ORIGINAL ARTICLE

The role of C-reactive protein to lymphocyte ratio in the differentiation of acute and perforated appendicitis

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ABSTRACT

BACKGROUND: This study aimed to investigate the superiority of C-reactive protein (CRP) lymphocyte ratio (CLR) in acute appendicitis (AA) and perforated appendicitis (PA) compared to routine laboratory parameters in patients where radiological tests were insufficient to clarify the diagnosis.

METHODS: In this cross-sectional and retrospective study, the patients were divided into two groups as PA and AA. Age, sex, length of hospital stay, leukocytes, neutrophil, lymphocyte, CRP, and CLR were recorded at the time of diagnosis. Regression analyses were performed for the parameters, which were found to be statistically significant in univariate analysis.

RESULTS: One hundred thirty-one patients were included in this study (111 patients in the AA group, and 20 patients in the PA group). Age (p=0.03), gender (p<0.001), length of hospital stay (p<0.001), CRP (p<0.001), NLR (p=0.004) and CLR (p<0.001) were significantly different between both groups. However, only CLR was found as a significant risk factor in PA cases (p=0.016). The ROC analysis showed the highest AUC value in CLR (0.83). The cut-off value for predicting PA was found 0.45.

CONCLUSION: This study provided that the CLR is an important parameter for the differentiation of AA and PA patients. Besides, it is a valuable predictor in the preoperative risk classification of these patients.

Keywords: Acute appendicitis; C-reactive protein to lymphocyte ratio; perforation.

INTRODUCTION

Acute appendicitis (AA) is one of the most common surgical diseases and causes of abdominal pain requiring acute surgery seen in emergency departments.[1,2] The rate of acute appendicitis is between 7.5 and 12.5/10000 throughout the world. The lifetime risk of an average individual is 7% and the complication rate is around 17–20 %. However, there are some reports of increased incidence of AA (22.71/10000) depending on the definition and detection method; the perforation rate is similar (2.9/10000).[3] Surgery provides recovery in the short-term in cases diagnosed with uncomplicated AA. However, delay in the diagnosis causes difficulties in complicated cases. Mortality risk is low in AA patients (0.3%) but increases when the patients have perforation (6%).[4,5]

The diagnosis of AA is easy and can be made by routine physical examination. Importantly, the diagnosis interval may increase in patients with retrocecal appendixes, children and elderly patients. Moreover, ovarian pathologies may lead to misdiagnosis, which subsequently leads to a delay in diagnosis.[2,6,7] Ultrasonography (USG) and computed tomography (CT) are frequently used techniques in the diagnosis of AA and PA. However, these techniques require special equipment and an experienced radiologist.[8,9]

White blood cells (WBC) and C-reactive protein (CRP) are routinely-used laboratory parameters, which strengthen the diagnosis of AA. Although recent studies have assessed several parameters, such as NLR, PLR, MPV, PLT, and serum bilirubin, there is no definitive parameter that is used to differ-

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entiate AA and PA.[7,8,10] A few studies reported that these laboratory parameters are useful in the diagnosis of complicated appendicitis, but could not reach a satisfactory level.[11,12] The lack of a marker in this field raised an interest to look for new parameters.

Recent studies performed with the inclusion of inflammatory parameters have shown that the ratio of lymphocyte and CRP (CLR) is more useful in demonstrating systemic inflammatory response, especially in malignancy patients. In the end, CLR was reported more sensitive and specific than other parameters.[13–16]

Since appendicitis is characterized by increased inflammation, we aimed to investigate whether the CLR is a diagnostic parameter for the differentiation of AA and PA. We also aimed to test the inflammatory parameters if they could be a predictor in the preoperative risk classification of these patients.

MATERIALS AND METHODS

This is a retrospective study and performed in a tertiary university Department of Emergency between June 2018 and January 2019. Central Provincial Health Directorate and Ethical Committee of University approved this study with number 20-KAEK-011. The data of the patients with the diagnosis of AA and PA were retrospectively collected from Central Provincial Health Database. We assessed the data related to appendicitis in all pathology reports from the central database of the hospitals and included the patients whose final diagnosis was AA and PA.

We included the patients with age >18 years, pathologically diagnosed with AA and PA, and whose laboratory parameters included at least complete blood count (CBC) and CRP tests. Patients under 18 years of age, patients with a pathologic diagnosis other than appendicitis, and patients with a lack of laboratory parameters were excluded from this study.

Age, gender, length of hospital stay, WBC, neutrophil, lymphocyte, and CRP were recorded from the database values at the time of diagnosis. SYSMEX XE2100 test and IMMAGE 800 Immunochemistry system were used to test CBC and CRP, respectively.

Because this study was planned as a cross-sectional study, all patients admitted to the emergency department in a 6-month period with the diagnosis of AA were examined and their information was recorded in the computer system. Patients were divided into two groups as AA and PA and compared concerning WBC, NLR, CRP, and CLR, as well as their age, gender, and length of hospital stay. CLR was calculated as (CRP/lymphocyte)x100.

Statistical Analysis

We presented parametric variables as mean and standard deviations and non-parametric variables as median and interquartile intervals (lower and upper quarters). Kolmogorov-Smirnov test and a histogram analysis were used to determine whether continuous variables were normally distributed. We used logarithmic for the variables, not showing normal distribution. We assessed the homogeneity of the variances with Levene's test. For categorical variables, we used the number of cases and percentages. We compared two independent parametric variable groups using Student's t-test and applied the Mann-Whitney U test for non-parametric variables.

ROC (receiver operating characteristic) curves were created to evaluate the presence of PA. We calculated the area under the curve of the ROC value (AUC) for the evaluation of perforation in AA. EasyROC (ver. 1.3) was used to compare the AUCs (WBC, CRP, NLR, and CLR) and perform the ROC curve analysis.

In multivariate analysis, we examined independent predictors for predicting treatment outcome using logistic regression analysis. We used the Hosmer-Lemeshow test for model fit. Cases with a type-I error level below 5% were considered statistically significant.

RESULTS

We found that 348 patients were operated with AA during the 6-month period. One hundred and twenty-seven of them were <18 years of age. Pathological diagnosis indicated reactive lymphoid hyperplasia (RLA) in nine patients, neoplasia in five patients, and ovarian pathology in seven patients. Sixty-nine patients' laboratory parameters did not include CRP as it had not been requested at the time of diagnosis. All these patients were excluded from this study. In the end, 131 patients were included in this study. One hundred eleven patients were diagnosed with AA and 20 were diagnosed with PA (Fig. 1).

Seventy-two of the patients were male (55%). The mean age of all patients was 33 (24; 46). When the patients were assessed separately, the mean age of AA and PA patients were 32 (24; 43) and 44.5 (25; 70), respectively (p=0.03). The duration of hospital stay was three (3; 5) days in AA patients and five (4; 6.75) in PA patients (p<0.001).

WBC, neutrophil, CRP, NLR, and CLR were compared between the AA and PA groups. In the PA group, CRP (7.9 vs. 0.6, p<0.001), CLR (0.55 vs. 0.04, p<0.001) and NLR (7.5 vs. 4.2, p=0.004) were significantly higher. However, no difference was shown in WBC (12700 vs. 13800, p=0.3) and neutrophil (9700 vs 11300, p=0.1) values between PA and AA cases (Table 1).

ROC curve analysis showed the highest AUC value as 0.83 in CLR. On the other hand, the AUC values for NLR and CRP were 0.70 and 0.82, respectively (Fig. 2). CLR sensitivity was 0.700 (upper-upper limit; 0.457–0.881) and specificity was 0.96 (lower-upper limit; 0.91–0.99). The cut-off value for

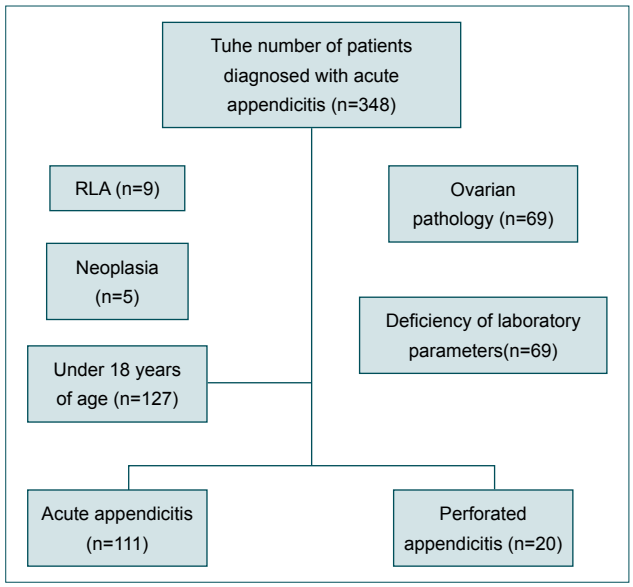

Figure 1. Follow chart of acute appendicitis, RLA: Reactive lymphoid hyperplasia.

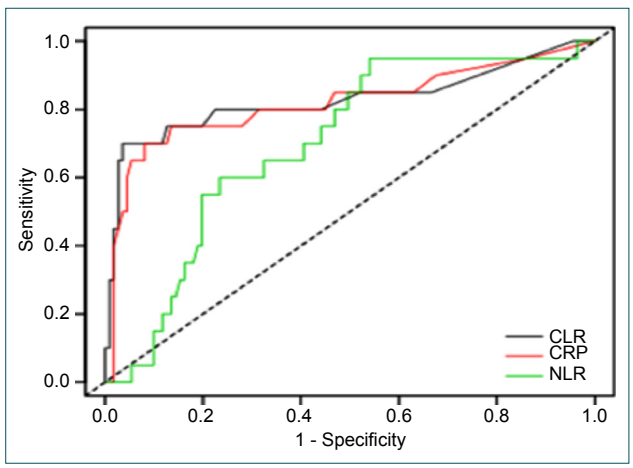

Figure 2. ROC analysis in the evaluation of PA (CLR: (CRP/lymphocyte ratio)x100; CRP: C-reactive protein; NLR: neutrophil/lymphocyte ratio).

predicting PA was 0.45. ROC analysis with this cut-off value revealed that positive predictive value was 0.78 (lower-upper limit; 0.57–0.92), negative predictive value 0.95 (lower-upper limit; 0.87–0.99), Positive Likelihood Ratio 19.4 (lower-upper limit) 7.2–53), Negative Likelihood Ratio 0.31 (upper-lower limit; 0.16–0.61) (Table 2). This finding showed that CLR had a higher significance value than WBC, CRP and NLR in showing AA perforation.

Age, CRP, NLR, and CLR were found significant in univariant analyses and further evaluated by multivariant analyses. In the end, CLR was found to be the only significant risk factor in PA cases (p=0.016) (Table 3).

DISCUSSION

Here, we studied some biochemical markers from patient serum to reveal whether perforated appendicitis can be differentiated from acute appendicitis. To our knowledge, this is the first study in the literature investigating the efficacy of CLR in the differentiation of PA and AA. We found that CLR was significantly higher in patients with PA than patients with AA. We have also shown that it has a high sensitivity and specificity ratio compared to the other measured inflammatory parameters.

We analyzed the demographic data of the patients: the median age was 32 (24;43, IQR) in and 44.5 (25;70, IQR) in the AA and PA groups, respectively. Although there was an age differ-

Table 1. Demographic characteristics and laboratory parameters in the differentiation of PA and AA

	Perforation (-)	Perforation (+)	p
Age	32 (24;43) (IQR)	44.5 (25;70) (IQR)	0.03
LOS*	3 (3;5) (IQR)	5 (4;6.75) (IQR)	<0.001
WBC	12.76±4.2	13.83±3.9	0.3
Neutrophil	9.7±4.2	11.3±3.8	0.1
CRP	0.6 (0.2;2.3)	7.9 (2.3;11.5)	<0.001
NLR	4.2 (2.6;6.7)	7.5 (4.8;9.8)	0.004
CLR	0.04 (0.009;0.1)	0.55 (0.16;0.7)	<0.001
Tables			

LOS: Length of stay; WBC: White blood cell; CRP: C-reactive protein; NLR: Neutrophil/lymphocyte ratio; CLR: (CRP/lymphocyte ratio)x100.

Table 2. ROC curve analyses of CLR

	Value	Lower	Upper
Sensitivity	0.700	0.457	0.881
Specificity	0.964	0.910	0.990
Positive Predictive Value	0.78	0.57	0.92
Negative Predictive Value	0.95	0.87	0.99
Positive Likelihood Ratio	19.4	7.2	53
Negative Likelihood Ratio	0.3	0.16	0.61

CLR: CRP/lymphocyte ratio.

Table 3. Statistical values of CLR in PA in the multivariate analysis

	OR (95% CI)*	p**
Age	1.05 (0.98–1.054)	0.365
CRP	0,91 (0.66–1.26)	0.578
NLR	1.14 (0.41–3.19)	0.407
CLR	1641,15 (4.09–658741.53)	0.016

CRP: C-reactive protein; NLR: Neutrophil/lymphocyte ratio; CLR: (CRP/lymphocyte ratio)x100.

ence between the groups, we do not think that it is clinically significant. The mean length of hospital stay was significantly lower in the AA group than in the PA group, as expected. Postoperative length of hospital stay has paramount importance concerning patient comfort and the costs of treatment. The length of hospital stay varies in the literature depending on several factors like whether the disease was complicated or the operation was performed laparoscopically or not.[17–19]

The imaging techniques are valuable for the differentiation of AA and PA. In this regard, CT was regarded as a highly sensitive and specific examination method. Compared with CT, the, sensitivity and specificity of USG has been found lower than CT in several studies.[20–24] To increase the sensitivity of CT in perforated apendicitis, the appendix sphericity index was defined and subsequently shown that the consideration of this index was well correlated with prediction of perforation.[6] On the other hand, both USG and CT have higher sensitivity and specificity than other laboratory parameters. The sensitivity and specificity of USG decrease especially in cases of obesity, atypical appendix location, abdominal rigidity due to perforation, and incompatible in abdominal distension.[21,25] CT has also some disadvantages; regional availability varies, it cannot be used in pregnant women, and uses contrast materials.[8,9]

In an attempt to search for simple and easily available biochemical indicators many reports have long been published. There have been several studies investigated the WBC, CRP, NLR, bilirubin, and PLR as the diagnostic parameters to differentiate between PA and AA. AUC value for WBC was 0.68, 0.84 for CRP, 0.72 for NLR, 0.62 for bilirubin and 0.65 for PLR.[1,8,26] Similarly, the sensitivity and specificity of CRP to differentiate between perforated and non-perforated cases were found to be 0.80 and 0.81, respectively.[1] Another study performed in 392 cases by Sevinç et al.[8] showed that the sensitivity of NLR was 0.78, the specificity was 0.41, the bilirubin sensitivity was 0.34, and the specificity was 0.8. In patients with acute appendicitis, the CRP value higher than 35 mg/dl had a positive likelihood ratio of 2.79 to differentiate between acute and perforated appendicitis cases.[27]

CLR has recently been introduced as a new parameter to determine the prognosis of malignancy in some studies.[14–16] It is a simple calculation obtained by the ratio of CRP to lymphocyte. Both CRP elevation and decrease in peripheral blood lymphocyte in patients with malignancy have been associated with poor prognosis.[28] Several studies have shown that the relationship between CRP and lymphocyte plays a significant role in certain types of cancer. Preoperative screening of CRP, lymphocyte and various ratio analysis (CLR, LCR, CLS) were more sensitive in predicting survival and prognosis in many cancers, including colorectal, hepatocellular, and stomach in the postoperative period.[14–16] This provoked the thought that inflammation-induced elevation of CLR in malignancy patients might also be observed in inflammations, such as appendicitis. The results obtained in this study showed that CLR was more accurate in differentiating AA and PA than other parameters, such as WBC, CRP, and NLR. In our study, although CRP alone was a good predictor of perforation, we found that CLR was more accurate in detecting perforation concerning sensitivity and specificity compared with other parameters in AA cases (AUC of CRP: 0.82 vs. AUC of CLR: 0.83 respectively). Therefore, we can propose CLR as a novel prognostic marker in differentiating acute appendicitis cases from perforations. The question of whether it can be used for other infectious conditions like cholecystitis awaits new studies.

Although the current study has added novel information to the literature, it also has some limitations. This is a retrospective study which has inherent deficiencies like in other retrospective studies. Missing data, such as lack of CRP resulted in the exclusion of some patients from this study. However, the group without CRP data did not affect the current outcome. Secondly, the sample size was limited and there was a proportional difference between the two groups.

Conclusion

In conclusion, this study suggests that CLR has a critical role in differentiating PA and AA. Since CLR is a ratio between CRP and lymphocyte, which are readily available in many hospitals, it can offer an alternative to sophisticated imaging modalities to differentiate acute appendicitis from perforated cases in resource-limited centers. Future prospective validation studies may shed further light on this subject.

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ORİJİNAL ÇALIŞMA - *ÖZET*

Akut ve perfore apandisit ayırımında C-reaktif protein lefosit oranının rolü

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AMAÇ: Bu çalışmada, CRP lenfosit oranının akut apandisit (AA) ve perfore apandisit (PA) ayırımında radyolojik tetkiklerin tanıyı netleştirmede yetersiz kaldığı vakalarda rutin kullanılan laboratuvar parametrelerine göre üstünlüğünü araştırmak amaçlanmıştır.
GEREÇ VE YÖNTEM: Kesitsel ve ileriye yönelik olarak plananlanan bu çalışmada hastalar perfore ve non-perfore akut apandisit olarak iki gruba ayrıldı. Her iki gruptaki hastaların yaşı, cinsiyeti, yatış süresi, tanı anındaki lökosit, nötrofil, lenfosit, C reaktif protein (CRP), lenfosit oranı (CLR) değerleri kayıt altına alındı. Tek değişkenli analiz ile istatistiksel olarak anlamlı sonuçlar saptanan değerler arasında regresyon analizleri yapıldı.
BULGULAR: Çalışmaya 131 hasta alındı (AA grubunda 111 hasta ve PA grubunda 20 hasta). Yaş (p=0.03), cinsiyet (p<0.001), hastanede kalış süresi (p<0.001), CRP (p<0.001), NLR (p=0.004), CLR (p<0.001) değerleri her iki grup arasında anlamlı olarak farklı tespit edildi. Ancak yapılan regresyon analizinde sadece CLR anlamlı bir risk faktörü olarak bulundu (p=0.016). ROC analizinde CLR'de en yüksek AUC değeri gösterildi (0.83). PA'nin kestirim değeri 0.45 olarak bulundu.
TARTIŞMA: Bu çalışma CLR'nin AA ve PA hastalarının ayırımı için önemli bir parametre olduğunu gösterdi. Ayrıca, bu hastaların preoperatif risk sınıflandırmasında değerli bir belirleyicidir.
Anahtar sözcükler: Akut apandisit; C-reaktif protein lenfosit oranı; perforasyon.

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