in the perforated appendicitis group, and 53 patients were in the control group. The mean IG % of was 0.31 ± 0.37 and 0.96 ± 5.1 in appendicitis and control group patients, respectively. No significant difference was found between appendicitis patients and control group in terms of IG number and percentage. No statistically significant difference was found between acute and perforated appendicitis in terms of IG number and IG%.

Conclusion: IG number and IG% did not provide any additional benefit and is not a conclusive biomarker for clinician in determination of acute appendicitis. A combination of anamnesis, physical examination and laboratory test remains gold standard for diagnosis of acute appendicitis.

Keywords: Acute appendicitis, Immature granulocyte, Pediatrics

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INTRODUCTION

Acute appendicitis is one of the most important and widely performed emergent surgery in pediatric surgery practice (1,2). Abdominal abscess, intestinal adhesion/ileus, sepsis are results of delayed intervention of acute appendicitis. Diagnosis of appendicitis in children is more challenging compared to adults. So, percentage of perforated appendicitis in children is reported to be much more higher (%22 to 52) (3). Treatment options of acute and perforated appendicitis are different. While acute appendicitis require urgent appendectomy, beside appendectomy, perforated appendicitis can be treated with intravenous antibiotics followed by interval appendectomy (4). This treatment option is thought to be cost-effective and decreases prolonged hospital stay and complication related to traditional urgent appendectomy (5). Distinguishing of acute and complicated appendicitis for prevention of possible complications is still remains challenge. After physical examination, to support the decision of acute appendicitis a lot of clinical, laboratory and radiological predictors have been investigated. C-reactive protein (CRP), White blood cell (WBC) count, absolute neutrophil counts (ANC), neutrophil to lymphocyte ratio (NLR), and bilirubin levels are the markers which have been used for early diagnosis of acute appendicitis (6).

The immature granulocyte percentage (IG%) is recently investigated laboratory parameter for detection of inflammation severity in adult population (7). Routinely, IG percentage detection is calculated in the White blood cell (WBC) count by visual microscopy (8). Nowadays, IG count and percentage can automatically be measured in the newest generation of hemogram devices (5) and can be used as a good predictive marker of severe infection, inflammation and sepsis (9). An elevated IG percentage is an indicator of early bone marrow activity against infection sources before onset of leukocytosis. Absence of IG thought to have a high negative predictive value in neonatal sepsis (10). The aim of the study was determination of IG count and percentage role in early detection of pediatric acute appendicitis.

MATERIALS AND METHODS

Study Design and Clinical Protocol

After the approval of University of Health Sciences, Adana City Training and Research Hospital local ethical committee (Protocol 21.04.2022/104/Number:1906), The procedures applied to all human participants were in accordance with ethical standards and the 1964 Helsinki declaration and its later amendments. The data of patients who applied to Emergency Room with the

complaint of abdominal pain and who were operated with a pre-operative diagnosis of acute appendicitis between January 2021 and December 2022 retrospectively reviewed from hospital records.

Patients under 18 years, operated due pre-operative diagnosis of acute appendicitis and who have hemogram included in the study. Preoperative administration of antibiotics, presence of chronic inflammatory diseases, significant additional comorbidities were defined as exclusion criterias. All operations were performed in the same hospital. Acute appendicitis was defined catarrhal and flegmonous appendicitis. Other demographic variables like age, gender and WBC were collected. Collected laboratory analyzes compared with control group.

Control Group

Control group consisted healthy children (similar age/gendre) who underwent minor surgical procedures (like inguinal hernia, circumcision or undescended testes) during the same time period without co-morbidities or inflammatory conditions. All patients had WBC values, as it is one of the preoperative evaluation criterias in our hospital.

Data Collection from Patients and the Laboratory

Age, gender, diagnosis, hospital stay length of operated patients were recorded. The WBC counts, IG count and percentage recorded. Two venous peripheral blood samples was drawn by venipuncture from patients and collected in K2E-EDTA tubes and in 5.0 mL vacuum collection tubes with no anticoagulant for serum separation in standardized conditions in order to minimize sources of pre-analytical variation. All of the blood samples with visible haemolysis were discarded. The K2E-EDTA samples (under appropriate conditions) without waiting were analyzed to Complete Blood Count Test, which included the IG% and IG count. The tubes with no anticoagulant were allowed to clot at room temperature for 15-20 min. and the serum sample separated by centrifugation at 4000 g for 10 min.

The IG percentage was calculated with an automated hematology analyzer Beckman Coulter UniCel DxH 800. The IG measurement that includes promyelocytes, myelocytes, and metamyelocytes was performed in the differential channel of the Beckman Coulter UniCel DxH 800. The IG percentage is defined as the percentage of the total WBC count. Detection of immature granulocytes by Beckman Coulter UniCel DxH 800 has shown a sensitivity, specificity, and efficiency of 92%, 81%, and 83%, respectively.

Statistical Analyzes

SPSS (Statistical Package for the Social Sciences) 25.0 package program was used for statistical analysis of the data. Categorical measurements were summarized as numbers and percentages, and continuous measurements as mean and standard deviation (median and minimum-maximum where appropriate). Chi-square and Fisher's exact tests were used in the comparison of categorical expressions. Shapiro-Wilk test was used to determine whether the parameters in the study showed a normal distribution. Independent Student's t-test was used for normally distributed parameters and Mann Whitney u test was used for non-normally distributed parameters. The protocol for this study was approved by the Local Ethics Committee (21.04.2022/104/Number:1906)

RESULTS

One hundred eight patients included in the study. Forty-eight patients were in the acute appendicitis

group, 9 patients were in the perforated appendicitis group, and 53 patients were in the control group. Demographic data of the patients (age, gender), definitive diagnosis, CRP, WBC, Platelet, neutrophil %, Lymphocyte %, Neutrophil/Lymphocyte ratio, IG number and percentage were examined in the data. Demographic and clinical data were compared between acute appendicitis and control groups. While comparing CRP, thrombocyte, neutrophil, lymphocyte and neutrophil/lymphocyte ratio values in terms of appendicitis patients and control group, statistically significant difference was found as expected. The mean IG % of was 0.31 ± 0.37 and 0.96 ± 5.1 in appendicitis and control group patients, respectively. The mean IG number was 0.05 ± 0.8 and 0.12 ± 0.7 in appendicitis patients and control group patients, respectively. No significant difference was found between appendicitis patients and control group in terms of IG number and percentage (Table 1). No statistically significant difference was found between acute and perforated appendicitis in terms of IG number and IG% (Table 2).

Table 1. Comparison of demographic, clinical and laboratory characteristics of patients diagnosed with appendicitis with control group patients

	Patients (n=55) n(%)	Control (n=53) n(%)	Total (n=108) n(%)	P
Gender				
Male	37 (67.3)	41 (77.4)	78 (72.2)	0.242 ⁺
Female	18 (32.7)	12 (22.6)	30 (27.8)	
Diagnosis				
Acute appendicitis	46 (83.6)		46 (83.6)	
Complicated appendicitis	9 (16.4)		9 (16.4)	
	Patients (n=55)	Control (n=53)	Total (n=108)	P
Age	11.7±3.8	8.4±5.7	10.1±5.1	0.001**^a
C-reactive protein	62.1±75.3 34.8 (0.6-366.9)	24.9±45.9 3.43 (0.7-229.1)	44.0±65.2 15.2 (0.6-366.9)	<0.001**^b
WBC	14.9±5.9	10.9±4.4	12.9±5.5	<0.001**^a
Thrombocyte	306.2±71.8	341.4±89.4	323.3±82.3	0.026*^a
%Neutrophil	79.0±12.6 83 (25.9-93.9)	56.7±20.9 58.6 (20.2-90.7)	68.2±20.4 75 (20.2-93.9)	<0.001**^b
%Lymphocyte	12.3±10.1 10.7 (1.4-60.3)	31.2±19.7 25.8 (4.4-71.5)	21.5±18.1 15.6 (1.4-71.5)	<0.001**^b
NLR	11.9±12.5 7.74 (0.43-79)	4.29±5.1 2.54 (0.28-20.86)	8.3±10.4 4.78 (0.28-79)	<0.001**^b
IG %	0.31±0.37 0.2 (0.0-1.8)	0.96±5.1 0.2 (0-37)	0.63±3.55 0.2 (0.0-37.0)	0.253 ^b
IG number	0.05±0.08 0 (0.0-0.3)	0.12±0.7 0 (0.0-5.1)	0.08±0.5 0 (0.0-5.1)	0.085 ^b

* p<0,05, **p<0,001, a: Independent-Samples t-test, b: Mann Whitney U, +: Chi-square
NLR: Neutrophil to lymphocyte ratio, WBC: White Blood Cells, IG: Immature granulocyte

Table 2. Comparison of acute and perforated appendicitis patient's demographic and laboratory results.

	Acute appendicitis (n=46)	Complicated appendicitis (n=9)	p
	n(%)	n(%)	
Gender			
Male	29 (63)	8 (88.9)	
Female	17 (37)	1 (11.1)	
Age	12.1±3.2 12 (6-18)	9.7±5.8 10 (3-18)	0.164
CRP	41.1±43.3 24.9 (0.6-151.9)	169.2±110.7 122.8 (89-366.9)	<0.001**
WBC	14.9±5.8 13.9 (5.4-26.4)	14.6±6.5 15 (3.4-25.2)	0.900
Thrombocyte	305.3±72.3 302 (162-542)	310.6±73.1 301 (224-430)	0.785
%Neutrophyl	78.2±13.2 81.4 (25.9-93.7)	83.4±8.0 84 (72-93.9)	0.339
%Lymphocyt	13.1±10.6 11.4 (1.4-60.3)	8.6±6.4 6.2 (1.4-20.2)	0.211
NLR	10.1±7.7 7.3 (0.43-36.2)	20.9±24.1 13.5 (3.4-79)	0.185
IG %	0.27±0.033 0.2 (0-1.8)	0.54±0.44 0.4 (0-1.3)	0.045*
IG number	0.03±0.06 0 (0-0.3)	0.1±0.12 0.1 (0-0.3)	0.092

* p<0,05, **p<0,001, Mann Whitney U

NLR: Neutrophil to lymphocyte ratio, WBC: White Blood Cells, IG: Immature granulocyte

CRP: C reactive protein

DISCUSSION

Acute appendicitis is the most common reason for abdominal surgery in children and a diagnosis is established by a combination of clinical, laboratory, and imaging methods.

Childhood appendicitis is more likely to be complicated than adult appendicitis due to lack in the self expression in this age group (10). Contrary to the literature, in our study 83.6% of patients were acute and 16.4% were complicated (**Table 1**). Distinguishing acute from complicated appendicitis is important for determination of treatment method. Despite being such a common condition, even today it is quite difficult to differentiate acute and complicated appendicitis. Many markers have been used for his purpose. C-reactive protein (CRP), white blood cell count (WBC) are widely used and studied markers (11-13). Most of these studies detected CRP and WBC to be significantly higher in patients with definitive appendicitis. WBC

count is widely ordered in children with suspicion of appendicitis but results are nonspecific and insensitive. Doraiswamy et al. reported leukocytosis to be 90% sensitive for those patients who have symptoms more than 48 hours (14). The reported sensitivities and specificities of these markers are variable and cannot exclude, confirm or differentiate acute and complicated appendicitis (15). As expected, there was a statistically difference between appendicitis cases and control group in terms of C-reactive protein and white blood count in our study (**Table 1**).

Immature granulocyte in peripheral blood is indicator of sepsis/infection which causes bone marrow activation. Immature granulocyte count (IGC) and percentage (IG%) can be measured automatically in new generation hemogram devices. Because of the quick, easy and free of extra cost determination of these parameters immature granulocyte count and percentage has been investigated as an inflammation marker

in adult and pediatric patient. In their study Korkut et al. found that the IG percentage did not have sufficient specificity and sensitivity in the diagnosis of complicated appendicitis (16). On the contrary, there are studies reporting IGC and IG% to be more sensitive in predicting inflammation compared to other biomarkers (17,18). Studies evaluating the IG percentage in the diagnosis of acute appendicitis and the distinction between complicated and simple appendicitis are limited in pediatric population.

Mathews et al. reported IG% not to be beneficial in differentiation of acute and perforated appendicitis (10). Pavare et al. in their study consisted of pediatric population, investigated IG% sensitivity between patients without serious infection and with serious bacterial infection. According to their results, IG% differs between patients with non-serious bacterial infection and those with serious bacterial infection. As a conclusion, IG% thought to be additional diagnostic tool for physicians in identifying of a small proportion of high risk children in very intensive flow of patients in emergency department (19). Immature granulocyte also investigated in neonatal population. Lack of immature granulocyte reported to have high negative predictive value in neonatal sepsis (19). In presented study, no significant statistically difference was found between appendicitis patient and control group in terms of IG number and IG%. To our knowledge, this is the first IG number and percentage study consisting control group in pediatric population.

Limited number of perforated appendicitis patients is major limitation of this study.

CONCLUSION

IG number and IG% did not provide any additional benefit and is not a conclusive biomarker for clinician in determination of acute appendicitis. A combination of anamnesis, physical examination and laboratory test remains gold standard for diagnosis of acute appendicitis.

Conflict of Interest and Financial Status: The authors declare that they have no competing interest.

Author Contribution Rate Statement Summary: The authors declare that, they have contributed equally to the manuscript.

Ethical Approval: Ethical approval was obtained from the local ethics committee of University of Health Sciences, Adana City Training and Research Hospital (Protocol 21.04.2022/104/Number:1906).

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