

Research Article



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Evaluation of laboratory parameters in the diagnosis of acute appendicitis

Akut apandisit teşhisinde laboratuvar parametrelerinin değerlendirilmesi

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Abstract

Introduction: The aim of this prospective study was to investigate the diagnostic value of the fibrinogen level, platelet (PLT) count, mean platelet volume (MPV), lymphocyte count, neutrophil/lymphocyte ratio (NLR) and C-reactive protein (CRP) level with white blood cell (WBC) and neutrophil count in acute appendicitis (AA).

Methods: One hundred and ninety-seven patients who were admitted with the findings of acute abdomen and operated on with a preoperative diagnosis of AA were included in this prospective observational study. After surgery, according to the histopathological results of the appendix, patients were classified as Group 1; with normal histology of appendix vermicularis, Group 2; patients with positive histology for appendicitis with or without perforation, periappendiceal abscess, suppurative, gangrenous or ulcerophlegmonous appendicitis.

Results: In the comparison of the two groups, the difference between CRP and MPV were insignificant ($p=0.12$ and $p=0.09$, respectively). WBC, neutrophil count, NLR were significantly higher in Group 2 ($p<0.001$ for each), whereas fibrinogen levels, lymphocyte count and the PLT counts were significantly higher in Group 1 ($p=0.03$, 0.002 and 0.003 , respectively).

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Discussion and conclusion: WBC, neutrophil and NLR are predictive for the diagnosis of AA, whereas elevated levels of fibrinogen, high lymphocyte and PLT count are predictive for non-appendicial pathology with low diagnostic accuracies.

Keywords: Acute appendicitis; Fibrinogen level; Platelet count; Neutrophile/lymphocyte ratio; Mean platelet volume.

Özet

Giriş ve Amaç: Bu prospektif çalışmanın amacı akut apandisit teşhisinde kan lökosit sayımı ve nötrofil oranı yanında kan fibrinojen düzeyi, trombosit sayımı, ortalama trombosit volume (MPV), lenfosit sayısı, nötrofil/lenfosit oranı (NLR) ve C-Reaktif Protein (CRP) düzeylerinin tanısai değerini araştırmaktır.

Yöntem ve Gereçler: Bu prospektif gözlemsel çalışmaya akut karın ile başvurmuş ve akut apandisit teşhisi konularak ameliyat edilen yüz doksan yedi hasta dahil edildi. Histopatolojik sonuçlarına göre, hastalar iki gruba ayrılmıştır: Grup 1, apendiks vermicularis histopatolojisi normal olan hastalar; Grup 2 apendiks vermiformis patolojisi; perforasyon, periappendiküler apse, süpüratif gangren veya flegmon olup olmadığına bakılmaksızın akut apandisit olan hastalar idi.

Bulgular: Grup 1’de 28 (% 14.2) hasta ve Grup 2’de 169 (% 85.8) hasta saptandı. İki grubun karşılaştırılmasında, CRP ve MPV değerleri arasındaki fark (sırasıyla $p=0.12$ ve $p=0.09$) istatistiksel olarak anlamlı bulunmadı. Lökosit değerleri, nötrofil sayımı ve nötrofil/lenfosit oranı Grup 2’de anlamlı olarak yüksek bulundu (her biri için $p<0.001$). Fibrinojen düzeyi, lenfosit ve trombosit sayımı Grup 1’de anlamlı olarak yüksek bulundu ($p=0.03$, 0.002 , 0.003 sırasıyla).

Tartışma ve Sonuç: Lökosit sayısı, nötrofil sayımı ve nötrofil/lenfosit oranı akut apandisitte yüksek tanısai özellikte

iken yüksek fibrinojen düzeyi, yüksek lenfosit ve trombosit sayısı, düşük tanısal doğruluk ile akut apandisit patolojisi olmayan grupta kullanılabilir.

Anahtar kelimeler: Akut apandisit; Fibrinojen düzeyi; Trombosit sayımı; Nötrofil/lenfosit oranı; Ortalama trombosit oranı.

Introduction

Acute appendicitis (AA) is one of the most common abdominal emergencies. Approximately 7% of the population will develop AA during their lifetime [1, 2]. Patients with AA usually present with typical abdominal pain and physical findings include right lower quadrant rebound tenderness and muscle guarding. Delayed diagnosis may cause bacterial peritonitis, ileus, abdominal abscess and even sepsis as a result of appendiceal perforations. Therefore, early diagnosis of AA and differentiation from other causes of abdominal pain are essential [3, 4]. However, despite the introduction of modern imaging techniques, differential diagnosis is still a challenging issue.

Usually AA is diagnosed by means of history, detailed physical examination and routinely used laboratory tests namely WBC and neutrophil count. On the other hand, abdominal ultrasonography and computerized tomography (CT) are most frequently used imaging modalities in the diagnosis of AA with atypical presentation and especially in women, whose urologic or gynecologic pathologies often mimic appendicitis [5]. Furthermore, the use of many other inflammatory markers such as NLR, fibrinogen level, PLT count and MPV for the diagnosis of AA have been claimed in the literature [6, 7].

The aim of this prospective study was to investigate the diagnostic value of these parameters in differential diagnosis of AA.

Materials and methods

One hundred and ninety-seven patients admitted to the obstetrics and gynecology department and general surgery department of Kanuni Sultan Suleyman Training and Research Hospital with findings of acute abdomen and operated on with a preoperative diagnosis of AA between April 2013 and May 2015 were included in this prospective observational study. The hospital's Ethics Committee approval was obtained to conduct this study. Informed consents include patients' approval for extra laboratory tests to be analyzed in the same blood samples taken for the routine

laboratory analysis. The study was conducted in accordance with the Helsinki regulations. The initial diagnosis was made by four different surgeons with at least 10 years' experience, based on patient's history, clinical examination, imaging results and laboratory findings (surgeons were blind to the laboratory findings except WBC and neutrophil count). Patients having liver disease, any type of cancer, nephritic syndrome, pregnancy, corticosteroid usage and immunosuppression which might affect the inflammatory status were excluded from the study. Blood and urine analysis were carried out in all patients. Blood samples were obtained from the patients at the time of admission to the emergency department. Demographic findings, WBC, neutrophil count, lymphocyte count, NLR, CRP level, fibrinogen level, PLT count and MPV were recorded.

The maximum waiting period from diagnosis to incision was approximately 4 h. Either an open or a laparoscopic appendectomy was performed. Twenty-five patients (12.6%) were operated on laparoscopically and 172 patients (87.4%) were operated with on with an open approach. The final diagnosis was made histopathologically. According to the histopathological results, patients were classified into two main groups: Group 1, patients with normal histology of appendix vermicularis; Group 2, patients with positive histology for appendicitis with or without perforation, periappendiceal abscess, suppurative, gangrenous or ulcerophlegmonous AA.

The two groups were compared with respect to basic characteristics including age, gender, WBC, neutrophil count, lymphocyte count, NLR, CRP level, fibrinogen level, PLT count and MPV. The comparisons between the two groups were made using univariate analysis (Student's t test) and significance was considered where the α -error probability was lower than 0.05. The parameters, which were found significant in the logistic regression, were then analyzed with ROC analysis to define optimum threshold values. For describing the diagnostic properties of the parameters, we used the area under the ROC curve (AUC). AUC of 1.00 indicates perfect diagnostic power while AUC of 0.50 indicates absence of discriminating power. Optimum threshold values, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy values were calculated. All analyses were made using Microsoft Excel 2003 and SPSS 17.0.

Results

One hundred and ninety-seven patients who underwent appendectomy with a clinical diagnosis of AA were

included in this prospective study. There were 28 (14.2%) patients in Group I (normal histology) and 169 (85.8%) patients in Group 2 (histopathologically confirmed AA). The basic characteristics of the patients in the two groups are shown in Table 1. Mean age was 27.8 years (min–max : 17–38). There was no statistically significant age difference between the two groups ($p=0.11$). There were 78 females and 119 male patients. Between the two groups there were statistically significant difference in the gender distribution. The female patients were more prone to be falsely diagnosed as AA in Group 1. Differential diagnosis of this group was mesenteric lymphadenitis, familial Mediterranean fever, pelvic inflammatory disease and ovarian pathologies. White blood cell count, neutrophil count, lymphocyte count, NLR, CRP level, fibrinogen level, PLT count and MPV were compared between the two groups by univariate analyses (Table 2).

There are no statistically significant differences in CRP level and MPV between two groups ($p=0.12$ and 0.09 , respectively). All the other parameters were significantly different between the two groups. White blood cell count, neutrophil count and NLR were significantly higher in Group 2 ($p<0.001$ for each), and they were found to be a significant predictive for AA in the final histopathology. On the other hand, fibrinogen level, lymphocyte count and PLT count were significantly higher in Group 1 ($p=0.03$, 0.002 and 0.003 , respectively) and predictive for non-appendiceal pathology in differential diagnosis of AA.

After univariate analyses, ROC analysis (Figure 1A) was made to define the AUC, optimum threshold value,

sensitivity, specificity, PPV, NPV and accuracy of the WBC, neutrophil count and NLR to define the positive AA cases (Table 3).

The AOC for WBC, neutrophil count and NLR were 0.73, 0.75 and 0.77, respectively, and all three tests had $>70\%$ accuracy for the diagnosis of AA (73.1, 70.6 and 73.1, respectively). The optimum threshold value for WBC, neutrophil count and NLR were $11 \times 10^3/\text{mL}^3$, $8 \times 10^3/\text{mL}^3$ and 3, respectively.

Also ROC curve analysis (Figure 1B) was made to identify the AUC, optimum threshold value, sensitivity, specificity, PPV, NPV and accuracy of fibrinogen level, lymphocyte count and PLT count to define the non-appendiceal pathology cases (Table 4).

The AOC for plasma fibrinogen level, PLT and lymphocyte counts were 0.64; and they had relatively lower accuracy levels of 60.4%, 58.3% and 20.8%, respectively, for the diagnosis of non-appendiceal pathology. Optimum threshold value for fibrinogen level, platelet count and lymphocyte count were 300 mg/dL, $232 \times 10^3/\text{mL}^3$ and $2 \times 10^3/\text{mL}^3$, respectively.

Discussion

Acute appendicitis is the most common indication for emergency surgery and affects a wide range of patients of all ages. Delayed operations might cause high morbidity and mortality rates. So, it is important to differentiate early AA from other non-specific or non-surgical causes of abdominal pain. On the other hand, false-positive diagnosis may result in unnecessary operations and surgical morbidity including; wound infections, incisional hernia, stump leakage, anesthesia related complications, brid ileus, chronic pelvic pain and fertility problems in young females.

The value of laboratory tests and imaging modalities for the diagnosis of AA are currently controversial. There is no optimal test for diagnosing AA, usually a combination

Table 1: Demographic characteristics of the study population.

	Total	Group I (n: 28)	Group II (n: 169)	p-Value
Mean age (years)	27.8	29.5	27.4	0.11
Male (n)	119	11 (9.4%)	108 (90.6%)	0.01 ^a
Female (n)	78	17 (21%)	61 (79%)	

^aChi-square test for gender distribution among the two groups.

Table 2: Univariate comparison of laboratory parameters among the two outcome groups.

	Normal R	Group I (mean \pm SD)	Group II (mean \pm SD)	p-Value
WBC ($10^3/\text{mm}^3$)	3.7–10.1	9.96 \pm 0.69	13.59 \pm 0.34	<0.001
Neutrophil count ($10^3/\text{mm}^3$)	1.63–6.96	6.64 \pm 0.66	10.55 \pm 0.34	<0.001
Lymphocyte count ($10^3/\text{mm}^3$)	1.09–2.99	2 \pm 0.18	1.54 \pm 0.07	0.002
NLR		2.68 \pm 0.41	6.64 \pm 0.4	<0.001
CRP level (mg/L)	< 5	20.9 \pm 5.7	35.84 \pm 3.8	0.12
Fibrinogen level (mg/dL)	200–400	349.82 \pm 18.7	305.47 \pm 7.54	0.03
PLT count ($10^3/\text{mm}^3$)	155–366	286.32 \pm 24.45	230.1 \pm 4.15	0.003
MPV (fL)	6.9–10.6	8.4 \pm 0.21	7.9 \pm 0.1	0.09

Bold text indicates that the p-Value was reported as significant when $p < 0.05$.

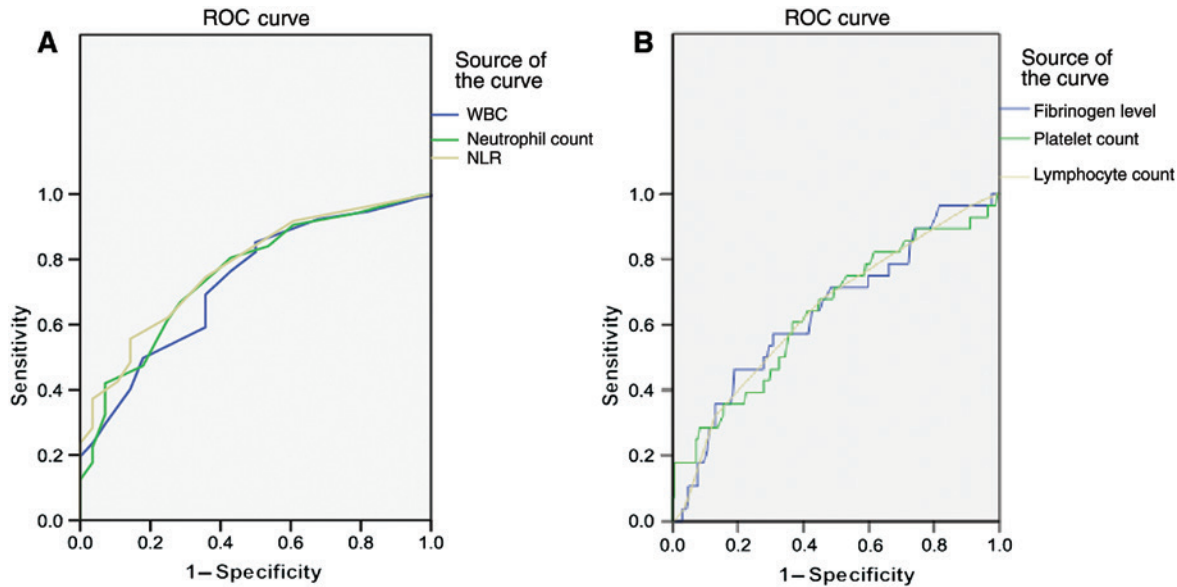


Figure 1: Diagonal segments are produced by ties. (A) ROC-curve [output variable appendicitis (+)] for WBC, neutrophil count and NLR. (B) ROC-curve [output variable appendicitis (-)] for fibrinogen level, PLT count and lymphocyte count.

Table 3: ROC curve analysis of WBC, neutrophil count, NLR.

	AUC	Cut-off	Specificity	Sensitivity	PPV (%)	NPV (%)	Accuracy (%)
WBC	0.73	11,000	0.60	0.73	75.7	57.1	73.1
Neutrophil count	0.75	8000	0.67	0.72	72.2	60.7	70.6
NLR	0.77	3	0.70	0.69	74.6	64.3	73.1

Table 4: ROC curve analysis of blood fibrinogen level, lymphocyte count and PLT count.

	AUC	Cut-off	Specificity	Sensitivity	PPV (%)	NPV (%)	Accuracy (%)
Fibrinogen level	0.64	300	0.59	0.57	60.4	60.7	60.4
PLT count	0.64	23,2000	0.60	0.60	57.1	58.6	58.3
Lymphocyte count	0.64	2000	0.58	0.71	67.8	13	20.8

of laboratory tests, physical examination and imaging methods are used for diagnosis. Symptoms, such as location of pain, anorexia, nausea, vomiting, tenderness and fever are criteria for diagnosing AA. However, 20%–33% of patients have atypical clinical and laboratory findings [8]. In these patients, scoring systems, ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI) and laparoscopy can be used.

Ultrasound is a safe and cost-effective method but it is highly operator dependent and less valuable in terms of accuracy [9]. Computed tomography has become the favored diagnostic tool in difficult to diagnose cases. The use of CT may, however, delay appendectomy and therefore may even elevate the risk for perforation [10]. Its use

is also associated with elevated risk for cancer especially in young patients [11]. In a review of CT vs. compression US, the respective sensitivities of CT and US were 91% and 78%, and the respective specificities were 90% and 83% [9].

White blood cell and neutrophil count are routinely used tests in nearly every center due to the easy interpretation for diagnosing AA. However, their increase is not specific to AA and may increase in many other acute or chronic inflammatory conditions [6]. Moderate leukocytosis ($15,000/\text{mm}^3$) is usually the earliest finding in the inflammation of the appendix [12]. In the current study WBC is statistically higher in positive appendicitis group ($p < 0.001$) and the sensitivity and specificity of WBC to detect AA was found 73% and 60%, respectively, with a

cut-off value of 11,000/mm³. In different clinical studies the sensitivities and specificities of WBC for diagnosing AA is ranges between 67%–97.8% and 31.9%–80%, respectively, which is consistent with our findings [7].

Neutrophil count is second most commonly used test in the diagnosis of AA. In the current study the neutrophil counts were statistically higher in positive AA group ($p < 0.001$) and sensitivity and specificity of the neutrophil counts were calculated as 72% and 67%, respectively, which are consistent with the literature. In different clinical studies sensitivity and specificity of neutrophil count for diagnosing AA ranges between 60%–98% and 76%–91%, respectively, which is consistent with our findings [12–14].

Also, we found that the NLR was statistically higher in positive AA group ($p < 0.001$) and sensitivity and specificity of the NLR were calculated as 69% and 70%, respectively. Marker et al. found that the AUCs for NLR and WBC were 0.86 and 0.77, respectively, which agrees with our findings (0.77 and 0.73, respectively) [15]. According to these results, NLR appears to be of greater diagnostic accuracy than WBC. Besides, Ishizuka et al. found that $NLR > 8$ shows a significant association with gangrenous appendicitis [16].

In our study, CRP levels were high in all our patients and did not help to differentiate between negative and positive appendicitis. The mean CRP level was 20.9 mg/L in the negative appendicitis group; and 35.8 mg/L in the positive appendicitis group. This difference was not statistically significant ($p = 0.12$). This could be explained due to various etiological factors other than appendicitis including gynecological, urological or any other pathologies associated with increased CRP levels presenting with acute abdomen. That means, an increase in CRP levels does not constitute a sufficient condition for diagnosing AA. Besides, patients with AA may also have normal blood CRP level. Zourai et al. evaluated whether CRP levels and US results on admission could improve the diagnostic accuracy of the Alvarado score in the pediatric population. They found that the difference between predictive values of Alvarado scores with or without CRP was not statically significant [17]. Tind et al. concluded that WBC and CRP level did not influence clinical decision making [18]. In another study, Bozkurt et al. found that the CRP level was not useful as a diagnostic marker, in accordance with our findings [19]. On the contrary, in two different studies, Xharra et al. and Marker et al. reported that the diagnostic value of CRP level was like that of WBC and the neutrophil count [15, 20]. They suggested that measuring these markers together may increase their specificity which contradicts our findings.

Platelets are a source of inflammatory mediators. Increased platelet activation is known to trigger atherosclerosis and plays a major role in its progression. Elevated peripheral blood platelet count is closely related to major adverse cardiovascular outcomes. It is thought that in diseases accompanied by inflammation and a late increase in the release of young platelets into the bloodstream from the bone marrow leads to an increase in platelet counts [21]. According to Ceylan et al. platelet counts were not different when compared in appendicitis and non-appendicitis [22]. Platelet count was evaluated in the current study; PLT count was statistically higher in the negative appendicitis group ($p < 0.003$) and sensitivity and specificity of the PLT counts were calculated as 60% for both. However, PLT count is statistically significant in the diagnosis of negative appendicitis with low accuracy (58.3%), which is more prone to be elevated in the false-positive group.

MPV, a marker of platelet activation, is being investigated for its correlation with both inflammation and thrombosis. Reportedly, while increased MPV values were observed in chronic disease conditions, decreased MPV values were observed in the acute activation setting. The size of the PLT is correlated with the activity and function of the platelet; larger ones are more active than smaller ones. Thus, MPV was suggested as a potential marker for inflammatory disorders such as AA [21]. Several recent studies evaluated the diagnostic value of MPV in AA [19, 23, 24]. Bozkurt et al. found that MPV was not useful as a diagnostic marker [19]. Similarly, in the current study, there was no statistical difference observed ($p = 0.09$). On the contrary, Tanrikulu et al. showed that MPV levels were significantly lower in the AA group, compared to the healthy control group ($p < 0.001$) [25]. In a different perspective, Ceylan et al. suggested that MPV was lower in complicated appendicitis cases [22]. In our study no difference was found between the two groups of MPV values due to acute inflammatory process in both groups.

Fibrinogen is a central factor in homeostasis, a contributor to inflammatory response and also an acute phase protein [24]. This current study also tried to explain if plasma fibrinogen has a predictive ability for the preoperative diagnosis of AA. In the present study, contrary to the literature, fibrinogen levels in the negative appendicitis group was statistically higher (349.8 ± 18.7) than the positive appendicitis group (305.5 ± 7.5) ($p = 0.03$). In the present study, the optimum threshold value for fibrinogen was 300 mg/dL with sensitivity and specificity values of 57% and 59%, respectively. This finding is not consistent with the study of Mentis et al. who defined elevated levels of fibrinogen as a marker for AA [6]. In their study, they found that the sensitivity, specificity, PPV, NPV and

accuracy were 70%, 50%, 92%, 17% and 68%, respectively, with a cut-off level of 245.5 mg/dL [6]. Li et al. compared appendectomy group with non-acute abdomen group retrospectively. Fibrinogen levels was found higher in acute appendicitis group in their study. Another study according to Feng et al. they compared perforated appendicitis with non-perforated appendicitis in children. Fibrinogen levels considerably higher in comparison with non-perforated appendicitis. The main reasons for confusion about the laboratory diagnosis of AA in literature include the retrospective designs and inconsistency about the control groups, some of which being healthy control individuals and still others being false-positive cases creating a main cause of bias [22, 25].

Also lymphocyte count was significantly higher in the non-appendicitis group; however, despite a similar AUC values, the lymphocyte count was far less accurate (20.8%) than the other negative predictive (PLT counts and fibrinogen). Other causes of clinical pictures similar to AA (e.g. mesenteric lymphadenitis, viral upper respiratory tract infections) might be the reason of this elevation.

Excluding the current findings in the medical literature indicating the predictive value of WBC, neutrophil count, NLR, in the diagnosis of AA; the utility of CRP, fibrinogen, PLT count and MPV may be being too accentuated. According to the current study, even these three laboratory markers have rather low sensitivity and specificity values in the vicinity of 69%–73% and 60%–70% values, respectively. In the diagnosis of AA, the clinical examination and personal experience still play a major role in surgical decision making [18].

Conclusion

White blood cell, neutrophil count and NLR are predictive for the diagnosis of AA, whereas elevated levels of fibrinogen, higher PLT and lymphocyte counts are predictive for non-appendicial pathology with low diagnostic accuracies. Neither MPV nor CRP level has a significant value in the differential diagnosis of AA. Considering the largely varied results reported in the literature, prospective studies with larger patient numbers are required, with acute abdomen cases comprising the control groups.

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