ORIGINAL ARTICLE

High C-reactive protein level as a predictor for appendiceal perforation

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ABSTRACT

BACKGROUND: Between 18% and 34% of acute appendicitis (AA) patients may have complicated appendicitis. Perforation is the most important complication of AA. Perforation increases morbidity and mortality. In this study, we aimed to investigate the role of basic inflammatory markers in the diagnosis of perforated AA.

METHODS: A retrospective chart review was conducted of patients who underwent appendectomy with a diagnosis of AA between January 2014 and October 2019 at Akdeniz University Faculty of Medicine; and between December 2017 and October 2019 at Istinye University Faculty of Medicine Hospital. Markers recorded were as follows: white blood cell count, neutrophils, lymphocytes, platelets, c-reactive protein, mean platelet volume, red cell distribution width and eosinophils. Hematological indices were combined to generate the following three ratios: white cell neutrophil ratio, platelet lymphocyte ratio and neutrophil-lymphocyte ratio.

RESULTS: A total of 536 patients with a diagnosis of AA underwent an operation. There were 344 (64.1%) male patients and 192 (35.9%) female patients. The mean age of the patients was 36.7±16.2 (15-88) years. There were 94 (17.5%) patients with perforated AA and 442 (82.5%) patients with non-perforated AA. C-reactive protein (AUC: 0.81, p<0.001) was the most accurate markers in distinguishing the perforated and non-perforated group.

CONCLUSION: Elevated CRP level is a nonspecific inflammatory marker in most of the inflammatory diseases. A high CRP level can, therefore, be used as a supplement in the diagnosis of perforated AA.

Keywords: Appendicitis; C-reactive protein; perforation.

INTRODUCTION

Acute appendicitis (AA) constitutes approximately 2% of the cases presenting to the emergency service with acute abdominal pain.[1] The first stage in the diagnostic process is the acquisition of the patient's history, and evaluation of this history together with symptoms and physical examination findings and is often supported by the laboratory and imaging modalities.[2] Between 18% and 34% of the patients may have complicated AA. Perforation is the most important complication of AA.[3] Perforation of the appendix, which increases the risk of abscess formation, wound infection, and sepsis is a major source of morbidity associated with the condition.[2] Early detection of perforation is crucial for the timely application of special antibiotic regimens and for estimation of the optimal time point for surgery.[3,4] In the diagnosis of AA, the supplemental roles of ultrasound and computed tomography scans are essential. However, they have a low sensitivity in detecting perforated AA.[5] Thus, there is still the need for a laboratory parameter for prediction of perforation that is inexpensive, readily available, quick, and able to provide high sensitivity and specificity rates.[6]

In this study, our aim was to perform an appraisal of inflammatory markers used in the diagnosis of AA and investigate their ability to accurately differentiate between perforated and non-perforated AA.

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MATERIALS AND METHODS

Patient Data

A retrospective chart review was conducted at two academic teaching hospitals of patients who underwent appendectomy with a presumptive diagnosis of acute appendicitis between January 2014 and October 2019. After IRB approval was obtained, ICD-9 code 540.9 (acute appendicitis) was used to procure a list of patient records for the given time frame. The patients who had the diagnosis of AA were hospitalized and undergone surgery. All patients had at least one imaging study ultrasonography (USG) or computed tomography (CT). Final pathology was regarded as a gold standard for the diagnosis of AA. The patients were divided into two groups, Group I was the perforated AA group, and Group II was the non-perforated AA group. The patients with negative appendectomy were excluded from this study.

Recording of Inflammatory Markers and Hematological Ratios

According to hospital protocol regarding patients with suspected AA, inflammatory markers were recorded at admission in Akdeniz University Hospital utilizing a Siemens Advia 2400 and Siemens Advia 2120 hematology and oto analyzer. At Istinye University Hospitalutilizing a Sysmex XN-1000, and Roche Cobas 6000 hematology and oto analyzer. Markers recorded were as follows: white blood cell count (WBC), neutrophils, lymphocytes, platelets, c-reactive protein (CRP), mean platelet volume (MPV), red cell distribution width (RDW) and eosinophils. Hematological indices were combined to generate the following three ratios: white cell neutrophil ratio (WNR), platelet lymphocyte ratio (PLR) and neutrophil-lymphocyte ratio (NLR).

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS Inc., Chicago, Illinois, USA) version 16.0 for Windows was used for the statistical analyses of the data. Shapiro–Wilk test was used for assessing normality. All values are expressed as mean±standard deviation or counts (percentage) unless otherwise specified. For comparison of two groups, an unpaired, 2-sided Student t-test was used to further evaluate inflammatory marker levels in study groups. We measured the clinical performance of inflammatory markers using receiver operating characteristic (ROC) curves and calculated positive likelihood ratios for cut-point with either high sensitivity and high specificity. The discrimination of a marker is considered perfect if AUC is equal to 1, good if AUC is greater than 0.8, moderate if AUC is 0.6–0.8 and poor if AUC is less than 0.6. A p-value of lower than 0.05 was considered to be statistically significant.

RESULTS

A total of 536 patients with a diagnosis of AA underwent an operation. There were 344 (64.1%) male patients and 192(35.9%) female patients. The mean age of the patients was 36.7±16.2 (15–88) years. There were 94 (17.5%) patients in Group I and 442 (82.5%) patients in Group II.

Inflammatory Marker Values in Group I and Group II

Mean inflammatory marker levels were compared between Group I and Group II. With respect to WBC (p<0.005), neutrophils (p<0.005), CRP (p<0.005), platellets (p<0.005), PLR (p<0.001), MPV (p=0.055) and NLR (p<0.005), mean values

Table 1. Classification of the American Association for the Surgery of Trauma (AAST)[19]

	Groups				p
	Acute appendicitis		Perforated acute appendicitis		
	Mean	Standard deviation	Mean	Standard deviation	
WBC (per mm^3)	12399.6	4780.0	14213.8	5120.8	0.001
PLT (per mm^3)	246324.7	72896.2	266322.6	113655.7	0.032
NEU (per mm^3)	9379.0	4022.0	12277.5	4775.8	0.001
LYM (per mm^3)	1778.5	1328.0	1046.5	543.5	0.001
NLR	7.1	5.9	14.8	9.5	0.001
PLR	177.4	131.9	327.4	229.8	0.001
EOS (per mm^3)	177.96	304.03	122.09	109.37	0.001
WNR	1.57	0.33	1.33	0.20	0.159
CRP (mg/L)	3.2426	4.5034	11.7666	8.9133	0.001
MPV (femtolitre)	8.09	1.60	8.86	2.66	0.055
RDW (%)	14.21	8.52	13.34	3.12	0.328

WBC: White blood cell count; NEU: Neutrophils; LYM: Lymphocytes; PLT: Platelets; CRP: C-reactive protein; MPV: Mean platelet volume; RDW: Red cell distribution width; EOS: Eosinophils; WNR; White cell neutrophil ratio; PLR: Platelet lymphocyte ratio; NLR: Neutrophil lymphocyte ratio.

Table 2. ROC analyses

Variables	Area	Std. Error	Asymptotic Significance	95% Confidence Interval	
				Lower Bound	Upper Bound
White blood cell count	.607	.034	.001	.540	.674
Platelets	.522	.036	.513	.451	.593
Neutrophils	.679	.032	.000	.616	.742
Lymphocytes	.235	.027	.000	.181	.288
Neutrophil lymphocyte ratio	.789	.027	.000	.736	.842
Platelet lymphocyte ratio	.754	.031	.000	.694	.814
Eosinophils	.414	.033	.009	.349	.478
C-reactive protein	.810	.027	.000	.757	.863
Mean platelet volume	.531	.034	.347	.466	.597
Red cell distribution width	.481	.034	.571	.415	.548
white cell neutrophil ratio	.231	.029	.000	.174	.288

were higher in Group I when compared to Group II (Table 1). The converse was true regarding lymphocytes (p<0.001), RDW (p=0.328), WNR (p=0.159) and eosinophils (p<0.001); mean values were higher in Group II (Table 1).

ROC Curve Analysis

ROC curve was employed to evaluate the accuracy of inflammatory markers in distinguishing between group I and group II. Curves representing each inflammatory marker were plotted and compared. CRP (AUC: 0.81, p<0.001) was the most accurate markers in distinguishing the 2 groups (Table 2). Positive likelihood ratio was 2.76 (95% confidence interval, 2.28–3.33) for CRP level more than 35 mg/L.

DISCUSSION

Untreated, AA progresses from inflammation to perforation with abscess formation or diffuse peritonitis, making timely operative intervention imperative. Generally, the morbidity and mortality of missing a case of AA with subsequent peritonitis or abscess formation far outweigh the complications associated with a negative appendicectomy.[7,8] Accurate identification of non-perforated AA is topical currently due to emerging evidence suggesting that AA can be managed successfully non-operatively.[6]

This study demonstrates that CRP was very accurate in distinguishing between perforated and non-perforated AA. The cut-off points generated in this study may be of future benefit in stratifying these patients when planning their management. Also, part of the difficulty in comparing results arises from the lack of a definite endpoint in patient classification. The current study population was restricted to a defined group of patients who underwent surgery with a clinical diagnosis of AA to eliminate this problem.

Several prognostic factors, such as duration of symptoms, pain migration, indirect pain, abdominal guarding, and fever, can be used in combination to predict a possible perforation of the appendix.[8] A systematic review has redfold.[2] It has shown that elevated bilirubin can be used as a prognostic factor for the assessment of perforated AA.[8] C-reactive protein is an important serum inflammatory marker in the diagnosis of AA in the pediatric age group. After 6 to 12 hours of inflammation, the concentration begins to rise and may increase a hundredfold.[2] It was demonstrated that in patients whose symptoms had lasted less than 24 hours, WBC count had a high sensitivity, whereas in those in whom the symptoms had lasted more than 24 hours, CRP had a high sensitivity. However, in a meta-analysis, CRP was shown to have a medium sensitivity (53%–88%) and specificity (46%–82%) for the diagnosis of AA.[7] Ahmed et al.[9] demonstrated that if CRP is more than 48 mg/dL, then, there is an increased risk of perforated AA. A recent study reported that the sensitivity and specificity of CRP to identify perforated AA were 71.0% and 100%, respectively, at this cut-off of 40.1 mg/dL.[10] Another recent study demonstrated that that CRP value >6.15 mg/L has a sensitivity of 100.0% and a specificity of 54% in predicting perforated AA.[11] The results of these studies demonstrate that there is no standard CTP cut-off value for the prediction of perforation. In general, when setting a low cut-off value, this generates a high sensitivity and low specificity and vice versa when setting a cut-off value.

Diagnostic scores have been developed in diagnosing acute appendicitis, such as the Alvarado score, Rajalsteri Pengiran Anak Saleha Appendicitis (RIPASA) score and appendicitis inflammatory response score. All of these scores have been proven useful in predicting AA, but none of them evaluate the risk of perforation.[5]

USG and CT are the most preferred imaging modalities. In a

meta-analysis, Al-Khayal et al.[12] stated that USG had a sensitivity of 83.7% and specificity of 95.9% in cases suspected to have AA. In a similar study, Eng et al.[13] reported the sensitivity and specificity as 83.1% and 90.9%, respectively, for USG, and as 89.9% and 93.6%, respectively, for CT. However, these two techniques have a low sensitivity in detecting perforated AA.[5] On the other hand, despite the higher specificity and sensitivity values, the downside of CT is exposure to ionized radiation. In a study by Smith-Bindman et al.,[14] it was demonstrated that there was an increase in the rate of cancer associated with CT-related radiation, particularly among young people.

In conclusion, we think that although elevated CRP level is a nonspecific inflammatory marker in most of the inflammatory diseases, a high CRP level is helpful in the diagnosis of perforated AA.

Ethics Committee Approval: Nil (Retrospective study).

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ORİJİNAL ÇALIŞMA - *ÖZET*

Yüksek C-reaktif protein seviyesi apendiks perforasyonu için belirteç olabilir

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AMAÇ: Akut apandisit (AA) hastalarının %18 ile %34'ü komplike apandisit tanısı almıştır. AA'nın en önemli komplikasyonu perforasyondur. Perforasyon morbidite ve mortaliteyi arttırır. Bu çalışmada temel enflamatuvar belirteçlerin perfore AA tanısındaki rolünü araştırmayı amaçladık.
GEREÇ VE YÖNTEM: Akdeniz Üniversitesi Tıp Fakültesi'nde; Ocak 2014–Ekim 2019 ve Aralık 2017–Ekim 2019 tarihleri arasında İstinye Üniversitesi Tıp Fakültesi Hastanesi'nde AA tanısı ile apendektomi yapılan hastaların retrospektif dosya incelemesi yapıldı. Kaydedilen belirteçler aşağıdaki gibiydi: lökosit sayısı, nötrofil, lenfosit, trombosit sayımı, C-reaktif protein, ortalama trombosit hacmi, kırmızı hücre dağılım genişliği ve eozinofiller. Aşağıdaki üç oranın üretilmesi için hematolojik endeksler çalıştırıldı; beyaz küre nötrofil oranı, trombosit lenfosit oranı ve nötrofil lenfosit oranı.
BULGULAR: Akut apandisit tanısı olan toplam 536 hasta ameliyat edildi. Bu hastaların 344'ü (%64.1) erkek ve 192'si (%35.9) kadın idi. Hastaların yaş ortalaması 36.7±16.2 (15–88) idi. Perfore AA olan 94 (%17.5) ve perfore olmayan AA olan 442 (%82.5) hasta vardı. C-reaktif protein (AUC: 0.81, p<0.001), perfore ve perfore olmayan grubun ayırt edilmesinde en doğru belirteç olarak tespit edildi.
TARTIŞMA: Yüksek CRP seviyesi, enflamatuvar hastalıkların çoğunda spesifik olmayan bir enflamatuvar belirteçtir, bu nedenle yüksek CRP seviyesi, perfore AA'nın tanısında bir tamamlayıcı olarak kullanılabilir.
Anahtar sözcükler: Apandisit; C-reaktif protein; perforasyon.

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