



Diagnostic value of procalcitonin, C-reactive protein, and erythrocyte sedimentation rate for acute complicated appendicitis

Akut komplike apandisitte prokalsitonin, C-reaktif protein ve eritrosit sedimentasyon hızının tanısal değeri

Diagnosis of complicated acute appendicitis

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Öz

Amaç: Akut apandisit (AA) en sık görülen cerrahi acillerdendir. Modern araştırmalarda görülen olağanüstü gelişmelere rağmen, AA'nın doğru bir şekilde teşhisi muazzam bir zorluk olarak kalmaktadır. Bu çalışmanın amacı, histopatolojik olarak AA tanısı alan hastalarda komplike / komplike olmayan apandisitinin ayırıcı tanısında C-reaktif protein (CRP), eritrosit sedimentasyon hızı (ESR) ve prokalsitonin (PCT) laboratuvar parametrelerini incelemektir. **Gereç ve Yöntem:** Bu çalışmada 106 hasta, 2 ana gruba ayrıldı; komplike olmayan apandisit grubu (n = 74) ve komplike apandisit grubu (n = 32). CRP, ESR ve PCT düzeyleri çalışmadaki tüm hastalar için hesaplandı. **Bulgular:** Hastaların cinsiyetlerine göre gruplar arasında anlamlı bir farklılık gözlenmedi. Bununla birlikte CRP, ESR ve PCT değerleri arasında anlamlı bir fark vardı (P > 0.05). ESR >31 (AUC = 0.706, P = 0.001, 95% GA: 0.610-0.791), PCT >1.8 (AUC = 0.709, P = 0.001, 95% GA: 0.568-0.754) ve CRP > 56.64 (AUC = 0.700, P <0.001, 95% GA: 0.603-0.785) serum seviye değerleri elde edildi. Hem komplike apandisitler hem de non-komplike apandisit analizlerinde bu değerlerin doğru olduğu tespit edildi. Bu çalışmada elde edilen kesme değerlerini kullanarak komplike apandisit için sınıflandırma ile ESR, CRP ve PCT serum değerleri ve odds oranları hesaplandı (odds oranı: 1.042 (0.990-1.097), 1.009 (0.998-1.020) ve 2.986 (1.135-7.858)). **Tartışma:** Biz PCT düzeyi > 1.8, CRP düzeyi > 56.64 ve ESR düzeyi > 31 olduğu zaman, komplike apandisit olasılığının yüksek olduğunu, acil ve dikkatli bir yönetim yapılmasını öneriyoruz.

Anahtar Kelimeler

Apandisit; İnflamatuvar Marker; Komplike Apandisit

Abstract

Aim: Acute appendicitis (AA) is one of the most common surgical emergencies. Despite extraordinary advances in modern investigations, an accurate diagnosis of AA remains an enigmatic challenge. The purpose of this study was to examine the laboratory parameters studied during the preoperative period in patients who were histopathologically diagnosed with AA; C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and procalcitonin (PCT) in the differential diagnosis of complicated/uncomplicated appendicitis. **Material and Method:** This study included 106 patients, separated into two main groups; the uncomplicated appendicitis group (n = 74) and complicated appendicitis group (n = 32). The CRP, ESR, and PCT levels were calculated for all of the patients in the study. **Results:** No meaningful differences were observed among the groups, with regards to the sex of the patients. There was, however, a significant difference obtained between the (P > 0.05) CRP, ESR, and PCT values. Serum levels of ESR >31 (AUC = 0.706, P = 0.001, 95% GA: 0.610-0.791), in PCT >1.8 (AUC = 0.709, P = 0.001, 95% GA: 0.568-0.754), and CRP > 56.64 (AUC = 0.700, P <0.001, 95% GA: 0.603-0.785) were obtained. In both complicated appendicitis and uncomplicated appendicitis analyses, these values were found to be accurate. Using the cut-off values obtained in this study, the ESR, CRP, and PCT serum values, and odds ratios were calculated for complicated appendicitis by classification (odds ratio: 1.042 (0.990-1.097), 1.009 (0.998-1.020), and 2.986 (1.135-7.858), respectively). **Discussion:** We suggest that with a PCT level >1.8, CRP level >56.64, and ESR level >31, immediate and careful management must be undertaken, as the probability of complicated appendicitis is high.

Keywords

Appendicitis; Inflammatory Markers; Complicated Appendicitis.

Introduction

Acute appendicitis (AA) is one of the most common abdominal surgical emergencies. After Fitz's [1] study, in 1886, an early appendectomy became the best-accepted treatment for AA. However, the present recommendation for uncomplicated appendicitis is inoperative management [2–4]. Hence, surgeries should be avoided due to possible complications such as ileus (1.2% of cases) and abdominal hernias (0.68% of cases) [5].

However, complicated appendicitis, like perforated appendicitis and gangrenous appendicitis, have the potential of progressing into acute peritonitis, necessitating emergency surgery. Complicated AA has been observed in 20%–30% of all appendicitis cases [6].

Presently, both clinicians and surgeons are challenged in forming a correct diagnosis and treatment program. It is difficult to form a correct clinical diagnosis of AA, which must be formed using imaging study parameters, and clinical and laboratory results. Although, differentiation between uncomplicated and complicated appendicitis (most often defined as appendicitis with gangrenous change, abscess, or perforation [7]), is often difficult, recently, diagnosis accuracy has been improved due to advances in both ultrasound and computed tomography. Diagnostic accuracy increases with the use of multiple markers, which can positively confirm an inflammatory process in the appendix [8].

The purpose of this study was to examine the laboratory parameters studied during the preoperative period of patients who were histopathologically diagnosed with AA; C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and procalcitonin (PCT) in the differential diagnosis of complicated/uncomplicated appendicitis.

Material and Method

We retrospectively evaluated 106 patients who underwent an appendectomy in our general surgery clinic between January 2012 and April 2017. Patients confirmed to have AA by histopathological examination were included in the study. Demographic data that belonged to patients, laboratory parameters, and monitoring examination with histopathology analyzing results were evaluated.

An appendectomy was performed conventionally or laparoscopically. The results of the CRP, ESR, and PCT were evaluated from the laboratory parameters of this disease. Leukocytosis was defined as a white blood cell count (WBC) >10.3 10³/μL, and the CRP was considered elevated if the level was >5 mg/L. An outer diameter of the vermiform appendix, measured with ultrasonography (USG), of >6 mm was considered positive for AA. USG assessments were performed with a Toshiba Aplio 300 device (Toshiba Medical Systems Corporation, Otawara, Japan) with a 3.5-MHz transducer.

Patients with acute focal/suppurative appendicitis were placed in the uncomplicated group (Group 1), perimetric abscess with perforated appendicitis were placed in the complicated group (Group 2). Blood samples were taken prior to antibiotic use. Patients were initially evaluated using USG from imaging studies. In patients without appendiceal imaging, computed tomography (CT) was applied with an oral contrast agent application. Patients having a normal abdominal examination, under 16

years of age, pregnant, or on steroids or antibiotics were excluded from the evaluation. All of the patients with sensitivity, defensiveness, and rebound on the right lower side of the abdomen were examined and all of the patients with at least 1 of the laboratory parameters, WBC, CRP, or neutrophil-lymphocyte ratio, were elevated and were above the normal limit of the appendiceal diameter on CT or USG.

Evaluation of the data

Analysis of the data was done using the IBM SPSS 23.0 and MedCalc 15.8 statistical package programs. A chi-square (x²) test was used to compare the descriptive statistics (frequency, percentage, median, min-max), as well as qualitative data when evaluating the study data. The normal distribution of the data was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests, and the data were not normal. In this study, the Mann-Whitney U test was used for a comparison between the groups. The receiver operating characteristic (ROC) curve method was used to determine the variability of the variables, and the binary logistic regression test was used to determine the risk ratios. The likelihood of P-values smaller than $\alpha = 0.05$ was significant, and there was a difference between the groups, with large values being insignificant and no difference between groups.

Power Analysis: Power analysis G * Power 3.1.9.2 was made with the statistical package program; N1 = 74, n2 = 32, $\alpha = 0.05$, effect size $d = 0.5$; power (power (1-beta)) = 0.96.

Results

Among the groups, no statistically significant difference was found regarding the sex of the patients ($P > 0.05$); however, there was a statistically significant difference found regarding the age values ($P < 0.05$). The age of the group 2 patients were found to be higher. (Table 1)

Among the groups, the ESR, PCT, and CRP values were statistically significant ($P < 0.05$). For the 3 variables, the values of the Group 2 patients were found to be higher than those of the Group 1 patients. (Table 2)

For complicated appendicitis, as a result of the evaluations made by the ROC analysis, cut-off values were obtained for the ESR as >31 (AUC = 0.706, $p = 0.001$, 95% GA: 0.610–0.791) for the PCT as >1.8 (AUC = 0.709, $P = 0.001$, 95% GA: 0.568–0.754) and for the CRP as >56.64 (AUC = 0.700, $P < 0.001$, 95% GA: 0.603–0.785). (Table 3)

Logistic regression analysis was performed to investigate the effects of the variables (ESR, PCT, and CRP), which were found to be statistically significant in the complicated and uncomplicated appendicitis groups, with the occurrence of complicated appendicitis. PCT has been found to be more valuable in diagnosing complicated appendicitis. It was found that there may be about 3 times as many complicated appendicitis patients with an elevated PCT level than those without an elevated PCT level (Table 4)

Discussion

Acute abdomen is commonly caused by AA, bringing about the necessity for immediate surgery, as delays in diagnosis or surgical treatment can result in complications and, in some cases,

Table 1. Comparison of the 2 groups: median (min-max), n (%), median (min-max).

		Group 1 (n = 74)	Group 2 (n = 32)	p
Sex	Female	30 (40.5%)	11 (34.4%)	0.703*
	Male	44 (59.5%)	21 (65.6%)	
Age (years)		34.5 (17–68)	43.5 (18–80)	0.013**

Group 1: uncomplicated appendicitis, Group 2: complicated appendicitis, * Chi-square test, **: Mann-Whitney U test.

Table 2. Comparison of the two groups: median (min-max).

	Group 1 (n = 74)	Group 2 (n = 32)	p*
ESR	19.5 (2.0–44.0)	28.0 (4.0–62.0)	0.001
PCT	1.0 (0.1–2.0)	1.3 (0.2–3.0)	0.001
CRP	9.5 (0.8–173.2)	28.5 (0.6–300.4)	0.001

Group 1: uncomplicated appendicitis, Group 2: complicated appendicitis, *: Mann Whitney U test.

Table 3. Cut-off values for the prediction of complicated appendicitis.

	AUC	Cut-off	Sensi- tivity	Speci- ficity	+LR	–LR	95% GA	P*
ESR	0.706	>31	43.8	91.9	5.40	0.61	0.610–0.791	0.001
PCT	0.709	>1.8	34.4	100.0	0.00	0.66	0.568–0.754	0.001
CRP	0.700	>56.64	43.8	94.6	8.09	0.59	0.603–0.785	0.001

Table 4. Estimated relative risk ratio (odds ratio) for the complicated appendicitis

Risk factors	OR (odds ratio)	95% GA	P
ESR	1.042	0.990–1.097	0.113
PCT	2.986	1.135–7.858	0.027
CRP	1.009	0.998–1.020	0.114

* Binary logistic regression (Hosmer & Lemeshow test P = 0.652, Nagelkerke R² = 0.322)

death. However, not every appendicitis case is surgically treatable, especially cases such as catarrhal appendicitis [9]. Although the use of supportive treatment and antibiotics for managing uncomplicated AA has been supported by several researchers in the literature [10,11]. Often, differentiation between complicated and uncomplicated appendicitis is difficult.

In the literature, in 3 randomized controlled trials, a 1-year cure rate of 74%–87% was reported for uncomplicated appendicitis patients treated with antibiotics; showing that conservative therapy is a possible treatment option for AA patients [10,11]. Recently, confirmation of this was provided by a meta-analysis of randomized controlled trials showing that initial antibiotic treatment for early uncomplicated appendicitis should be considered [12]. That said, delays in surgical treatment remain the main reason for morbidity and mortality, as an exact diagnosis of AA preoperatively is often difficult.

Various laboratory tests can aid in the determination of AA severity. Conventionally, clinical/laboratory parameters, such as body temperature (BT), CRP level, WBC, and neutrophil/lymphocyte ratio (N/L ratio), have been used to differentiate between complicated and uncomplicated appendicitis [13]. A biomarker is an objectively, measurable characteristic which research in

the literature has proven is a valid marker of normal physiology, disease, or a disease's response to treatment [14]. Recently, acute-phase reactants (APRs) have increasingly been used in infection management because these markers are present in the serum, which signifies the presence of inflammation or injury. APRs are a group of heterogeneous plasma proteins which increase or decrease when inflammatory stimuli like infections, trauma, systemic autoimmune disorders, acute arthritis, or neoplasms are present. In the present study, the cut-off values, as well as the laboratory and monitoring parameters, were examined to differentiate between complicated and uncomplicated appendicitis.

In a study by Assicot et al., in 1993, a notable increase in the plasma PCT levels of patients with sepsis or other clinically significant bacterial infections was reported. In cases of sepsis, bacterial inflammation, and multi-organ failure syndrome, PCT is selectively induced. Bacterial endotoxin, which has a half-life of 25–30 h, is the primary trigger. Contrary to CRP, in patients with sterile inflammation or viral infection, the PCT level does not increase [15].

Surgically eliminating inflammatory agents combined with effective antibiotics brings about a decrease in PCT levels [16]. Kafetzis et al. [17] reported that PCT values >0.5 ng/mL are a good indication of the possible development of complications, perforation, or necrotic changes. In the present study, similar results were obtained in the PCT levels in patients with AA who developed complications, as well as in patients with complicated appendicitis.

Currently, in clinical practice, the most commonly used acute-phase markers are the ESR and CRP. Today, the CRP concentration is a widely used indicator in patients suspected of having AA [18]. When diagnosing AA, CRP sensitivity varies between 40%–95.6% and the specificity varies between 53%–82% [19,20].

Yang et al. conducted a study of 897 patients who were assumed to have AA. In their study, the average CRP was found as 39,6 mg/L. For inflated appendicitis, the CRP was 24,1 mg/L, and it was 96,8 mg/L for perforated appendicitis, which was statistically significant [21]. In complicated cases, CRP sensitivity and specificity were higher, which is in line with the findings in the literature [22]. Moreover, the results of our study regarding CRP sensitivity and specificity were also in line with literature (43.8% and 94.6%, respectively).

In the literature, few studies have been performed with regards to the efficacy of ESR for the prediction acute complicated appendicitis. ESR is a non-protein 'indirect' APR, which means that it changes according to fluctuations in plasma fibrinogen levels and plasma viscosity [23]. Within 24–48 h of the onset of inflammation, the ESR rises, and as the inflammation subsides, it and slowly returns to a normal level [24]. The results of our study regarding the ESR sensitivity and specificity were also in line with the results in the literature (43.8% and 91.6%, respectively).

In a study by Tanrikulu et al., examination of the CRP, PCT, and ESR values did not result in a diagnostic value when estimating a normal appendix or AA. However, the PCT and CRP values had a significant impact with regards to the diagnosis of perforated and necrotizing appendicitis, whereas the ESR elevation did not result in similar findings [25].

The stages of AA in the present study were defined based on findings found intraoperatively (peri-appendiceal abscess), macroscopically (resected specimen perforation), and microscopically. In our study, PCT was found to have a similar diagnostic value for complicated appendicitis compared to that of CRP or ESR; however, the PCT value was higher than the other inflammatory indices for the identification of complicated appendicitis.

We should note that this study also had some limitations: 1) It was performed retrospectively. 2) We investigated a relatively small number of patients, young patients and those undergoing conservative treatment were not included, thus limiting the properties of the study.

In conclusion, the PCT, ESR, and CRP levels were statistically different between groups 1 and 2. This allowed us to differentiate complicated and uncomplicated appendicitis between patients more accurately, and better determine the surgical strategy, as well as which medical treatment to apply for those patients with uncomplicated appendicitis. Evaluation of the PCT, ESR, and CRP levels indicated that the inflammation process is a strong prediction of complications such as gangrene, perforation, or abscess.

Ethical Statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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