ORIGINAL ARTICLE

The Value of Immature Granulocyte and Immature Granulocyte/Total Granulocyte Ratio in Predicting the Need for Surgical Treatment in Patients Diagnosed with Intestinal Ileus in the Emergency Department

Acil Serviste İnce Bağırsak İleusu Tanısı Alan Hastalardaki İmmatür Granülosit ve İmmatür Granülosit/Total Granülosit Oranının Cerrahi Tedavi İhtiyacını Öngörmedeki Değerliliği

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ABSTRACT

Objectives: Although many biomarkers that can predict the need for surgical treatment of patients with intestinal ileus have been investigated, effective, inexpensive, and fast-resulting biomarkers have not been determined. In our study, it was aimed to show the value of immature granulocyte (IG) and immature granulocyte/total granulocyte (IG/TG) ratio in predicting the need for surgical treatment in patients diagnosed with intestinal ileus in the emergency department.

Method: Our study was carried out as a prospective cross-sectional. Patients aged 18 years and older admitted to the emergency department and diagnosed with intestinal ileus after clinical, laboratory and radiological evaluation were included in the study consecutively. Demographic characteristics, comorbidities, treatments, laboratory tests and IG, IG/TG results of the patients were recorded. The patients were divided into two groups as those who underwent surgical treatment and those who did not, and they were compared. p value <0.05 was considered statistically significant.

Results: A total of 78 patients were included in the study. 46.2% (n=36) of the patients were female and the median age was 65 years. While surgery was performed in 41% (n=32) of the patients, 59% (n=46) were followed up with medical treatment. IG number and IG/TG ratio were found higher in patients who underwent surgical intervention than in those who underwent medical treatment, and these differences were statistically significant (p<0.05). In receiver-operating characteristic (ROC) analysis AUC: 0.658 was found for IG number. With the best cut-off value of 0.03, the sensitivity was 56.3% specificity: 71.7%; and the AUC value for IG/TG was: 0.627 (95% CI; 0.500-0.753), and when the best cut-off value was taken as 0.2, the sensitivity for this value was 59.4%, and the specificity was 63%.

Conclusion: In this study, in which we examined the IG numbers and IG/TG ratios in patients with intestinal ileus, although we showed that these parameters were higher in patients who needed surgical treatment, upon the analysis done, we believe that it is not a clinically significant marker.

Keywords: Intestinal ileus, immature granulocyte, immature granulocyte to total granulocyte ratio.

ÖZ

Giriş ve amaç: İnce bağırsak ileusu olan hastaların cerrahi tedavi ihtiyacını ön gördürebilen birçok biyobelirteç araştırılmış olsa da etkin, ucuz ve hızlı sonuç veren biyobelirteçler belirlenebilmiş değildir. Çalışmamızda acil serviste ince bağırsak ileusu tanısı alan hastalardaki immatür granülosit (IG) ve immatür granülosit total granülosit (IG/TG) oranının cerrahi tedavi ihtiyacını öngörmedeki değerliliğini göstermek amaçlandı.

Gereç ve yöntem: Çalışmamız 23.11.2021–07.04.2022 tarihleri arasında prospektif kohort olarak gerçekleştirildi. Acil servise başvuran, klinik, laboratuvar ve radyolojik değerlendirme sonrası ince bağırsak ileusu tanısı alan 18 yaş ve üstü hastalar çalışmaya dahil edildi. Hastaların demografik özellikleri, komorbiditeleri, tedavileri, laboratuvar tetkikleri ve IG, IG/TG sonuçları kaydedildi. Hastalar cerrahi tedavi uygulananlar ve uygulanmayanlar olarak iki gruba ayrıldı ve karşılaştırmalar yapıldı. p değeri <0,05 istatistik olarak anlamlı kabul edildi.

Bulgular: Çalışmaya toplamda 78 hasta alındı. Hastaların %46,2'si (n=36) kadın cinsiyette olup yaş ortancası 65 yaş bulundu. Hastalardan %41'ine (n=32) cerrahi yapılırken, %59'u (n=46) medikal tedavi ile takip edildi. Cerrahi girişim yapılanlarda IG sayısı ve IG/TG oranı medikal tedavi uygulanan hastalara göre daha yüksek saptandı ve bu farklar istatistiksel olarak anlamlıydı (p<0.05). Receiver-operating characteristic (ROC) analizinde IG sayısı için AUC: 0.658 bulundu. En iyi eşik değeri 0.03 olarak alındığında, sensitivite %56.3 spesifite: %71.7; IG/TG için AUC değeri 0.627 (%95 GA;0.500-0.753) bulundu ve en iyi kesme değeri 0,2 olarak alındığında, bu değer için sensitivite %59,4 spesifite %63 olarak hesaplandı.

Sonuç: İnce bağırsak ileusu olan hastalarda IG sayı ve IG/TG oranlarını incelediğimiz bu çalışmada, cerrahi tedavi ihtiyacı olan hastalarda bu parametrelerin daha yüksek olduğunu göstermiş olsak da yapılan analizler sonrasında klinik açıdan anlamlı bir belirteç olmadığı kanaatindeyiz.

Anahtar Kelimeler: Intestinal ileus, immature granulocyte, immature granulocyte to total granulocyte ratio.

Introduction

Ileus is a condition in which the regular progression of intestinal contents from proximal to distal does not occur because of mechanical obstruction that prevents intestinal contents or disrupts peristalsis for a neurogenic/functional reason (1). Ileus is one of the most common acute abdomen cases in the emergency department. Ileus is an emergency situation, which can progress with a high mortality rate

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if treatment management is not performed properly.

Multinucleated leukocytes such as neutrophils, basophils, and eosinophils are called granulocytes, but the forms of these cells that have not completed their granulopoiesis are called immature granulocytes. While immature granulocytes (IG) are not normally found in the peripheral blood of adult humans, it is present in conditions such as infection, stress, and systemic inflammation. Today, with modern technology, the IG ratio (the ratio of immature granulocytes to total granulocytes; IG/TG) is calculated automatically in the laboratories of hospitals using advanced blood counting devices. In recent years, studies on the IG/TG ratio have increased. These conducted studies generally evaluate the usability of the IG/TG ratio instead of lactate, procalcitonin, white blood cell, and CRP (C-reactive protein) parameters as a predictor of mortality and morbidity in diseases such as sepsis, appendicitis, and pancreatitis (2-7). Recent studies show that IGs are more effective markers than white blood cells and C-reactive proteins in determining the severity of inflammation (7). Delta neutrophil index (DNI) is the proportion of IGs in the circulating blood (8). Since infectious conditions are associated with high IG levels, many researchers have investigated whether they can be used to predict the occurrence of sepsis (9).

Although laboratory parameters examined after anamnesis and physical examination are helpful in the diagnosis of intestinal obstructions, they are insufficient for a definitive diagnosis. Patients are usually directed to advanced imaging methods, particularly to exclude differential diagnoses(10). However, delays in diagnosis using these methods can increase morbidity and mortality in patients who require urgent surgical intervention. Additionally, the unnecessary use of these methods causes economic losses in the health system (11, 12). In this context, it is important to determine the appropriate treatment with fast, cheap, and easy methods.

In our study, we aimed to determine the IG and IG/TG ratio levels in patients diagnosed with intestinal ileus in the emergency department and to show the value of these inflammatory markers in predicting the need for surgical treatment.

Material and Method

This research was a single-centre and prospective cross-sectional study. The local ethics committee approval was obtained (23.11.2021 2012-KAEK-15/2422). Our study included patients aged 18 years and older admitted to the emergency department between 23.11.2021 and 07.04.2022 and were diagnosed with small bowel intestinal obstruction after clinical laboratory and radiological evaluation. The patients who complained of nausea, vomiting, abdominal distension, abdominal pain, and inability to pass gas were considered to have intestinal ileus. This was diagnosed according to clinical guidelines, clinical presentation (with four cardinal symptoms of intestinal obstruction in their history, such as abdominal

pain, vomiting, constipation/absolute constipation, and flatulence), abdominal X-ray, and/or IV contrast abdominal tomography. In our study, patients with clinical signs and imaging of intestinal obstruction were included after receiving the final diagnosis following general surgery consultation. The patients were divided into two groups: those who underwent surgery and those who did not. Conservative treatment was the first treatment option for patients without signs of strangulation, in which a nasogastric tube, decompression, and intravenous fluid resuscitation were performed. Patients were mobilized as much as possible to increase bowel movement. If gas passage was confirmed with improved radiological findings, the nasogastric tube was removed, and a diet plan was formed. Indications for surgical intervention were based on closely monitoring clinical symptoms and serial radiological findings. Their surgeon, who followed up on each patient, made the final decision for surgical intervention.

Demographic characteristics such as age and gender, presence of comorbidities (diabetes, hypertension, heart diseases, and other diseases), blood gas parameters (pH, bicarbonate, and lactate), complete blood count parameters (white blood cell, lymphocyte, neutrophil, haemoglobin, platelet, immature granulocyte count, and immature granulocyte ratio), the status of having undergone surgery, post-emergency service status (discharge, hospitalization, intensive care unit admission, exitus), and the duration of stay in the emergency clinic of the patients were recorded. IG and IG/TG, which were studied in the parameters of the complete blood count (CBC) of the blood sample taken from the patients at admission to the emergency department, were evaluated. The immature granulocyte ratios and other complete blood count parameters of the patients participating in the study were studied on the Mindray BC-6800 (CHINA) device. Patients with malignancy, with incarcerated hernia, colonic obstruction, inflammatory bowel disease, adynamic ileus, and other acute and chronic inflammatory conditions that change the immature granulocyte ratio (such as acute infection, sepsis, pancreatitis, cirrhosis, chronic renal failure) those receiving chemotherapy and pregnant women were excluded from the study.

Statistical Analysis

The sample size of our study was calculated using the G-Power for Mac OS X (version 3.1.9.2; Universitat Düsseldorf, Germany) program, and it was decided to include 32 patients per group for the two-way analysis, and 70 patients in total considering possible protocol bias provided that Type-1 error level was accepted as 5% and Type-2 error level was accepted as 80%, the difference between the immature/total granulocyte ratios being approximately 0.2 units and a standard deviation being 0.07 between the groups that did and did not undergo surgery in our study.

All data obtained during the study and recorded in the study form were analysed using the IBM SPSS

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20.0 (Chicago, IL, USA) statistical program. Whether the distribution of discrete and continuous numerical variables is suitable for normal distribution was investigated by Kolmogorov Smirnov test. Descriptive statistics were presented as median (IQR–Inter Quartile Rate 25-75) for discrete and continuous numerical variables, and as number of cases and (%) for categorical variables. Categorical variables were evaluated with Chi-square and continuous variables were evaluated with Mann Whitney U test. Receiver-Operating Characteristic (ROC) analysis was performed for immature granulocyte and immature granulocyte/total granulocyte ratio, and Area Under Curve (AUC) values were calculated to distinguish between patients who did and did not undergo surgery. The statistical significance level was determined as p value <0.05.

Results

During our study, 86 patients met the inclusion criteria, and 8 patients were excluded because their data was missing (8 patients could not be included in the study because they went to another hospital or were referred). A total of 78 patients were included in the study. 46.2% (n=36) of the patients included in the study were female. The median age was 65 (IQR 25-75; 51-77.2) (n=32) when surgical intervention was performed. The median IG of all patients included in the study was 0.02 (IQR 25-75; 0.01-0.03), and the median per cent of IG/TG was 0.1% (IQR 25-75; 0.1-0.2). Demographic, clinical descriptive characteristics, and laboratory parameters of the patients are given in Table 1.

The patients were divided into two groups: those who underwent surgical treatment and those who were followed conservatively. There was no statistically significant difference between the two groups regarding age, gender, and comorbid diseases (p>0.05 for all values). It was determined that neutrophil, platelet, IG, and IG/TG ratios were higher, lymphocyte values were lower, and hospital stays were longer in patients who underwent surgical intervention (p<0.05 for all values) (table 2).

ROC analysis was performed, and AUC was calculated to determine the threshold value of the IG level between the patients who did and did not undergo surgery. Accordingly, the AUC value was 0.658 (95% CI: 0.533-0.782). When the best cut-off value of IG was taken as 0.03 to distinguish between patients who did and did not go surgery, the sensitivity for this value was calculated as 56.3% and the specificity as 71.7%. When the same analyses were performed for IG/TG, the AUC value was found as 0.627 (95% CI; 0.500-0.753), and when the best cut-off value for IG/TG was taken as 0.2, the sensitivity for this value was calculated as 59.4% and the specificity as 63% (figure 1).
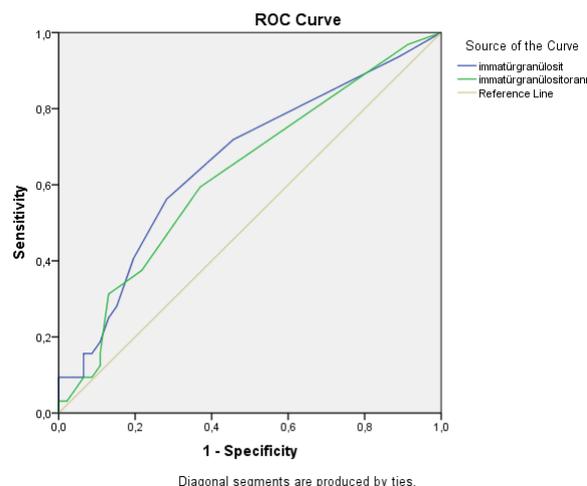

Figure. 1. ROC analysis for IG levels and IG/TG ratios between patients who underwent surgery and those followed conservatively

Table 1. Demographic Data of Patients (n=78)

Median age, IQR (25-75)	65 (51-77.2)
Gender, n (%) Male Female	 42 (53,8) 36 (46,2)
Comorbid diseases, n (%) Hypertension Diabetes Coronary heart disease Other	 23 (29,5) 19 (24,4) 5 (6,4) 20 (25,6)
Those who underwent surgery, n (%)	32 (41)
Laboratory, Median, IQR (25-75) White Blood Cell Neutrophil Lymphocyte Haemoglobin Platelet pH HCO3 Lactate Immature granulocyte Immature granulocytes/total granulocytes %	 13.2 (8.1-15.5) 10.2 (5.4-13) 1.4 (0.82-2.06) 13.4 (11.8-15.8) 298 (223-346) 7.40 (7.34-7.44) 24 (21-27) 1.7 (1.3-2.97) 0.02 (0.01-0.04) **0.1 (0.1-0.3)**
Length of stay in the emergency department, hours, median, IQR (25-75)	3 (2-3)
Emergency Service Exit, n (%) Hospitalised in ward Admission to the intensive care unit Discharged In-hospital death	 51 (65,4) 12 (15,4) 14 (17,9) 1 (1,3)
30-Day Mortality, n (%)	12 (15,4)

Table 2. Comparison of Patients who underwent surgery and those followed conservatively

	Those who underwent surgery (n= 32)	Medical follow-up (n=46)	P value
Age, Median, IQR (25-75)	68 (60-77)	63 (47-77)	0,344
Gender n (%) Male Female	19 (59,4) 13 (40,6)	23 (50) 23 (50)	0,491
Comorbid diseases n (%) Hypertension Diabetes Coronary heart disease Other	11 (34,4) 10 (31,2) 4 (12,5) 8 (25)	12 (26,1) 9 (19,6) 1 (2,2) 12 (26,1)	0,430 0,165 0,153* 0,914
Laboratory Parameters White Blood Cell Neutrophil Lymphocyte Haemoglobin Platelet pH HCO3 Lactate Immature granulocyte Immature granulocyte ratio	13.6 (10.1-15.7) 11.8 (8.4-13.6) 1.3 (0.73-1.6)2 13.4 (11.4-16.6) 312 (256-399) 7.39 (7.34-7.45) 24 (21-27.5) 2 (1.6-3.7) 0.03 (0.01-0.57) 0.2 (0.1-0.4)	13.1 (7.37-14.9) 8.7 (4.7-11.9) 1.7 (0.96-2.74) 13.7 (11.9-15.2) 276 (203-316) 7.41 (7.36-7.43) 24 (19.1-26) 1.5 (1.3-2.2) 0.01 (0.01-0.03) 0.1 (0.1-0.2)	0,164 **0,025** **0,019** 0,566 **0,007** 0,840 0,442 **0,048** **0,016** **0,044**
Length of stay in the emergency department, hours, median, IQR (25-75)	3 (2.5-3)	2.5 (2-3)	0,040
30-day mortality n (%)	5 (15,6)	7 (15,2)	0,961

*Fisher exact test is applied.

Discussion

Although many biomarkers that can predict the need for surgical treatment of patients diagnosed with intestinal ileus have been investigated, more effective, inexpensive, and fast-resulting biomarkers have not been determined yet. This study examined the relationship between IG and IG/TG ratios and treatment outcomes in patients diagnosed with intestinal ileus in the emergency department. We found that IG counts and IG/TG ratios were higher in patients with intestinal ileus who underwent surgical treatment than those who were followed conservatively. However, we had a weaker result in the ROC analysis that we performed to determine the threshold value of immature granulocyte and immature granulocyte percentages for predicting surgical treatment. The limited number of studies on immature granulocytes in patients with ileus makes our results important.

Although we found the IG and IG/TG ratio high in patients who underwent surgery for intestinal ileus, we do not think they are clinically significant markers.

In the physiopathology of intestinal obstruction, septic shock occurs when the hypovolemic picture progresses, and this inflammatory process also affects blood parameters. The causes of this inflammatory process can be counted as excessive bacterial proliferation due to the deterioration of the intestinal flora. Bacterial translocation may develop with the progression of the clinical condition, mucosal damage in the intestine due to hypovolemia, and increased intestinal wall permeability. In inflammatory processes, a "left shift", i.e., the appearance of immature granulocytes in the peripheral blood, occurs in adults. Today, studies examining immature granulocyte values in peripheral blood in diseases such as acute appendicitis, acute pancreatitis, and sepsis are used to predict diagnosis, prognosis, mortality, disease severity, or treatment need. However, the results of studies on this subject in the literature seem to contradict one another (13, 14-17).

In the literature, studies have investigated the use of IG, which represents the number of IG in the peripheral circulation, mortality, diagnosis, and treatment of infection-related conditions (18, 19). The effectiveness of IG as an early predictor of surgery in patients with intestinal obstruction in South Korea in 2017 was evaluated retrospectively by Lee et al. The study was conducted with 171 ileus patients, and 22% required early operation. As a result of the study, ROC analysis related to the need for the operation was performed according to the IG value, and the sensitivity was 23.7%, the specificity was 89.5%, and AUC = 0.543. Although a statistically weak result was obtained, the authors evaluated the number of IG as an early predictor of the need for operation (20). We obtained similar results in our study but we think this is not clinically usable since the AUC value was low.

In another study by Cha et al., the number of IG in predicting strangulation in mechanical intestinal ileus was investigated. This study had 160 ileus patients divided into two groups: the strangulation and non-strangulation groups. Afterwards, separate ROC analyses were performed for the number of IG, abdominal computed tomography (CT) results only, and the number of IG-CT combinations. The areas under the ROC curve were 0.713, 0.883, and 0.983, for DNI only, CT only, and the number of IG-CT combinations, respectively. In addition, when the number of IG and CT strangulation prediction levels were compared separately, it was stated that there was no statistically significant difference. As a result, it was reported that the initial number of IG measured in the emergency services was higher in the group that developed strangulation than in the group that did not, and there was a statistically significant difference. Cha et al. explained that their results were significant with bacterial overgrowth, increased intestinal permeability, and/or physical deterioration of the mucosal barrier in mechanical intestinal obstructions that developed strangulation. It has been interpreted that immature granulocyte levels may increase in mechanical intestinal obstruction independent of strangulation. It has also been stated that the number of IG in the first

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application can be a useful parameter that can be used to increase its predictiveness, although it cannot replace CT (21). However, our findings differ from these results. The systemic inflammatory process is affected by many conditions and parameters. Our older patient group may have affected our results due to the insufficient inflammatory response in the geriatric population. In conclusion, intestinal obstructions are usually managed according to clinical symptoms and preference of the surgeon. Initial IG and IG/TG ratio are not useful predictors of surgical intervention in patients with intestinal obstruction.

Limitations

There are certain limitations of our study. First, we may have fallen short of what was expected to represent the universe since it occurred in a single centre. The fact that the patient population admitted to the emergency department with intestinal ileus consists of patients with advanced age and comorbidities may have affected our analyses and results. Our study was observational, and no changes were made in the treatment process of the patients. The treatment of patients related to our study (patient's clinical condition, patient's own surgery decision, etc.) may have affected our results that were not determined by standard protocols. In our study, automatic counting hemogram devices were used instead of the flow cytometry method, accepted as the gold standard in calculating IG number and IG/TG ratio, which may have affected our results.

Conclusion

Our study found that IG and IG/TG ratios were higher in patients who underwent surgery and were first diagnosed with intestinal ileus. However, we think that these are not clinically significant markers. There are limited number of studies in the literature on IG count or IG/TG ratio in patients with intestinal ileus. For this reason, more studies are needed on this subject.

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Availability of data and materials: The dataset generated and/or analyzed during the current study are available from corresponding author.

Conflict of interest: The authors declare that there is no conflict of interest.

Informed consent: Written informed consent could obtained from patients

Ethical approval: Ethical approval for this study was obtained from Atatürk Sanatoryum Training and Research Hospital Ethics Committee (12/07/2020, number:2012-KAEK-15)

Human rights: The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Author Contributions

Conception: H.Y, E.E., Data Collection and Processing: H.Y, M.Y., Design: E.E., M.Y., Supervision: E.E, Ş.K.Ç., Y.Ç Analysis and Interpretation: E.E, Ş.K.Ç., Y.Ç, Literature Review: H.Y., M.Y., Writer: H.Y., E.E; Critical Review: Ş.K.Ç., Y.Ç.

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