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The value of serum fibrinogen level in the diagnosis of acute appendicitis

Akut apandisit tanısında serum fibrinojen düzeyinin değeri

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BACKGROUND
The aim of this study was to investigate the importance of serum fibrinogen level in the diagnosis of acute appendicitis.

METHODS
This study was performed on 201 patients who admitted to our clinic. Symptoms, signs, duration of symptoms, and laboratory indicators of appendicitis were recorded, in keeping with the Alvarado score for acute appendicitis. The ultimate diagnosis was based on histopathological results. Serum fibrinogen levels were detected before surgery. The sensitivity, specificity, and predictive values of single test and test combinations were calculated at different cut-off levels.

RESULTS
During the study period, 201 patients underwent surgery for suspected acute appendicitis. Appendicitis was confirmed in 179 (89%) patients. The mean age was 24.8±7.7 (range, 20-57) years, and 154 (76.6%) patients were male and 47 (23.4%) female. The best diagnostic cut-off point for fibrinogen was found at 245.5 mg/dl, for white blood cells (WBC) at 11,900x10^9/L and for Alvarado score at 7.

CONCLUSION
The use of fibrinogen blood level may be a new diagnostic acute-phase reactant in the diagnosis of acute appendicitis. The formulation of a triple test is recommended as criteria in deciding emergency surgery or observation.

Key Words: Acute appendicitis; fibrinogen; diagnosis.

AMAÇ
Bu çalışmada akut apandisit tanısında serum fibrinojen düzeyinin önemi araştırıldı.

GEREÇ VE YÖNTEM
Kliniğimize başvuran 201 hasta çalışmaya alındı. Hastaların semptomları, semptom süreleri, muayene bulguları, laboratuvar bulguları ve akut apandisit için Alvarado skorları kaydedildi. Kesin tanı histopatolojik inceleme ile konuldu. Ameliyat öncesi kan fibrinojen değerine bakıldı. Tek bir testin ve test kombinasyonlarının duyarlılık, özgüllük ve öngörü değeri farklı seviyelerinde hesaplandı.

BULGULAR
Çalışma süresinde 201 hasta akut apandisit ön tanısı ile ameliyat edildi. Histopatolojik inceleme sonrası 179 (%89) hasta akut apandisit tanısı aldı. Hastaların yaş ortalaması 24,8±7,7 (dağılım 20-57) yıldı, 154 (%76.6) hasta erkek, 47 (23.4%) hasta kadındı. Akut apandisit tanısı için kesim değeri fibrinojen için 245,5 mg/dl, beyaz küre sayımı için 11.900x10^9/L ve Alvarado skoru için 7 olarak bulundu.

SONUÇ
Akut apandisit tanısında fibrinojenin serum değeri yeni bir akut faz reaktamı olarak kullanılabilir. Üçlü test formülünün kullanılması gözlem veya acil cerrahi kararını vermede yardımcı olabileceği düşünülmektedir.

Anahtar Sözcükler: Akut apandisit; fibrinojen; tanı.

Acute appendicitis (AA) is the most common indication for emergent surgery and affects a wide range of patients at any age. Approximately 7% of the population will develop appendicitis at some time during their lives.[1,2] The aim of the clinical evaluation of patients with suspected AA is primarily performed in

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order to avoid appendiceal perforation and subsequent complications, while minimizing the number of unnecessary laparotomies.[3] The goal of modern surgical management is essentially the same and focuses on a balance between the rate of false-negative laparotomy and the rate of perforation at the time of surgical exploration.[4,5]

Various imaging modalities, biochemical markers, and scoring systems have been introduced, with a view to lower the negative appendectomy rate. However, there is continuing controversy about their routine use, while studies are ongoing to investigate how to improve the diagnostic accuracy in AA.[6]

In the past, studies have discussed the high incidence of negative appendectomy as a way of preventing perforation of the appendix. It was assumed that the morbidity associated with a negative appendectomy was not severe enough to allow the risk of appendiceal perforation. This aspect was challenged by Flum et al.,[7] who showed that patients who underwent negative appendectomy were also observed to have more comorbidities, longer length of hospital stay, and higher infection and case fatality rates. This and other studies have described the significant burden of negative appendectomy and have aimed to identify better diagnostic tests in the management of AA.

The aim of this study was to determine the predictive value of serum fibrinogen level in indicating appendectomy immediately.

MATERIALS AND METHODS

This study was performed on 201 patients who admitted to our clinic between March 2005 and May 2007 with suspected AA. Patient demographics and presenting signs and symptoms were documented. The patients' symptoms, signs, duration of symptoms, and laboratory indicators were recorded, in keeping with the Alvarado score for appendicitis.[8] Based on these findings, Alvarado score was calculated for each patient. Patient symptoms included nausea, vomiting, migratory pain, anorexia, right lower quadrant pain, body temperature >37.3°C, and white blood cell (WBC) count, left shift on differential. The WBC count was determined by a technical hematological cell counter (Beckman-Coulter, Krefeld), and the upper limit was defined as $10.0x10^9$/L. All removed appendixes were examined by a routine protocol in which the ultimate diagnosis was based on histopathological results.

Blood samples for determining fibrinogen serum levels were collected before the surgical procedure and measured by the clotting assay of Clauss method. The upper normal limit was defined as 400 mg/dl. The sensitivity, specificity, and predictive values of single test and test combinations were calculated at different cut-off levels.

The decision to operate was the prerogative of the surgeon based on overall clinical judgment.

Statistical Analysis

The non-parametric Kruskal-Wallis test was used for multiple group comparisons. In case of significance, individual differences were identified with the Mann-Whitney U test. All p values of <0.05 were considered as statistically significant. Receiver operating characteristic (ROC) curves and the related areas under the curve (AUC) were calculated. Tests for significance of AUC to be >0.5, calculation of 95% confidence limits of the AUC and comparison of ROC curves were done.

RESULTS

During the study period, 201 patients underwent surgery for suspected AA. Appendicitis was confirmed in 179 (89%) patients. The mean age was 24.8±7.7 (range, 20-57) years, and 154 (76.6%) patients were male and 47 (23.4%) female. To investigate the diagnostic value of fibrinogen, WBC, and Alvarado score, ROC curves were calculated. For the diagnosis of appendicitis, the best cut-off point for fibrinogen was found at 245.5 mg/dl, for WBC at 11,900, and for Alvarado score at 7 (Fig. 1). Predictive value, sensitivity, specificity, and accuracy of combined tests in the diagnosis of AA are shown in Table 1. Distribution of fibrinogen blood level, WBC and Alvarado score according to the final pathology are shown in Table 2.

According to the cut-off levels, risk factors were derived from an unconditional logistic regression

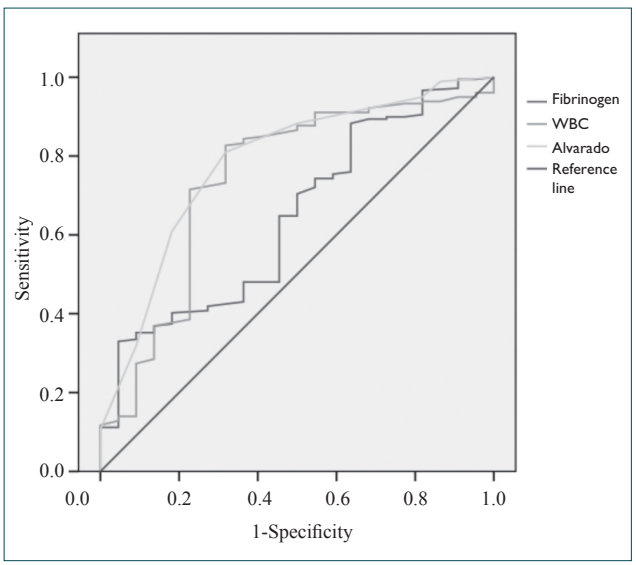

Fig. 1. ROC curve for fibrinogen blood level, WBC, and Alvarado score.

Table 1. Predictive value, sensitivity, specificity, and accuracy of combined tests in the diagnosis of acute appendicitis

Tests	PPV	NPV	Sensitivity (%)	Specificity (%)	Accuracy (%)	OR	95% CI for OR	
							Lower	Upper
Fibrinogen >245.5 mg/dl	91.97	17.18	70.39	50.0	68.16	2.38	0.97	5.82
WBC >11.950/L	96.24	25.0	71.51	77.27	72.14	8.53	2.99	24.35
Alvarado Score >7	96.43	20.22	60.34	81.82	62.69	6.85	2.22	21.06
Fibrinogen >245.5 mg/dl WBC >11.950 /L	96.81	36.0	85.05	75.0	84.03	17.06	4.16	69.92
Fibrinogen >245.5 mg/dl Alvarado score >7	94.77	29.03	77.78	81.81	78.18	15.75	3.17	78.30
Alvarado >7 WBC >11.950 /L	96.94	29.63	71.42	84.21	73.02	13.33	3.67	48.4
Fibrinogen >245.5 mg/dl Alvarado score >7 WBC >11.950 /L	98.55	42.86	85.0	90.0	86.0	51.0	5.91	440.11

analysis. According to the model, the probability of AA for an individual patient can be calculated as:

$1/1+2.66^{-y}$

y= -2.8066 + (0.0076 x fibrinogen blood level) + (0.5094 x Alvarado score) + (0.000035 x WBC) – (0.7082 x duration of symptoms [<24 h (1); ≥24 h (0)]).

The score had a minimum of zero and maximum of one point. The cut-off level for AA is ≥0.75. Over this level, we can estimate the real AA case in over 92.18%. If the score was <0.75, the possibility of appendicitis was less and the patient should be kept under observation. When the score reaches ≥0.75, the patient should be taken for surgery.

DISCUSSION

The aim of this study was to evaluate the value of the serum fibrinogen level in the diagnosis of suspected AA and to determine the relationship between the Alvarado score and WBC.

Many attempts have been made to determine ways of decreasing the negative laparotomy rate in clinically suspected AA. It would be very important to differentiate early appendicitis from non-specific abdominal pain. However, a carefully detailed history, physical examination, and standard laboratory studies do not always clearly detect early AA. Furthermore, delays in diagnosis can be harmful and may convert a relatively uncomplicated case to substantial morbidity or even mortality in patients with comorbid illnesses.

Table 2. Distribution of fibrinogen blood level, WBC, and Alvarado score according to the final pathology

Diagnosis (according to final pathology)	Fibrinogen blood level* (mg/dl) Mean ±SD$^{\Delta}$ (range, -)		White blood cell* Mean ±SD$^{\Delta}$ (range, -)		Alvarado score* Mean±SD$^{\Delta}$ (range, -)	
	≤245.5	>245.5	≤11.950/L	>11.950/L	<7	≥7
Normal appendix	9	13	18	4	15	7
	200.3±37.22 (range, 122-245)	327±56.63 (range, 246-449)	9030±1682.07 (range, 9100-11,800)	16.100±1186.03 (range, 15,200-17,700)	4.8±1.08 (range, 3-6)	7.75±0.88 (range, 7-9)
Simple acute appendicitis	24	60	25	59	22	62
	206.82±32.06 (range, 111-245)	339±71.64 (range, 246-505)	9487.5±2172.22 (range, 3900-11.800)	15.160±2350.23 (range, 12.000-21.300)	5.04±084 (range, 3-6)	8.16±1.05 (range, 7-10)
Gangrenous appendix	19	43	14	48	9	53
	219.15±20.35 (range, 160-245)	362.95±79.75 (range, 251-596)	9542.85±2145.01 (range, 4600-11,600)	16.229.16±3118.8 (range, 12,000-24,400)	4.8±1.16 (range, 3-6)	8.3±0.76 (range, 7-10)
Perforated appendix	8	25	3	30	2	31
	215.25±25.7 (range, 170-245)	37.4±83.84 (range, 250-605)	10.600±608.27 (range, 9900-10,900)	14.900±2208.65 (range, 12,000-21,300)	5.5±0.5 (range, 5-6)	8.29±0.9 (range, 7-10)

*Cut-off levels of parameters, Δ Standard deviation.

The optimal test should combine a high sensitivity with a high predictive value of a negative result. When using the test's standard reference interval, the manual determination of bands showed a significantly lower sensitivity compared with the other tests. Further, the diagnostic accuracy of a test may be improved by changing the cut-off level if the test result is considered positive. If the cut-off level is elevated, the sensitivity or number of true-positive patients detected by the test will decrease, while the specificity or number of true-negative patients will increase. The exact value of the test is determined by ROC calculation. We determined the exact value for WBC, Alvarado score and fibrinogen blood level by ROC calculation.

The WBC count is the test probably used most often to support the diagnosis of AA. However, WBC is a non-specific reaction induced by many different causes like physical stress, acute or chronic inflammation and several other conditions. In patients with AA, WBC show an average elevation to approximately $15.0x10^9$/L.[9] Pieper and colleagues[10] reported experience with 493 patients of whom only 67% had WBC greater than $11.0x10^9$/L. Cardall and colleagues[11] found the sensitivity of WBC as 76%, specificity as 52%, positive predictive value (PPV) as 42%, and negative predictive value (NPV) as 82%.

In our study, the best cut-off point of WBC for early diagnosis of AA was found as $11,900x10^9$/L, and at this point, the sensitivity, specificity, PPV, NPV, and accuracy were calculated as 72%, 77%, 96%, 25%, and 72%, respectively. In this respect, it can be said that if the WBC level is accepted as over $11,900x10^9$/L, its diagnostic value will be more reliable in the diagnosis of AA. In addition, we determined the probability of AA to be 8.53 times more when WBC is over $11,900x10^9$/L.

Diagnostic scores for AA have been claimed to lower the non-therapeutic operation rate. The Alvarado scoring system is a point scoring system for the diagnosis of appendicitis based on clinical science and symptoms and a differential WBC. The accuracy of the Alvarado score in a clinical preoperative diagnosis of AA has been reported as ranging from 50% to 95%.[9,10] In his original paper, Alvarado recommends surgery for all patients with a score of 7 or more and observation for patients with scores of 5 or 6.[8]

In our study, the best cut-off point of the Alvarado score for early diagnosis of AA was found as 7, and at this point, sensitivity, specificity, PPV, NPV, and accuracy were calculated at 60%, 82%, 96%, 20%, and 63%, respectively. According to our study results, probability of AA was found to be 6.85 times more when the Alvarado score was over 7. Plasma fibrinogen is an acute phase protein and therefore probably increases with inflammation or tissue necrosis. Interpretation of raised fibrinogen may be complicated by its behavior as an acute-phase reactant. For example, plasma fibrinogen concentrations are raised after acute stroke and acute myocardial infarction.[12] Among all known thrombin substrates, fibrinogen stands out as a central factor in hemostasis and a contributor to the inflammatory response.[13]

Fibrinogen deposition is a universal feature in injured tissues and inflammatory foci. *In vitro* studies have shown that fibrinogen can profoundly alter WBC function, leading to changes in cell migration, phagocytosis, production of chemokines and cytokines, degranulation, and other processes. Many of the effects of fibrinogen on leukocyte activity appear to be mediated by a specific receptor on leukocytes, the integrin receptor αMβ2.[14,15]

Leukocyte interaction with fibrinogen or its degradation products has special importance at sites of inflammation since fibrinogen may gain access to the extravascular compartment by exudation, where it encounters migrating leukocytes.[16] It is well known that both the extent of leukocyte recruitment and the proinflammatory action of the migrating leukocytes determine the intensity of an inflammatory reaction, and peripheral human neutrophils are capable of phagocytosis, spreading, and chemotaxis.[17-19]

We aimed to investigate serum fibrinogen level as a new marker in the diagnosis of AA. Our study is probably the first report to use fibrinogen blood level in the diagnosis of AA. In our current study, the best cut-off for serum fibrinogen level was found as 245.5 mg/dl, and at this point, the sensitivity, specificity, PPV, NPV, and accuracy were calculated as 70%, 50%, 92%, 17%, and 68%, respectively. Probability of AA was found to be 2.38 times more when fibrinogen blood level was over 245.5 mg/dl. Fibrinogen results were found to have similar efficacy to WBC and Alvarado scores in the diagnosis of AA.

Blood tests have been shown to have low sensitivity and specificity in differentiating simple AA from a perforated appendix in a majority of the studies.[20,21] However, in a few studies, the WBC was more sensitive than C-reactive protein (CRP) in the diagnosis of simple AA,[22] and CRP was reported as more sensitive than WBC in cases of a perforated appendix.[23]

Numerous studies have shown that increased CRP levels in the blood aid in the accurate diagnosis of AA. Han-ping Wu and colleagues[24] noticed that the mean CRP level in patients with perforated appendicitis was much greater than in patients with simple appendicitis, and they found the role of CRP did serve in the differential diagnosis of perforated appendicitis. That study

mentioned CRP levels using different cut-off values based on how long the patient's symptoms were present to improve the diagnostic accuracy of simple and perforated appendicitis, and that CRP would be helpful in predicting appendicitis earlier and reducing the rate of complications caused by delay in diagnosis. In our study, we found the same results according to fibrinogen blood level and the duration of symptoms (<24 h or >24 h). Fibrinogen blood level and duration of symptoms have shown to contribute greatly to the diagnosis of AA.

The diagnostic value of a single test in AA is limited because this process cannot be differentiated from other acute inflammatory conditions. The triple test combination's sensitivity, specificity, PPV, NPV, and accuracy were calculated as 85%, 90%, 99%, 43%, and 86%, respectively. Probability of AA was found to be 51 times more when the triple test levels were over cut-off levels.

In conclusion, AA remains the most common condition requiring emergent surgery. Early diagnosis plays a key role in preventing complications originating from perforation. However, surgeons must achieve a balance between premature operation with a high negative appendectomy rate and a delayed diagnosis (and surgery) with a higher perforation rate. There is no sign, symptom, or laboratory test that is 100% reliable in the diagnosis of AA.

Our results suggest that the use of fibrinogen blood level may be a new diagnostic acute-phase reactant in the diagnosis of AA. The formulation of the triple test's result is recommended as a guide in deciding which patient undergoes emergency surgery or observation.

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