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Original Article

Diagnostic value of basic laboratory parameters for simple and perforated acute appendicitis

Basit ve perfore akut apandisit için temel laboratuvar parametrelerinin tanısal değeri

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ABSTRACT

Aim: The aim of the present study was to investigate the efficacy of simple laboratory parameters including neutrophil-to-lymphocyte ratio (NLR), leukocyte count (WCC), C-reactive protein (CRP) and red cell distribution width (RDW) values in both diagnosing simple appendicitis and predicting complicated appendicitis.

Material and Methods: A database of 413 patients who underwent surgery was appreciated. Based on postoperative histopathological examination, the patients were divided into two groups: negative appendectomy (G1) and positive appendectomy (G2). Patients in the positive appendectomy group were further divided into two subgroups: simple appendicitis (G2a) and complicated (gangrenous and perforated) appendicitis (G2b).

Results: WCC and NLR were significant parameters for the diagnosis of acute appendicitis. Cut-off values were 11950/mm3 for WCC (sensitivity: 71.7%; specificity: 50%; OR: 2.53) and 3.7 for NLR (sensitivity: 75.1%; specificity: 42.8%; OR:2.25). WCC, CRP and NLR were independent variables for the diagnosis of complicated appendicitis. Cut-off values were 14450/mm3 for WCC (sensitivity: 66.7%; specificity: 59%; OR: 2.87), 25.5 mg/dl for CRP (sensitivity: 63.8%; specificity: 58.2%; OR: 2.47) and 6.94 for NLR (sensitivity: 61.1%; specificity: 61%; OR: 2.51).

Conclusion: As a result, preoperative NLR is a useful parameter to aid in the diagnosis of acute appendicitis and differentiate between simple and complicated appendicitis and can be used as an adjunct to the clinical examination.

Keywords: Appendicitis; neutrophil-to-lymphocyte ratio; laboratory parameters

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ÖZ

Amaç: Bu çalışmanın amacı nötrofil-lenfosit oranı (NLR), lökosit sayısı (WCC), C-reaktif protein (CRP) ve kırmızı kan hücre dağılım genişliği (RDW) gibi değerleri içeren basit laboratuar parametrelerinin basit apandisit ve komplike apandisit tanısı koyma etkinliğini araştırmaktı.

Gereç ve Yöntemler: Ameliyat edilen 413 hastanın postoperatif histopatolojik incelemesine göre hastalar negatif apendektomi (G1) ve pozitif apendektomi (G2) olmak üzere iki gruba ayrıldı. Pozitif apendektomi grubundaki hastalar, basit apandisit (G2a) ve komplike (gangrenöz ve perfore) apandisit (G2b) olmak üzere iki alt gruba ayrıldı.

Bulgular: WCC ve NLR akut apandisit tanısında önemli parametrelerdir. Cut-off değerleri WCC için 11950 / mm3 (duyarlılık:% 71.7, özgüllük:% 50; OR: 2.53) ve NLR için 3.7 (duyarlılık:% 75.1, özgüllük:% 42.8; OR: 2.25) bulundu. WCC, CRP ve NLR komplike apandisit tanısında bağımsız değişkenlerdi. Cut-off değerleri WCC için 14450 / mm3 (duyarlılık:% 66.7, özgüllük:% 59; OR: 2.87), CRP için 25.5 mg / dl (duyarlılık:% 63.8; özgüllük:% 58.2; OR: 2.47) ve 6.94 NLR (duyarlılık:% 61.1, özgüllük:% 61; OR: 2.51).

Sonuç: Sonuç olarak preoperatif NLR, akut apandisit tanısında, basit ve komplike apandisitleri ayırt etmede yararlı bir parametredir ve klinik muayene için yardımcı olarak kullanılabilir.

Anahtar kelimeler: Apandisit; nötrofil-lenfosit oranı; laboratuvar parametreleri

Introduction

Acute appendicitis (AA) is one of the most common causes of acute abdomen. The lifetime incident of this disease is approximately 7%, with perforation rates of 17-20% [1]. Generally the mortality risk is less than 1%, but in elderly risk rise to 50% among [2,3]. This presence has some well-known signs and symptoms, like increased leukocyte count and right lower quadrant pain. However, these predictors are not fixed and their precision is debatable.

Complicated AA (perforation, gangrenous appendicitis, intraabdominal abscess, plastron formation and generalized peritonitis) may be perceived in 20 to 30% of all appendicitis patients. It is related with increased risk of morbidity and mortality. Complicated appendicitis is associated with increased rate of wound infection, intraabdominal abscess and postoperative ileus [4]. Due to these serious problems, early diagnosis of appendicitis is essential in order to prevent these complications.

The aim of the present study was to evaluate the predictive value of simple laboratory parameters including WCC , NLR, RDW and CRP in the diagnosis of acute appendicitis and its complications.

Material and Methods

The current retrospective study was approved by local ethical committee and all procedures were performed according to Helsinki declaration. Records of patients who underwent open or laparoscopic appendectomy between January 2017 and December 2017 were reviewed. All of 413 patients aged ≥18 years with clinically suspected AA admitted to the emergency depertmant with abdominal pain and nausea who underwent urgent laparotomy or laparoscopy and were pre-diagnosed with acute appendicitis. Patients with incomplete medical records, known hematological disease, allergic disease, malignant or inflammatory disease or receiving drugs that can affect hematological parameters were excluded from the study. Patients' ages, genders, laboratory results (including neutrophil-to-lymphocyte ratio from total blood count), and intraoperative findings were collected.

Blood tests were conducted within 1 hour of the patient's application for emergency services. The clinical diagnosis of AA was established preoperatively by means of clinical history, physical examination, traditional laboratory tests, and in some patients, by imaging studies like ultrasonography.

Totally, the data of 413 patients were analyzed. Pathology reports were used to define whether the appendix was inflamed or normal. According to pathology reports, patients were grouped into two as negative appendectomy (G1) and positive appendectomy (G2) groups. For subgroup analysis, G2 was divided into two as non-complicated (G2a) and (G2b) complicated appendicitis according to the intraoperative findings. Complicated appendicitis was defined as gangrenous and/or perforated appendicitis.

Statistical analysis

Statistical analysis was conducted using the Statistical Package for the Social Sciences 18.0 program (SPSS Inc.; Chicago, USA). In univariate analysis, normally distributed continuous variables were expressed as mean± standard deviation and compared using t-test. Variables not normally distributed were expressed as median (range) and compared using Mann-Whitney U test. Nominal data were expressed as case numbers

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and percentages, and were compared using Fisher's exact test. Logistic regression analysis was performed as multivariate analysis on parameters with significant differences observed in univariate analysis. Diagnostic accuracy was evaluated using receiver operating characteristic (ROC) curve analysis. Appropriate cut-off values were identified, and sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio were calculated for parameters with an area under the curve (AUC) of above 0.600. All tests were two-sided. A value of $p<0.05$ was considered statistically significant.

Results

The data of 413 patients were analyzed. The mean age of the analyzed group was 33.92±14.2 and 66.2% of the patients were male. There were 28 patients in G1 and 385 patients in G2. In subgroups, there were 313 patients in G2a and 72 patients in G2b. Negative laparotomy was more common in females. WCC and NLR values were significantly different between Groups 1 and 2 in univariate analyses. These parameters were independent variables for the diagnosis of AA in multivariate logistic regression analysis. Comparison between Groups 1 and 2 is detailed in Table 1. In ROC curve analyses of these independent variables, AUC was above 0.600 for WCC and NLR (Figure 1). Proposed cut-off values and performance characteristics for these variables are shown in Table 2. Each parameter considered (WCC, NLR and CRP) were significantly different between patients with complicated and non-complicated appendicitis. Each parameter was an independent variable for recognition of complicated appendicitis in multivariate logistic regression analysis. Comparison of groups is detailed in Table 3. In ROC curve analyses of these independent variables, AUC above 0.600 was found in WCC, CRP and NLR (Figure 2). Proposed cut-off values and performance characteristics for these variables are shown in Table 4.

Table 1. Comparison of the two groups

	Univariate analysis			Multivariate analysis			ROC curve analysis		
Parameters	**Group 1**	**Group 2**	**p**	**OR**	**95% CI (min-max)**	**p**	**AUC**	**95%CI (min-max)**	**p**
Number of cases	28	385							
Age (years)†	30(18-79)	30(18-89)	0.47						
Gender (n)		0.74							
Male (%)	13(46.4%)	244(63.4%)							
Female (%)	15(53.6%)	141(36.6%)							
WCC($x10^3/mm^3$‡	12.3±4.5	14.4±4.5	0.016	1.05	0.94-1.17	0.016	0.639	0.531-0.748	0.014
NLR†	4.9±3.1	8.2±6.8	0.005	1.15	1.00-1.32	0.014	0.665	0.561-0.77	0.004
RDW (%)	13.7±1.3	13.9±1.4	0.905						
CRP (mg/dL)‡	59.1±109.5	46.6±61.2	0.73						

†Median (range); ‡Mean (±standard deviation). OR: Odds ratio; AUC: Area under the curve; WCC: White cell count; NLR: Neutrophil-to-lymphocyte ratio ;RDW : red cell distribution width ; CRP: C-reactive protein

Table 2. Proposed cut-off values for significant parameters in diagnosis of acute appendicitis

	Cut-off value	Sensitivity (%)	Specificity (%)	PPV	NPV	OR	pLLR	nLLR	AUC
WCC ($x10^3/mm^3$)‡	11.95	71.7	50	0.95	0.11	2.53	1.43	O.56	0.639
NLR	3.7	75.1	42.8	0.94	0.11	2.25	1.31	0.58	0.665

WCC: White cell count; NLR: Neutrophil-to-lymphocyte ratio; PPV: Positive predictive value; NPV: Negative predictive value; OR: Odds ratio; pLLR: Positive likelihood ratio; nLLR: Negative likelihood ratio; AUC: Area under the curve.

Table 3. Comparison of the subgroups of Group 2

	Univariate analysis			Multivariate analysis			ROC curve analysis		
Parameters	**Group 2A**	**Group 2B**	**p**	**OR**	**95% CI (min-max)**	**p**	**AUC**	**95%CI (min-max)**	**p**
Number of cases	313	72							
Age (years)†	32.5±13.1	40.9±17.4	<0.001						
Gender (n)			0.046						
Male (%)	191(61%)	53(73.6%)							
Female (%)	122(39%)	19(26.4%)							
WCC($x10^3/mm^3$)‡	13.8±4.1	17.1±5.2	<0.001	1.06	0.99-1.14	<0.001	0.67	0.601-0.739	<0.001
NLR†	4.9±3.1	7.6±6.4	<0.001	1.00	0.96-1.05	<0.001	0.645	0.554-0.716	<0.001
RDW(%)	13.7±1.3	13.9±1.4	0.789						
CRP (mg/dl)	40.6±54.9	72.6±78.3	<0.001	1.00	1.00-1.01	<0.001	0.602	0.528-0.676	0.007

†Median (range); ‡Mean (±standard deviation). OR: Odds ratio; AUC: Area under the curve; WCC: White cell count; NLR: Neutrophil-to-lymphocyte ratio ;RDW : red cell distribution width ; CRP: C-reactive protein

Table 4. Proposed cut-off values for significant parameters in prediction of perforation

	Cut-off value	Sensitivity (%)	Specificity (%)	PPV	NPV	OR	pLLR	nLLR	AUC
WCC (x10^3/mm^3)‡	14.45	66.7	59	0.25	0.89	2.87	1.62	0.56	0.67
NLR	6.94	61.1	61	0.25	0.88	2.51	1.56	0.63	0.645
CRP	25.5	63.8	58.2	0.24	0.88	2.47	1.52	0.62	0.602

WCC: White cell count; NLR: Neutrophil-to-lymphocyte ratio; PPV: Positive predictive value; NPV: Negative predictive value; OR: Odds ratio; pLLR: Positive likelihood ratio; nLLR: Negative likelihood ratio; AUC: Area under the curve.

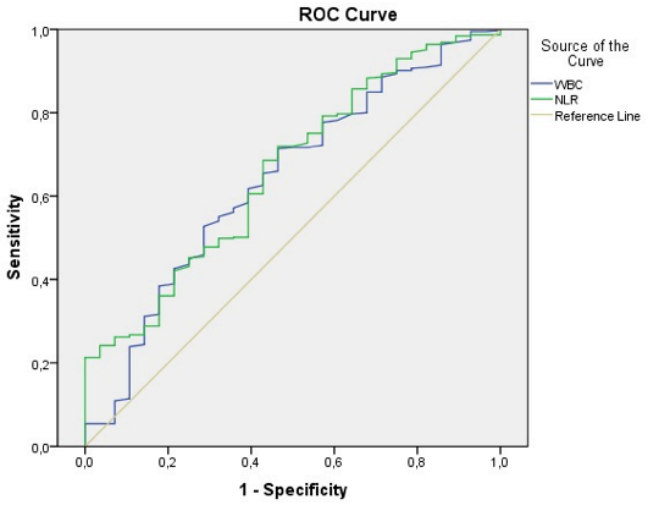

Figure 1. Receiver operating characteristic curve (ROC) for for negative and positive appendectomies (WBC: white blood cell; NLR: Neutrophil-to lymphocyte ratio).

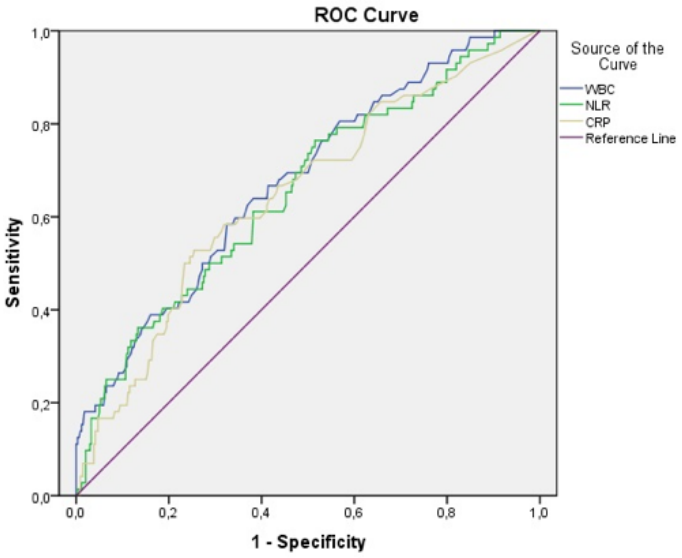

Figure 2. Receiver operating characteristic curve (ROC) ROC curve for complicated and non-complicated appendectomies. (WBC:white blood cell; NLR: Neutrophil-to lymphocyte ratio; CRP: Creactive protein).

Discussion

AA is one of the most common causes of emergency surgery. About 7.0% of the general population suffers from appendicitis during their lifetime. The diagnosis of AA is still a problem even in this modern period. The combination of history, physical examination, laboratory tests, and imaging studies are used for an accurate diagnosis. Several diagnostic tests are used for appendicitis including leucocyte count, neutrophil percentage, CRP, d-dimer, and procalcitonin [5-8]. Thus the potential of simple laboratory parameters to support in diagnosis of AA and prediction of perforations has attracted interest of surgeons. In the present study, simple, well-studied parameters were given particular consideration, and comprehensive and reliable data from a very large case series was provided.

Leucocyte count is the most frequently used laboratory test in diagnosing appendicitis. It is found easily in every medical center. According to the present results, WCC is a significant parameter for the diagnosis of AA. However, it is not a perfect indicator, due to relatively low sensitivity and specificity. With a cut-off value of 11950/mm3, 71.7% sensitivity and 50% specificity were found. In several clinical reports, the range of sensitivity and specificity of WCC in the diagnosis of AA have been reported to be 67%-97.8% and 31.9%-80%, respectively [9,10]. In this study, both sensitivity and specificity of leucocyte count was found low for the diagnosis of AA, being 71.7% and 50%, respectively. The very low ratio of specificity may be explained by small sample size of the negative appendectomy group.

NLR is a simple, cheap and effective biomarker that has been studied properly in the literature in order to predict morbidity, mortality and survival rates of multiple diseases, including inflammatory conditions, neoplastic diseases like gastric cancer, thyroid cancer, breast cancer, and solid tumors. NLR, as a single parameter, showed important promise in the diagnosis of AA with an admissible sensitivity and specificity [11-15]. The significance of neutrophil/lymphocyte ratio in emergency, evaluation of scoring systems is not always easy. A study by Yavuz et al. revealed that NLR with a cut-off value of 3.93 has 92.5% sensitivity and 59.3% specificity [16]. Another study by Shimizu et al. suggest a NLR cut-off value of 5.0 for the diagnosis of acute appendicitis, with 44% sensitivity and 22% specificity [17]. Another study by Kahramanca et al. suggested that the preoperative neutrophil-to-lymphocyte ratio could be a useful parameter to discriminate complicated appendicitis under a cut-off value of 5.72, with a sensitivity of 70.8% and specificity of 48.5% [18]. Another study by Ishizuka et al. showed that a NLR over 8 had a significant association with gangrenous appendicitis respectively [19]. According to the

present results, NLR cut-off values were 3.7 (75.1% sensitivity, 42.8% specificity) and 6.94 (61.1% sensitivity, 61% specificity) to discriminate AA from normal appendix and complicated appendicitis from non-complicated appendicitis, respectively (Tables 2 and 4). There are very few studies on this subject, but all reported that NLR appears to have greater diagnostic accuracy than traditional diagnostic laboratory tests (either WCC or CRP alone). It is also reported that NLR on admission to the hospital is an independent predictor of positive appendicitis histology [20]. Since the NLR may increase in many cases of intraabdominal inflammation, the specificity may be very low. In spite of conflicting suggestions regarding cut-off values, the authors believe that NLR is a significant parameter for diagnosing AA and differentiating complicated cases. Another interesting finding is that the female to male ratio is significantly higher in the negative appendectomy group. This may be attributed to gynecological diseases mimicking AA

The accurate diagnosis of AA and its severity can be elusive. Negative appendectomy rates of >20% have been reported in the past, but in recent years, this has reduced significantly [21-22]. The use of biomarkers like NLR could further reduce this, while helping to delinate those requiring urgent surgery due to complicated/severe appendicitis.

RDW is thought to be a marker for many pathological conditions (rheumatoid arthritis, inflammatory bowel disease, colon cancer, celiac disease, etc.) [23-26]. Some reports have argued that RDW as a marker like other inflammatory markers such as CRP and WBC [27,28]. Ertekin et al. found RDW values were found to be higher in the AA group than in the control group and therefore RDW is a marker of inflammation and might have predictive value [29]. In our study there was no significant relationship between RDW and AA.

CRP is a sensitive acute-phase protein of which the level increases according to the duration and severity of inflammation [28]. Hallan and Asberg stated that WCC, CRP, and neutrophil levels increase the accuracy of the diagnosis of AA [30]. They also reported a sensitivity of 40%-99% and a specificity of 27%-90%. Asfar et al. claimed that normal CRP levels most probably indicated a non-inflamed normal appendix [28]. In the present study there was no significant difference in CRP levels between negative and positive appendectomy groups ($p=0.73$) but CRP levels significantly higher in complicated appendicitis ($p<0.001$).

Complicated appendicitis is associated with perforation, gangrene and intraabdominal abscess formation. The main event to occur in complicated appendicitis is the perforation of the appendix. In a study performed by Barreto et al. found that male and old patients over the age of 60 are at significantly increased risk of developing perforated appendicitis , neutrophil count and CRP levels were also detected as an important marker associated with perforation [31]. In our study complicated appendicitis rate was significantly higher in male patients. WCC, NLR and CRP were found another parameter associated with complicated appendicitis.

There are many scoring systems used in the diagnosis of AA based on signs and symptoms. These scoring systems utilize routine clinical and laboratory assessments and are simple to use in a variety of clinical settings [9,10,20]. Scoring systems represent an inexpensive, non-invasive and easy to use diagnostic aid. The use of NLR with parameters used in these score systems could increase sensitivity of these score systems. Prospective study is needed in this regard.

This study has several limitations. First, this retrospective study was carried out without estimating adequate sample size, so for it to have adequate power. The cohort was relatively small and its results should be regarded with caution. Second, symptom onset to blood test time interval was not considered in this study. Last, laboratory findings such as symptoms and physical examinations were not investigated in this study. Especially as the duration of inflammation increases, it is expected to progress to complication. For this reason, prospective studies are needed to examine the effect of the onset of symptoms on laboratory parameters.

Conclusion

In conclusion, it was demonstrated that no simple yet perfect test currently exists for diagnosing AA and its complications. However, increases in WCC and NLR can be considered moderately reliable indicators for the diagnosis of acute appendicitis. WCC ,CRP and NLR are useful indicators for the recognition of complicated appendicitis.

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

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