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C-reactive protein and red cell distribution width as indicators of complications in patients with acute appendicitis

Akut apandisit tanısı konmuş hastalarda komplikasyon belirteçleri olarak C-reaktif protein ve kırmızı küre dağılım indisinin yeri ve önemi

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Abstract

Aim: Acute appendicitis is one of the most common operations in general surgery. When complicated, mortality and morbidity increases. We aimed to find out whether use of C-reactive protein (CRP) and red cell distribution width (RDW) may help to find out development of complications with acute appendicitis at initial evaluation in an emergency department.

Methods: Files of the patients who underwent operations for acute appendicitis between January 2017 and August 2017 were reviewed. Development of complications was recorded and the patients were grouped as with and without complications and were compared about age, sex RDW, CRP, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels. Diagnostic efficiency of CRP and RDW on the development of complications in acute appendicitis was investigated with regression analysis and by receiver operator characteristic curve analysis.

Results: Age, CRP and RDW were found to be significantly related to perforation ($p<0.001$ for all) (Bonferoni correction), while white blood cell (WBC), AST and ALT were found to be insignificant ($p=0.052$, $p=0.806$ and $p=0.804$, respectively. There was a significant correlation between RDW and CRP in the Spearman non-parametric correlation analysis (correlation coefficient $r=0.244$ and $p<0.001$). There was no significant correlation of WBC to CRP and RDW.

Conclusion: CRP and RDW are biochemical parameters that help us to identify the development of complications in acute appencitis. CRP may be elevated in acute appendicitis; however, it must be kept in mind to be cautious about a potentially complicated acute appendicitis after a certain level, RDW in our study has been found to be elevated in complicated appendicitis cases; but, it may not helpful to detect for perforated or gangrenous appendicitis.

Keywords: acute appendicitis, hematologic tests, laboratory analysis, complications.

Öz

Amaç: Akut apandisit genel cerrahide en sık karşılaşılan operasyon sebeplerinden biridir. Komplike olduğu zaman mortalite ve morbidite artmaktadır. C-reaktif protein (CRP) ve kırmızı küre genişlik dağılım indisi (RDW) değerlerinin kullanılmasının komplike olan akut apandisit vakalarını acil servisteki ilk muayenede ayırt etmemizde faydalı olup olmadığını incelemeyi amaçladık.

Yöntemler: Ocak 2017 ve Ağustos 2017 tarihleri arasında akut apandisit nedeniyle opere edilmiş olan hastaların dosyaları tarandı. Hastalar yaş, cinsiyet, CRP, RDW, alanin aminotransferaz, aspartat aminotransferaz değerleri açısından komplike olan ve olmayan akut apandisit vakalarında karşılaştırıldı. Artmış serum CRP ve RDW değerlerinin komplike apandisit tanısı koymada ne kadar etkin olduğu regresyon analizi ve alıcı işlemci nitelikleri eğrisi analizi ile değerlendirildi.

Bulgular: Yaş, RDW ve CRP, perforasyon ve gangrenöz apandisit ile belirgin olarak ilişkili olarak bulundu, $p<0,001$, beyaz küre, aspartat aminotransferaz (AST), alanin aminotransferaz (ALT) düzeyleri ise P değerleri açısından anlamsız olarak bulundu (sırasıyla $p=0,052$, $p=0,806$ ve $p=0,804$). RDW ile CRP arasında korelasyon olmakla birlikte (korelasyon katsayısı $r=0,244$ ve $p<0,001$), beyaz küre ile RDW ve CRP arasında anlamlı bir ilişki yoktu.

Sonuç: CRP ve RDW komplike apandisit tanısını koymamızda biyokimyasal parametreler olarak değerlendirilmelidir. CRP akut apandisit vakalarında artmış olarak tespit edilebilir ancak belli bir seviyeden sonra komplike olmuş bir apandisite işaret edebilir. RDW bizim çalışmamızda komplike apandisitlerde artmış olarak bulundu. Ancak bu yükseklik için bir eşik değer tespit edilemedi.

Anahtar kelimeler: akut apendisit, hematolojik testler, laboratuar analiz, komplikasyonlar.

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Introduction

In the emergency surgery, acute appendicitis (AA) is one of the most common operations [1]. The lifetime risk of developing an AA is 7% [2]. Even though it is such a common situation in the emergency department, the diagnosis may not be so easy at all the times causing challenges [3]. In addition to non-classical clinical presentation, what makes the diagnosis uneasy is that symptoms may sometimes overlap with other medical situations [4]. The condition may progress to perforation during almost 48 hours following the occurrence of AA and the delay is mostly responsible for most of perforated appendices [5].

C-reactive protein (CRP) is an acute inflammatory protein that rises up to a thousand times at sites of infection or inflammation [6]. IL-6 is the main promoter of the protein with IL-1 enhancing its effect [7]. CRP is elevated in inflammatory conditions such as rheumatoid arthritis, some cardiovascular diseases, and infection [8]. CRP has also been used as a diagnostic tool in appendicitis [9].

Red cell distribution width (RDW) is a well-known erythrocyte parameter that shows the variation and heterogeneity in the diameter of red blood cells. This old erythrocyte indice is now regarded as an inflammation related bio-marker. RDW and CRP values were shown to be correlated and an elevated RDW may be associated to elevation in erythrocyte sedimentation rate and interleukin-6 levels as well [10]. Elevated RDW has been found to be predictive or prognostic in various health conditions such as acute myocardial infarction and pulmonary hypertension [11, 12]. RDW has been also used diagnostic tool in appendicitis [13].

There is a great difference between the complications of a perforated appendicitis and a non-perforated case, thus, in order to use the sources in an efficient way and to help the accurate assessment of the patient at the initial evaluation in the emergency room, we hypothesized that we could identify predictive factors for an appendicitis case which has been complicated. To achieve this goal we studied efficiency of blood parameters of CRP, RDW and white blood cell count (WBC).

Material and methods

The study was designed as a retrospective cohort study in the Department of General Surgery, Haseki Training and Research Hospital. The files of the patients who underwent operation for AA between January 2017 and August 2017 were reviewed. The permission was obtained from the local ethics committee (29.11.2018/270). The preoperative diagnosis is carried out by a combination of physical examination, laboratory tests and radiological findings. The laboratory tests comprise of complete blood count and liver function tests. All patients had an ultrasound or a computerized tomography scan.

All the patients who underwent appendectomy (both open appendectomy and laparoscopic appendectomy) were taken in the study; then, the patients who had an appendectomy for purposes other than appendicitis (histologically normal appendix vermiformis, parasitic appendicitis, intra-operative diagnosis of Crohn's disease, accompanying gynecological operations, appendiceal mucocele and plastrone formation) were excluded. Then, the patients were checked for the availability of the blood parameter tests within the specified time and they were included in the study (Figure 1).

The complicated and simple appendicitis (SA) were verified by the pathology report and perforated or gangrenous appendicitis (PGA) is given as a cardinal output. The blood samples were obtained six to eight hours prior the operation.

The complicated and non-complicated appendicitis were verified by the pathology reports and perforated or gangrenous appendicitis is given as a cardinal output. The blood samples were obtained at the six to eight hours prior the operation.

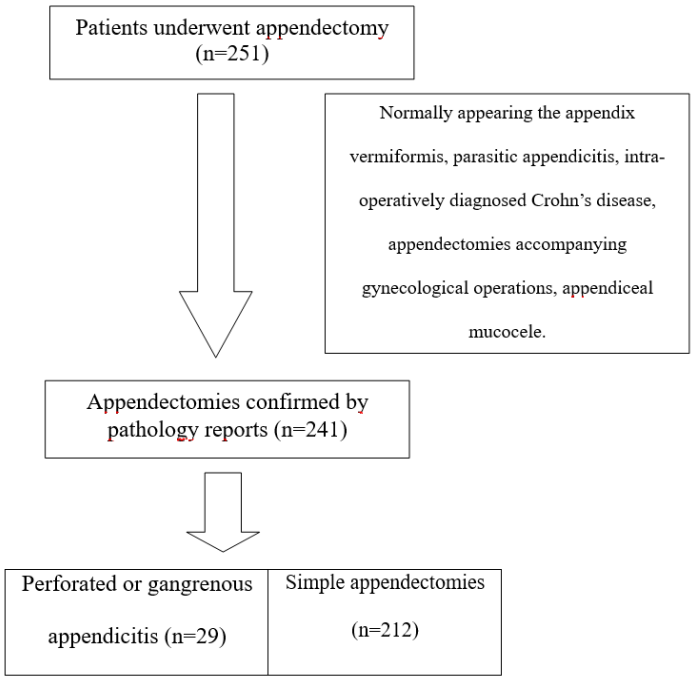

Figure 1: Flow chart of the study.

Surgical technique

Single dose antibiotic was administered pre-operatively (2nd generation cephalosporins or metronidazole and gentamycin) to all patients. Foley′s catheter was selectively employed In LA group Veress needle was used to induce pneumo-peritoneum under general anesthesia. A 3-trocar technique using 5- and 10-mm cannulas was the preferred way under general anesthesia. Electrocautery or other energy devices were used to dissect the mesoappendix and the stump was closed with endoclips. The appendix was placed inside a disposable bag to avoid contamination while taking out. Peritoneal cavity was irrigated with warm saline until the drainage fluid became clear and then pelvic drains were placed. Open appendectomy was carried out through a traditional McBurney operation and in rare cases by lower midline incision either by general or spinal anesthesia. Post-operative intravenous antibiotics (3rd generation cephalosporins combined with metronidazole) were given. Non-steroidal anti-inflammatory drugs were given either as intramuscular injection or via intravenous route to all patients during their hospital stay. Oral intake was started with return of bowel function in both groups. Patients were discharged when proper oral intake and mobilization are achieved save for those with post-operative complications. Oral antibiotics (ciprofloxacin and metronidazole) were given for one week after discharge. The follow up in the outpatient clinic was at the first and seconds weeks, and the first month. Patients were instructed to report back immediately for any complaints after the discharge. Complications recorded were wound infections (purulent discharge from wounds), intra-abdominal abscess (symptomatic post- operative collections in the peritoneal cavity), ileus (absence of peristaltic activity beyond 48 h) and fecal fistula. Clavien-Dindo grading system for the classification of surgical complications was used for evaluation of complications following appendectomy. These were graded into overall

complications (Grade I–V), severe complications (Grade III–IV) and mortality (Grade V) [14].

Statistical Analysis

The variables age, white blood cell count (WBC), aspartate aminotransferase (AST), alanine aminotransferase (ALT), RDW and CRP values were tested for normality with Shapiro-Wilk test. The variables WBC, RDW, CRP, AST, age and hospital stay were tested for normality and all were found to be non-normally distributed except for the hospital stay. Accordingly, the non-normally distributed data was represented in median and percentiles and normally distributed parameters as mean±standard deviation (SD). Mann-Whitney U test, Student's t test and $\chi 2$ test were used to assess differences where appropriate. Binary logistic regression analysis (with Bonferoni correction) was carried out to identify factors significantly associated to PGA.

We measured the prognostic performance of the RDW using receiver operating characteristic curves and calculated sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (+LR), and negative likelihood ratio (−LR) for different cutoff values We also made a correlation analysis to see if serum CRP levels correlated with RDW and WBC. All statistical tests were rendered with SPSS 22 (SPSS Inc, Chicago, Illinois). A value of P<0.05 was considered significant.

Results

The average age of 241 patients was 32.21±12.62 years. Twenty-nine (12%) patients were found to have a perforated or gangrenous appendicitis confirmed in the pathology report.

The values of the whole study group parameters were as follows: hospital stay was 2±0.13 (1-18) days, WBC 13.85 10^3uL (interquartile range (IQR)10.99-16.32), AST 20 U/L (IQR 16-25), ALT 18 (IQR 13-27) U/L, CRP 19.80 mg/L (IQR 5.55-80.60), RDW 13% (IQR 12.60-13.60).

Table 1: The general characteristics of the study groups.

	PGA (n=29)	SA (n=212)	p
Age (year)[¥]	46 (29.5-51.5)	28 (22-36)	0.005
Stay (day)[µ]	3.42±4.01	1.79±1.45	0.008
Gender[β]			0.045
Female	11 (4.6)	45 (18.6)	
Male	18 (7.4)	167 (69.4)	

[¥]: median (interquartile range), [µ]: mean±standard deviation, [β]: n (%). SA: Simple acute appendicitis group, PGA: perforated or gangrenous appendicitis group.

Table 2: The main outcomes of the study groups.

	PGA (n=29)	SA (n=212)	P
WBC (10 ^3uL) [¥]	14.35 (11.84-17.16)	13.62 (10.94-16.19)	0.202
CRP (mg/L) [¥]	82.9 (19.48-171.30)	16.95 (4.00-65.40)	<0.001
RDW (%) [¥]	13.5 (12.90-14.70)	12.90 (12.60-13.50)	0.005
AST (U/L) [¥]	24.47 (15-25.50)	23.00 (17.00-24.00)	0.980
ALT (U/L) [¥]	23 (12.75-24.25)	23.14 (14.00-26.00	0.562

[¥]: median (interquartile range), SA: simple acute appendicitis group, PGA: perforated or gangrenous appendicitis group, WBC: white blood cell, CRP: C-reactive protein, RDW: red cell distribution width, AST: aspartate aminotransferase, ALT: alanine aminotransferase.

In the nonparametric analysis the PGA group was found to be significantly older than the SA group, 46 (IQR 29.5-51.5) years vs 28 (IQR 22-36), (p=0.002). The mean hospital stay for the PGA group was 3.42±4.01 days vs 1.79±1.45 days in the SA group, (p=0.008, Table 1). The median CRP was 82.9 mg/L (IQR 19.48-171.30) vs 16.95 mg/L (IQR 4.00-65.40) in the PGA and SA groups respectively, (p<0.001). Median RDW was 13.5% (IQR 12.90-14.70) in the PGA group vs 12.90% (IQR 12.60-13.50) in the SA group (p=0.005) (Table 2).

In the binary logistic regression analysis, age, CRP and RDW were found to be significantly related to perforation, (p<0.001), while WBC, AST and ALT were found to be insignificant (p=0.052, p=0.806 and p=0.804, respectively. To identify perforated or gangrenous cases, receiver operating characteristics (ROC) curves were plotted for CRP with a statistically significant area under the curve (AUC) of 0.716 (95% confidence interval, 0.615–0.818) (Figure 2). ROC curves were also plotted for WBC and RDW, as well, yielding AUCs as 0.604 and 0.671 respectively (Figure 3), It was only significant for RDW (p=0.005). However, it did not give a specific threshold for discrimination (Table 3).

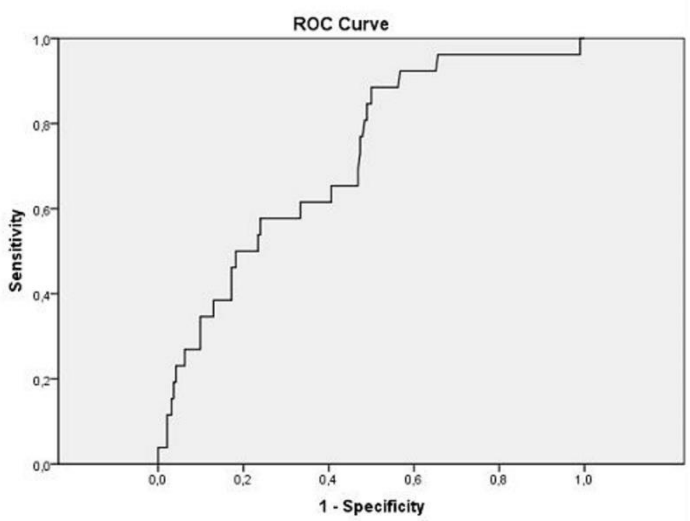

Figure 2: The area under the curve (AUC) for CRP was 0.716 (95% confidence interval, 0.615–0.818, p<0.001).

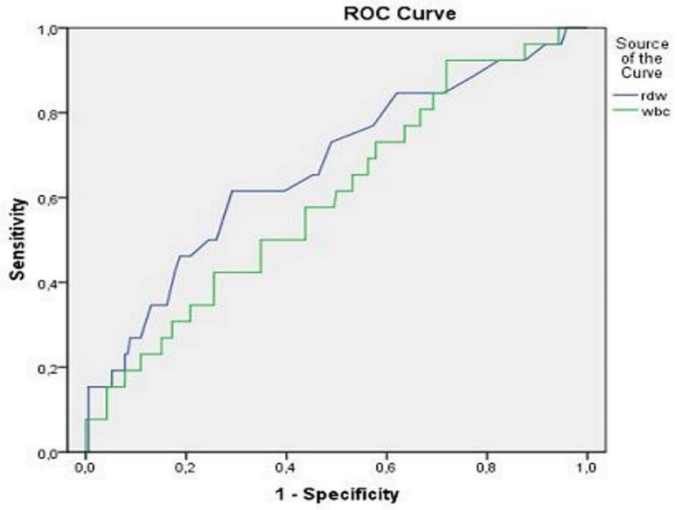

Figure 3. Receiver operator characteristics for WBC and RDW.

Table 3: Area Under Curve (AUC) for WBC and RDW.

	AUC	P	95% Confidence Interval	
RDW	0.671	0.005	0.556	0.787
WBC	0.604	0.086	0.490	0.718

WBC: white blood cell, CRP: C-reactive protein.

Around a level of 4.95 for CRP, the sensitivity in this study was 96.15% with a specificity of 32.29 % and with a positive predictive value of 16.13%. By the ROC curve analysis, a cut-off level was defined and with that level of 16.7 mg/dL,

these values were 88.46%, 49.48 % and 19.17%, respectively (Table 4).

Table 4: The predictivity of CRP at different cut-off values.

Cutoff for CRP	Sensitivity	Specificity	PPV	NPV
5 mg/L	96.15	32.29	16.13	98.41
16.7 mg/L	88.46	49.48	19.17	96.94

CRP: C reactive protein, PPV: positive predictive value, NPV: negative predictive value.

There was a significant correlation between RDW and CRP (correlation coefficient r=0.244 and p<0.001). But no significant correlation of WBC to CRP and RDW was observed (p>0.05 for all).

Overall, there were 13 wound infections, 10 intra-abdominal fluid collections, one fecal fistula encountered in the follow up. There were nine simple wound infections that required bed-side opening or drug therapy (grade 1); three abscess and hematoma in the wound that required recurrent draining (grade 3a). One case that underwent multiple debridement and resturing of the wound was classified as grade 3b.

Of 10 intra-abdominal fluid collections, four resolved by drug therapy alone (grade 2). Six cases were sent to ultrasound guided drainage (grade 3a). Ultrasound guided drainage was effective in treatment of intra-abdominal fluid collections combined with antibiotherapy.

One fecal fistula following appendectomy occurred in a patient who discontinued medication after a removal of appendicitis with pericecal abscess (grade 3b). Six cases of postoperative ileus resolved by medical therapy (grade 1).

Discussion

Appendicitis is still the most common non-elective surgical operation carried out by the general surgeons [15]. Traditionally, appendectomies are carried out as soon as possible after the diagnosis to avoid the progression of the inflammation and potential complications of of the disease[16]. However, there are also other factors which effect the timing of the operation like the availability of the surgery room, or delays in the diagnostic procedure [17]. Giraudo et al. [18] in a retrospective study report that a delayed appendectomy more than 24 hours after the initial admission increase rate of the postoperative complications. Earley et al. [19] report that the decrease in the time elapsed between the admission to hospital and the intervention reduces the perforation and postoperative complication rate. Dtillo et al. [20] classified the appendicitis cases with regard to the pathological state. They figured out that the pathological condition, defined as a higher pathology grade, progressed with the total time taken to intervene. There are also other studies which advocate a traditional prompt operation [21]. However, some recent studies report about a somewhat delayed appendectomy (until the working hours) does not increase the postoperative complications [22,23]. There are also other reports about treatment of appendicitis with antibiotics. In 1995, in a randomized prospective study they treated patients with antibiotics with the criterion that the symptoms had an onset less than 72 hours [24]. In another prospective study they report that non-perforated appendicitis can be treated successfully with antibiotics with a risk of recurrence of 14% in the following year [25].

For a more efficient utilization of available sources, identification of complicated cases is crucial. The importance of CRP in diagnosing appendicitis is well-known, and our study is no exception, either. In harmony with our study, Ortega-Deballon et al. [26] report that CRP has more accuracy in diagnosing appendicitis than the WBC and granulocytes counts. Sack et al. [27] found that WBCs count was clearly elevated in children with phlegmonous and perforated appendicitis. In a study by Xharra et al. [28] they reported that the elevated level of the CRP directly correlated to the severity of inflammation, as they classified the appendicitis in three stages, normal, simple (catarrhal and phlegmonous), complicated (gangrenous and perforated) (p-value <0.05). Yokoyama et al. [29] designed a study to display the importance of C-reactive protein (CRP) as a surgical indication marker for appendicitis to discriminate between the simple cases to be cured medically and complicated appendicitis which necessitate surgery . The AUC for CRP to identify necrotic appendi-citis in their study was 0.862. This value is 07.16 in our study and is significant, p<0.001. Around a level of 4.95 for CRP, they reached a sensitivity of 84.3%, specificity of 75.8%, positive predictive value of 64.2%, and a negative predictive value of 90.4%. Around this cut-off the sensitivity in this study is 96.15% with a specificity of 32.29 %, a positive predictive value of 16.13% and a negative predictive value of 98,41%. In our study with a cut-off level of 16.7 mg/dL, these values are 88.46%, 49.48 %, 19.17%, 96.94, respectively (Table 4). Our threshold seems to be higher than their estimation and this gives us more space to start medication for a presumably uncomplicated appendicitis case.

In a study Boshnak et al. [30] observed a conclusion that RDW level was significantly elevated in the complicated AA cases, (13.30±0.58 vs13.02±0.40, p=0.006). Our study confirms that RDW is elevated in the complicated AA cases (14.28±2.12 vs 13.25±1.11, p=0.005). However, these elevated values are within the normal range of the laboratory test; even though, in our study the median RDW for a complicated appendicitis is close to the upper limit of normal (11.5%-14.5%). In a study by Bozlu et al. [31] they found out that RDW was elevated in children with AA but they did not find a significant difference in complicated cases, unlike our study. In the same study they confirmed that CRP levels were significantly different between complicated and SA cases, in agreement with our findings.

Our study has some shortcomings. Due to the retrospective nature of the research, selection bias may be possible. All consecutive patients were included in the study, besides all the information was readily available in the database.

In conclusion, an elevated level of CRP in an acute appendicitis is an expected finding; however, the volume of this elevation may be related to a complicated appendicitis. Beyond a certain threshold prediction capability of CRP for a potentially complicated AA increases. We compared our suggested threshold with the findings of a previous study and found similar predictivity but for a much higher threshold. For a decisive threshold the number of total observations must be increased and supported by meta-analysisses. RDW in our study has been found to be elevated in complicated appendicitis cases; however, this finding is not conclusive for a potentially perforated or gangrenous appendicitis.

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