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Use of platelet large cell ratio as a new biomarker in the diagnosis of acute appendicitis

Akut apandisit tanısında yeni bir biyobelirteç olarak trombosit büyük hücre oranının kullanımı

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Abstract

Aim: Acute appendicitis (AA) is one of the common causes of acute abdomen. Despite classical signs and symptoms, it may not always be easily and quickly diagnosed. Although many laboratory and imaging methods and risk scoring systems are available, studies are currently underway to find new biomarkers. In this study, we aimed to investigate whether Platelet-Large Cell Ratio (P-LCR), one of the platelet parameters, can be used as a new biomarker.

Methods: This retrospective cross-sectional study was performed by scanning the hospital records of AA patients, as determined with histopathological examination, who were diagnosed between 01 January-November 2019.The patients were divided into three as normal appendectomy (Group 1), non-complicated appendicitis (Group 2) and complicated appendicitis (Group 3) groups, which were compared in terms of P-LCR and other platelet parameters.

Results: A total of 425 patients were included in the study. The number of female patients in Groups 1, 2 and 3 were 12 (36.4%), 42 (45.7%), and 121 (40.3%), respectively. The mean age of the patients was 27.2 (16.1) years. Among all, complicated and uncomplicated appendectomy groups had significantly higher WBC and lower PDW and P-LCR values compared to the normal appendectomy group (P=0.007, P=0.027 and P=0.036, respectively). The cut-off values of WBC and P-LCR were 11.47 (71.9% sensitivity, 51.5% specificity) and 19.85 (75.8% sensitivity, 32.4% specificity), respectively. The WBC and P-LCR values had strong distinguishing features compared to other parameters (AUC=0.630, P=0.013 and AUC=0.604, P=0.047, respectively).

Conclusion: This is the first study investigating the P-LCR value in the diagnosis of AA. We found that WBC, PDW and P-LCR values, which are whole blood count parameters, can be used in the diagnosis of AA.

Keywords: Acute appendicitis, Platelet large cell ratio, Platelet count, Mean platelet volume, Platelet distribution volume

Öz

Amaç: Akut apandisit, akut karnın yaygın nedenlerinden biridir. Klasik belirti ve semptomlara rağmen, her zaman kolay ve hızlı bir şekilde teşhis edilemeyebilir. Birçok laboratuvar ve görüntüleme yöntemi ve risk skorlama sistemi mevcut olmasına rağmen, yeni biyobelirteçleri bulmak için çalışmalar devam etmektedir. Bu çalışmada trombosit parametrelerinden biri olan Trombosit-Büyük Hücre Oranının (P-LCR) yeni bir biyobelirteç olarak kullanılıp kullanılamayacağını araştırmayı amaçladık.

Yöntem: Çalışma, retrospektif tanımlayıcı bir çalışma olarak planlanarak, 01 Ocak 2019 ve Kasım 2019 tarihleri arasında gerçekleştirildi. Akut apandisit tanılı hastaların kayıtları tarandı. Hastalar histopatolojik sonuçlarına göre normal apendektomili, non-komplike apandisitli ve komplike apandisitli olmak üzere üç gruba ayrıldı. Gruplar P-LCR ve diğer trombosit parametreleri açısından karşılaştırıldı.

Bulgular: Toplam 425 hasta çalışmaya dâhil edildi. Gruplardaki kadın hasta sayıları sırasıyla 12 (%36,4), 42 (%45,7) ve 121 (%40,3) idi. Hastaların yaş ortalaması 27,2 (16,1) idi. Komplike ve komplike olmayan apendektomi grupları, normal apendektomi grubu ile karşılaştırıldığında, anlamlı derecede yüksek WBC düzeyleri ve düşük PDW ve P-LCR değerleri saptandı (P=0,007; P=0,027 ve P=0,036). WBC sayısı eğri altındaki alan (AUC) 0,63 idi ve diğer parametrelere göre güçlü ayırt edici özelliğe sahip idi (P=0,013). WBC'nin cut-off değeri 11,47 alındığında sensitivitesi %71,9, spesifisitesi %51,5 bulundu. P-LCR'nin cut-off değeri 19,85 alındığında ise sensitivitesi %67,6, spesifisitesi %32,4 idi (AUC=0,396; P=0,047).

Sonuç: P-LCR'nin akut apandisit tanısında kullanılabilirliği ile ilgili yapılan bu ilk çalışmada, tam kan sayımı parametreleri olan WBC, PDW ve P-LCR değerlerinin akut apandisit tanısında kullanılabileceği bulunmuştur.

Anahtar kelimeler: Akut apandisit, Trombosit büyük hücre oranı, Trombosit sayısı, Ortalama trombosit hacmi, Trombosit dağılım hacmi

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Ethics Committee Approval: Approval was obtained from Ataturk University Medical Faculty Ethical Committee with the date and number of 07.11.2019/07-51. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
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Introduction

Acute appendicitis (AA) is one of the most common causes of acute abdominal surgery in all age groups [1,2]. The probability of having AA in any period of life is 7-8% [3]. It is more common in developed countries and males [4,5]. The diagnosis of AA in patients admitted to the emergency department is usually based on the patient's history, physical examination, laboratory parameters, and radiological tests. Several risk scoring systems have also been developed to avoid missing the diagnosis [6-8]. Despite this, some patients are still misdiagnosed, who may later present with perforated appendicitis. In such cases, the risk of mortality increases, and the healing process is prolonged. However, patients who were operated for suspected appendicitis had normal appendectomy pathology postoperatively.

Complete blood count (CBC) is one of the most frequently requested tests by the emergency department physicians. It is also routinely requested by surgeons preoperatively to evaluate inflammatory pathologies [9]. Although elevated white blood cells (WBC) and neutrophil count, which are among the CBC parameters, are early indicators of AA, their sensitivity and specificity may vary according to the duration of symptoms and population [10,11]. These laboratory tests cannot definitively diagnose or exclude AA but may support its diagnosis [11]. Various biomarkers and blood parameters have been studied for the diagnosis of AA. Leukocyte count and C-reactive protein (CRP) levels are widely used in emergency departments [10,12-14]. Recently, platelet count (PC) and morphological tests have also been frequently investigated for the diagnosis of AA [1,2]. It was emphasized that these tests may have a prominent place in various gastrointestinal diseases and surgical outcomes [15].

The appendix is a structure with intense lymphatic activity. Excessive lymphatic activity in inflammation of the appendix may have the potential to affect platelet parameters. Early diagnosis of AA is sometimes impossible despite classical symptoms and clinical findings. Recent studies suggest that platelet parameters play a significant role in inflammation and may be inflammatory biomarkers [16,17]. There has been no previous research on platelet-large cell ratio (P-LCR) levels in acute appendicitis.

We assessed platelet-large cell ratio (P-LCR) levels in acute appendicitis, as well as the relationship between AA and PC, mean platelet volume (MPV), platelet distribution volume (PDW), plateletcrit (PCT) and WBC levels.

Materials and methods

Study design and population

This study was conducted on patients admitted to the emergency department of a third-level university hospital. It was a single-center retrospective analysis of patients diagnosed with AA between January 01, and November 2019. Approval was obtained from Ataturk University Medical Faculty Ethics Committee with the date and number of 07.11.2019/07-51. Information about patients diagnosed with AA and the procedures performed were obtained from the hospital registry.

Three groups were formed based on the histopathological findings of the patients operated for AA. The groups were categorized by histopathological reports as those with normal appendices (normal appendectomy group), positive appendicitis findings (non-complicated appendicitis group), and complicated cases with abscesses, perforation, gangrene, phlegmon, and plastron (complicated appendicitis group).

Patients with hematologic disease, chronic infectious disease or inflammatory disease, heart failure, liver disease, cancer, vascular disease, medications that could affect platelet counts and indices, and data deficiency were excluded from the study. P-LCR, PC, PDW, MPV, PCT, and WBC values were compared between the appendicitis vs. non-appendicitis and complicated vs. non-complicated groups.

Laboratory examination

Blood samples were collected into ethylene diamine tetraacetate (EDTA) sample tubes for CBC in our hospital, which was performed using a Sysmex XN-1000 hematology analyzer. The reference ranges of the parameters used for the study are as follows: Red blood cells (RBC = 4.7-6.1X10^6 /μL), MPV (5.91–11.32 fl), PCT (0.17-0.39%), PDW (12.2-15.9%), WBC (3.9-10.8X103 /μL), hemoglobin (HBG: 14.4-18.3 g/dL), PC (145–344 × 103 /μL) and P-LCR (17.5-42.5%).

Statistical analysis

SPSS 25 Statistics version (IBM Corporation, New York, NY, USA) software package was used for statistical analysis. Data were presented as mean, standard deviation, median, minimum, maximum, percentage and number. The normal distribution of continuous variables was analyzed by Shapiro Wilk test. To calculate the difference between the groups, ANOVA and Kruskal Wallis tests were used for normally and non-normally distributed data, respectively. Tukey test was used as a post hoc test between the groups. The receiver operating characteristic (ROC) curve analysis was performed to identify the role of CBC parameters in AA diagnosis between the groups. The comparison between the categorical variables was made using the Chi-square test and Fisher's Exact test. The statistical significance level was $P<0.05$.

Results

A total of 469 patients' electronic files were accessed from the hospital automation system. Forty-four patients were excluded after the implementation of the exclusion criteria, which left 425 patients to be included in the study. The inclusion and exclusion status of the participants were briefly given in the Figure 1. The histopathological reports of 76.6% (n=300) of the patients was compatible with uncomplicated appendicitis, since they did not have abscess, perforation, gangrene, phlegmon, and plastron in histopathological examination.

There were 250 males (58.8%). The mean age of the patients was 27.2 (16.1) years. Complicated and uncomplicated appendectomy groups had significantly higher WBC levels and lower PDW and P-LCR values compared to the normal appendectomy group (P=0.007, P=0.027 and P=0.036, respectively). Other demographic characteristics and laboratory findings of the patients are presented in Table 1.

According to ROC analysis shown in Table 2, PDW, WBC and P-LCR values were statistically significant in the

differential diagnosis of acute appendicitis, but only WBC number (AUC=0.63) had a strong distinguishing feature (P=0.013). The cut off value of WBC was 11.47 with a sensitivity and specificity of 71.9% and 51.5%, respectively (AUC=0.630, P=0.013).

The cut-off value of P-LCR was 19.85, with a sensitivity and specificity of 75.8% and 32.4%, respectively (AUC=0.604, P=0.047), which were enough for discrimination between the groups (Table 2, Figure 2).

All other parameters had an AUC of less than 0.60 and were insufficient for differential diagnosis. In the diagnosis of acute appendicitis, the cut off value of PDW was 10.05, with a sensitivity and specificity of 63.3% and 30.3%, respectively (AUC=0.397, P=0.049).

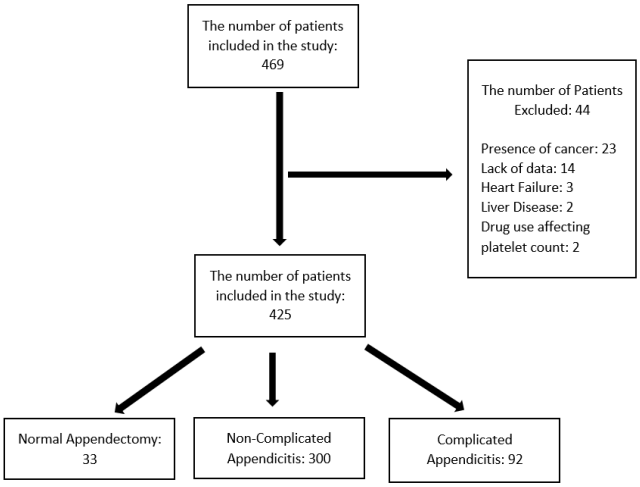

Figure 1: Flow chart of study

Table 1: Comparison of demographic and laboratory values in normal appendectomy, complicated appendicitis and non-complicated appendicitis groups

Characteristic	Normal appendectomy (n=33)	Complicated appendicitis (n=92)	Non-complicated appendicitis (n=300)	*P*-value
Age, years	28.6 (20.6) (3-81)	26.9 (17.7) (3-88)	27.2 (15.1) (3-82)	0.042[a]
Gender Female n (%)	12 (36.4%)	42 (45.7%)	121 (40.3%)	0.560[b]
RBC(10^6/µL)	4.8 (0.7) (3.1-5.6)	4.9 (0.6) (2.8-6.1)	4.9 (0.6) (3.2-6.3)	0.683[b]
MPV (7,4-10,4 fL)	10.6 (1.2) (8.5-14)	9.8 (0.8) (8.5-12)	9.9 (0.9) (8.2-13.7)	0.052[c]
PCT (%)	0.3 (0.1) (0.1-0.9)	0.3 (0.1) (0.1-0.5)	0.3 (0.1) (0.1-0.6)	0.555[c]
PDW (%)	11.9 (3) (8.3-24.1)	10.8 (1.4) (8.4-15.2)[d]	11 (2.1) (7.9-23.2)[d]	0.027[b]
WBC (10^3/µL)	11.9 (3.6) (5.7-19.8)	14.8 (4.7) (3.4-27.2)[d]	13.8 (4.9) (3.4-39.5)[d]	0.007[c]
HGB (g/dL)	13.7 (2) (8.6-17.2)	13.8 (1.9) (8.9-17.4)	14 (2.2) (8.6-38.1)	0.884[c]
PC (10^3/µL)	287.5 (148.4) (130-917)	272.3 (81.8) (110-569)	267.9 (79.4) (60-608)	0.736[c]
P-LCR (%)	27 (9.2) (13.9-53)	23.2 (5.9) (12.3-38.7)[d]	23.8 (7.5) (10.7-53.6)[d]	0.036[b]

[a] Pearson Chi-Square Test, [b] One Way ANOVA Test, [c] Kruskal Wallis Test, [d] Complicated and uncomplicated appendectomy were significant compared to normal appendectomy (P<0.05)

Table 2: Receiver operating characteristic curve for the predictors of cases with positive appendectomy

Parameter	Cut off	AUC	*P*-value	Sensitivity (%)	Specificity (%)	95% CI
RBC(10^6/µL)	>4.75	0.504	0.946	63.8	39.4	0.394-0.613
MPV (fL)	>9.45	0.399	0.053	64.3	24.2	0.297-0.501
PCT (%)	>0.235	0.466	0.513	63	33.3	0.355-0.576
PDW (%)	>10.05	0.397	0.049	63.3	30.3	0.289-0.505
WBC (10^3/µL)	>11.47	0.630	0.013	71.9	51.5	0.538-0.723
HGB (g/dL)	>13.25	0.521	0.686	65.8	36.4	0.412-0.631
PC (10^3/µL)	>231.5	0.498	0.972	65.1	39.4	0.386-0.610
P-LCR (%)	>19.85	0.604	0.047	75.8	32.4	0.291-0.501

CI: confidence interval, AUC: area under curve

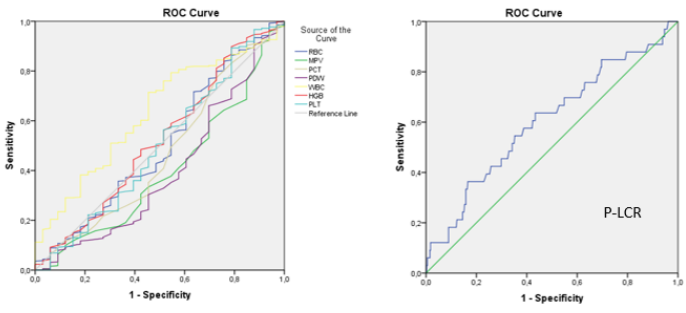

Figure 2: ROC curve of parameters for the diagnosis of acute appendicitis

Discussion

With this study, P-LCR test results are assessed in the diagnosis of AA for the first time in the literature. Although P-LCR was statistically significant in its diagnosis, ROC analysis revealed that AUC was low, and it was negatively correlated with AA. Also, the increase in the number of WBC was important in the diagnosis of AA, while the increase in other CBC parameters was not.

Despite developing laboratory and radiological imaging methods, the differential diagnosis of acute appendicitis can still lead to complications due to delayed or incorrect diagnosis in some atypical cases [9]. Imaging methods may not be available in various health centers. More easily accessible and inexpensive methods are being tried out to reduce these complications. Since AA is an inflammatory process, CBC parameters are one of the most commonly used methods in studies predicting AA.

There are many studies on CBC parameters in the diagnosis of AA, the results of which differ. Some parameters deemed useful in diagnosis by numerous studies have been contrarily reported in others [2,9,11,14,15,18]. In these studies, it was emphasized that WBC was useful and available in predicting the diagnosis of AA. A consensus is yet to be reached on the other CBC parameters. In our study, WBC was significant in the prediction of AA, with a sufficient AUC value in ROC analysis and a positive correlation with AA.

Recently, platelet and indices of these parameters have been investigated frequently. Platelets have been found to play significant roles in inflammation. The activity and function of platelets have been associated with their size. Larger platelets are thought to be younger and more reactive [1,2,9,19]. Our study contradicts these studies in terms of PC, and the statistical significance of PC in the diagnosis of AA could not be determined.

Among platelet indices, PDW and MPV are markers which indicate platelet activation. Several studies in the literature have also given conflicting results with many diseases. Some have emphasized that they can be used in the diagnosis while others reported conflicting results. Boshnak et al. [9] emphasized that high WBC and PDW values can be used as diagnostic tests for diagnosis of acute appendicitis, and MPV cannot. Biomarkers such as WBC and CRP have been considered useful in predicting AA, but some studies have reported that these do not safely exclude AA [1]. Yigit et al. [1] determined that MPV and PDW values could not be used as biomarkers in the diagnosis of AA. Gunes et al. [20] emphasized that high WBC and PCT levels support AA diagnosis, while other parameters, MPV and PDW, do not. Sepas et al. [2] reported that MPV and PDW values may be significantly associated with AA and used as new biomarkers in its diagnosis. As a result of this study, we foresee that WBC can be conveniently used for the diagnosis of AA and other CBC parameters cannot.

P-LCR represents the percentage of circulating platelets greater than 12 fL and is more reactive than other platelet parameters [21]. In the literature, P-LCR has not been reported for use in the diagnosis of acute appendicitis, rather, its elevation is investigated in atherosclerotic vascular diseases and its relationship with coronary vessel diseases is assessed. While some argued that P-LCR may be related to coronary vascular

diseases, further studies stated otherwise [21-23]. Cerit et al. [22] compared coronary ischemia with platelet parameters and found that P-LCR value was significantly higher in coronary artery patients than in the control group. In their study on coronary artery diseases, De Luca et al. [23] emphasized that P-LCR levels could not be used in coronary diseases. Our study is the first in the literature investigating whether P-LCR level can be used to predict AA diagnosis.

Limitations

The retrospective and single-center design of the study were its main limitations. Due to its retrospective nature, we could not question whether patients used drugs affecting platelet parameters. Only drugs used from hospital data could be accessed. Our other limitation was hematological malignancies, which were undiagnosed and more common in the elderly population. Only appendiceal malignancies were excluded. Further prospective and multi-center studies are needed.

Conclusion

In our study, hemogram parameters were investigated in patients with normal appendices, non-complicated appendicitis, and complicated appendicitis with histopathological identification of acute appendicitis. From these parameters, it was determined that WBC, PDW and PLCR can be used in the differential diagnosis of acute appendicitis.

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