RECEIVER OPERATING CHARACTERISTIC ANALYSIS AND DISCRIMINATIVE EFFECT OF NEUTROPHIL-TO-LYMPHOCYTE RATIO IN PATIENTS WITH SUSPECTED APPENDICITIS

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ABSTRACT

Introduction*: Acute appendicitis (AA) is one of the most common causes of abdominal pain and emergent abdominal surgery. The incidence is approximately 10% during the lifetime. Although appendectomy is a most common surgical procedure worldwide, it's complication rate is 5-28% A delay in diagnosis of AA is associated with prolonged hospitalization, an increased rate of perforation (34%-75%), wound infection (0%-11%), pelvic abscess (1%-5%) and late intra-abdominal adhesions. Appendectomy is first described by McBurney in 1894 and still remains the standart procedure for AA. Although patients with AA often present with a characteristic symptom complex and physical findings, atypical presentations are common. The aim of this study was to assess the diagnostic value of neutrophil-to-lymphocyte ratio (NLR) in patients who were operated for suspected acute appendicitis and to assess the discriminative effect of this ratio between uninflamed, uncomplicated and complicated appendicitis.*

Materials and methods*: The medical records of 3212 patients who underwent appendectomy for suspected acute appendicitis during a 10-year period were reviewed retrospectively. Patients were divided into 3 groups; group 1, 208 consecutive patients who had uninflamed appendix at appendectomy; group 2, 2111 consecutive patients who had uncomplicated acute appendicitis at appendectomy; group 3, 893 patients who had complicated appendicitis (perforated appendix or peri-appendicular abscess) at appendectomy. Data for three groups of patients were analyzed to calculate the sensitivity and specificity of the NLR in the diagnosis of acute appendicitis. Receivers operating characteristic (ROC) curves were used to evaluate this ratio in a relation with true diagnosis and severity of acute appendicitis.*

Results*: 1792 (55.8%) of the patients were male and 1420 (44.2%) of them were female. The mean age of the groups were 30.28±14.18, 29.98 ± 12.63 and 33.81±16.27 respectively. The discriminative effect of NLR was higher between uninflamed and complicated appendicitis groups with a cut-off value of 3,94. The recommended cut-off value of the preoperative NLR was decided using ROC curve analyses. The recommended cut-off value of the NLR was based on the most prominent point on the ROC curve for sensitivity (82.2%) and specificity (56.5%). The area under the ROC curve was 0.74.*

Conclusion*: AA is one of the most common surgical emergencies and the most common source of infection in community-acquired intra-abdominal infections. However the diagnosis is often challenging and the decision to operate, observe or further work-up on a patient is often unclear. Initial management of patients with suspected AA is based on the history of the patient, physical examination, basic laboratory tests reflecting the inflammatory response and radiologic imaging. NLR is a helpful biochemical parameter for the diagnosis of acute appendicitis but it has limited value on differentiating patients with complicated appendicitis from patients with uninflamed and uncomplicated appendicitis.*

Key words*: Appendicitis, Receiver operating characteristic curve, neutrophil to lymphocyte ratio.*

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Introduction

Acute appendicitis (AA) is one of the most common causes of abdominal pain and emergent abdominal surgery. The incidence is approximately 10% during the lifetime. Although appendectomy is a most common surgical procedure worldwide, it's complication rate is 5-28%[(1)]. Appendectomy is first described by McBurney in 1894 and still remains the standart procedure for AA[(2)].

Incidence rates have differences between ethnical groups with a low incidence rate in black and Asian populations and high incidence rate in Hispanic population[3]. Although patients with AA often present with a characteristic symptom complex and physical findings, atypical presentations are common. The diagnosis depens on symptom onset, type of pain, and physical examination[4].

A delay in diagnosis of AA is associated with prolonged hospitalization, an increased rate of perforation (34%-75%)[5-7], wound infection (0%-11%)[8-10], pelvic abscess (1%-5%)[8-10] and late intra-abdominal adhesions. Although there are a number of useful diagnostic modalities for AA, including evaluation of clinical symptoms, scoring systems[11-13], and imaging methods[14-16], the diagnosis of AA still remains a challenging problem. Appendectomy is the gold standart for AA[4].

AA is classified as catarrhal, phlegmonous or gangrenous in Japan and because of reflecting the severity of AA based on inflammation, it may be better correlated with data for inflammatory markers such as white blood cell (WBC) count[17,18], neutrophil count[19], and platelet count (20) along with the NLR[21-22]. There are a lot of study that assessed the diagnostic accuracy of different inflammatory markers in AA with heterogeneous designs and results, including total WBC, granulocytes, C-Reactive protein, leukocyte elastase activity, D-lactate, phospholipase A2 and interleukine-6[23-25].

The aim of this study was to assess the diagnostic value of NLR in patients who underwent appendectomy due to suspicion of AA. Using ROC curves, sensitivity and specificity were calculated by correlating the preoperative NLR with histological diagnosis. In addition, this study will attempt to determine cut-off point for NLR with best sensitivity and specificity for determination of AA.

Materials and methods

We retrospectively reviewed a total of 3212 patients between 2002 and 2013 who underwent appendectomy with a clinical diagnosis of AA at the emergency department of two training centers. The clinical diagnosis was established preoperatively by clinical history, physical examination, laboratory tests including WBC count, neutrophil percentage and NLR. Laboratory tests were performed on blood samples obtained on admission to the hospital. In those patients who had repetitive tests before surgery, the final test data was used for statistical analysis. The WBC count and differential neutrophil count were measured by an automated hematology analyzer (Coulter Hmx; Beckman Coulter [UK] Ltd, Buckinghamshire, England). All the excised appendices were sent for histopathologic examination, and the final diagnosis of AA was based on histologic examination of the appendix. Demographic, surgical and histopathologic variables were recorded retrospectively. All patients with a diagnose of suspected AA who were admitted to the emergency department and underwent appendectomy in 24 hours were included into the study. The exclusion criteria is rule out the diagnosis of AA with anamnesis, physical examination, laboratory, and radiological imaging modalities. Patients were divided into 3 groups; group 1, 208 consecutive patients who had uninflamed appendix at appendectomy; group 2, 2111 consecutive patients who had uncomplicated AA at appendectomy; group 3, 893 patients who had complicated AA (perforated appendix or periappendicular abscess) at appendectomy.

Statistical analysis

Statistical analysis was carried out using Statistical Package for the Social Sciences (SPSS) 15.0 for Windows (SPSS inc, Chicago,I15) and Medcalc version 14.12.0. One-way Anova tested variance homogenity. Tukey HSD test was used for comparison of groups between homogeneously distributed parameters while Tamhane test was used for comparison of groups between non-homogeneously distributed parameters. The data were expressed as mean + SD. The clinical performance of NLR and sensitivity, specificity and cut-off levels were measured by using ROC curve analysis. A p value of $< .05$ was considered to be statistically significant.

Discrimination refers to a model's ability to distinguish survivors from nonsurvivors. Model discrimination was measured by the area under the ROC curve (AUC) to evaluate how well the model distinguished patients who experienced the event (ie, death) from those who did not[10]. The AUC represents the probability that a patient who died had a higher predicted probability of dying than a patient who survived. An AUC of 0.5 indicates that the model does not predict better than chance. The discrimination of a prognostic model is considered perfect if AUC = 1, good if AUC >0.8, moderate if AUC is 0.6 to 0.8, and poor if AUC < 0.6[10,26].

Results

Demographic characteristics of patients for all 3 groups are given in Table 1.

		Normal Appendix	Uncomplicated Appendicitis	Complicated Appendicitis
Age (Years)		30,28±14,18	29,98 ± 12,63	33,81±16,27
Gender	M	82	1180	530
	F	126	931	363

Table 1: Demographic characteristics of patients (n=3212).
M: Male; F: Female

1792 (55.8%) of the patients were male and 1420 (44.2%) of them were female. The mean age of the groups were 30.28±14.18, 29.98 ± 12.63 and 33.81±16.27 respectively. The WBC, lymphocyte, neutrophil counts and NLR of the patients in Group 1, Group 2 and Group 3 was found to be statistically significant in comparison of Group 1 and 2, Group 1 and 3, Group 2 and 3 (p<0,001) (Table 2).

	Normal Appendix	Uncomplicated Appendicitis	Complicated Appendicitis	p
WBC	11,56±4,25	13,67±4,33	14,89±4,37	**<0.001**
NEU	70,28±12,63	75,40±11,78	78,95±10,46	**<0.001**
LYM	20,52±10,62	16,00±9,22	12,32±7,26	**<0.001**
NEU/LYM	5,33±5,16	7,23±5,93	9,34±6,86	**<0.001**

Table 2: Hematologic findings of patients (n=3212).
WBC: White Blood Cell Count; NEU: Neutrophil Count; LYM: Lymphocyte Count; NEU/LYM: Neutrophil- Lymphocyte Ratio

ROC curve analysis was performed to evaluate the diagnostic discriminative effect of NLR and to evaluate the diagnostic test performance of NLR between Group 1, 2 and 3. Sensitivity, specificity and cut-off values were calculated. Comparison of the ROC curve analysis between groups are given in Table 3 and ROC curves are given in Figure 1, 2 and 3. A p value <0,001 and an AUC % > 0,5 represents the discriminative effect of NLR between the two compared group. This discriminative effect is higher between Group 1 and Group 3 with a cut-off value of 3,94. The recommended cut-off value of the preoperative NLR was decided by using ROC curve analyses. The recommended cut-off value of the NLR was based on the most prominent point on the ROC curve for sensitivity (82.2%) and specificity (56.5%). The area under the ROC curve was 0.74.

	Lym/Neu		
	Group 1-2	Group 1-3	Group 2-3
(AUC)(%)(Area Under Curve)	0,63	0,74	0,62
p	**<0,0001**	**<0,0001**	**<0,0001**
Standard Deviation	0,02	0,02	0,01
95% CI (Confidence Interval)	0,61-0,65	0,71-0,77	0,60-0,64
Cut-off value	3,45	3,94	6,31
Sensitivity (%)	72,76	82,29	61,55
Specificity (%)	51,69	56,52	56,94

Table 3: Comparison of the results of Receivers operating characteristic (ROC) curve analysis between groups.
** Group 1: Normal Appendix; * Group 2: Uncomplicated Appendicitis; * Group 3: Complicated Appendicitis; NEU/LYM: Neutrophil- Lymphocyte Ratio; AUC: Area Under the Curve*

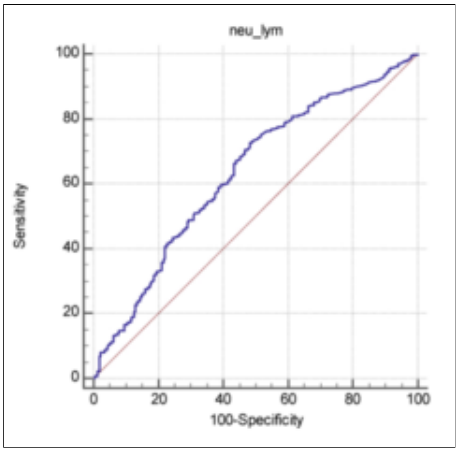

Figure 1: Receiver operating characteristic curve for the neutrophil-to-lymphocyte ratio between uninflamed (Group 1) and uncomplicated (Group 2) appendicitis patients (AUC=0.63, p< .001).

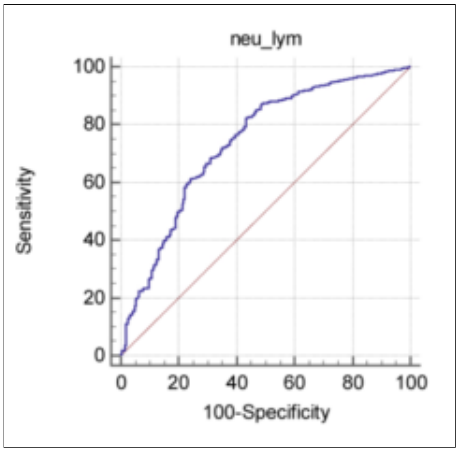

Figure 2: Receiver operating characteristic curve of neutrophil-to-lymphocyte ratio between uninflamed (Group 1) and complicated (Group 3) appendicitis patients. (AUC=0.74, p< .001).

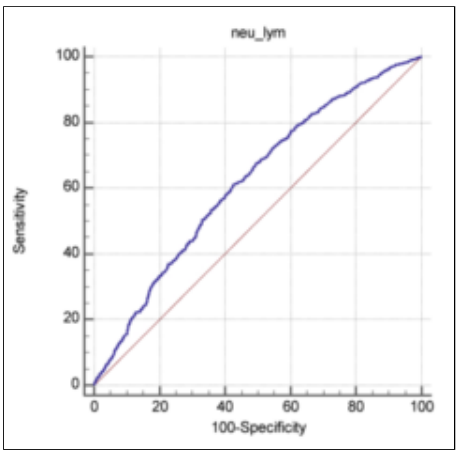

Figure 3: Receiver operating characteristic curve of neutrophil-to-lymphocyte ratio between uncomplicated (Group 2) and complicated (Group 3) appendicitis patients. (AUC=0.62, p< .001)

Discussion

AA is one of the most common surgical emergencies and the most common source of infection in community-acquired intra-abdominal infections[27-29]. However the diagnosis is often challenging and the decision to operate, observe or further work-up on a patient is often unclear. Initial management of patients with suspected AA is based on the history of the patient, physical examination, basic laboratory tests reflecting the inflammatory response and radiologic imaging. Other than radiological diagnostic techniques, two hematological variables are used on a widespread basis in the differential diagnosis of abdominal pain: total leucocyte count and neutrophil count[30,31]. Both of these variables are mainly affected by inflammation; nonspecific increases in leucocytes and neutrophils are observed in AA. The tests are easy and quick to perform but they do not reveal significant results regarding the existence and severity of AA[32].

The leukocyte count is probably the most often used test to diagnose AA. An elevated leukocyte count is suggested to be the earliest laboratory test to indicate appendicular inflammation and most of the patients with AA present with leukocytosis[33-35]. The increases of complete blood count (CBC) components are very rapid in comparison to the dynamics of acute phase proteins, such as the increase in the serum level of CRP and the decrease in the serum level of albumin. This is because protein synthesis in the liver requires a longer time than proliferation of CBC components in the bone marrow. Therefore, it seems rational that gangrenous AA would have a closer association with acute phase proteins than with CBC components, except for the neutrophil count, because of the longer period until surgery than that for other grades of AA. At the beginning of the acute phase of inflammation, when lymphocyte count is normal, the increase at the number of neutrophils may elevate the NLR. Even in cases with both neutrophilia and lymphocytosis, NLR may still be elevated since neutrophilia is noticeably more marked at the beginning of inflammation. The discriminative effect and prognostic value of NLR was investigated in different patient groups such as abdominal surgery, cardiovascular surgery and intensive care unit patients.

Goodman et al. have searched for a diagnostic criterion using the NLR; they compared the relationship of neutrophil and lymphocyte counts and stated that a NLR higher than 3.5 was a sensitive indicator for the diagnosis of AA in adults[21]. They also suggested that marked lymphopenia may be the other major factor changing this ratio in the existence of gangrenous AA, which was reported in another study[36]. Zahorec suggested the use of the NLR as a rapid and simple parameter for systemic inflammation and stress in critically ill patients, when he observed a correlation between the severity of their clinical course and the grade of neutrophilia and lymphopenia in his preliminary study[37]. In a systematic review Tan et al. concluded that elevated NLR were associated with increased long-term mortality and morbidity after major cardiac and vascular surgery[38].

Acarturk et al. investigated the utility of NLR as a simple and available predictor for clinical disease activity in inflammatory bowel disease (IBD) and they demonstrated that NLR in subjects with IBD is strongly associated with active disease and correlated with clinical and laboratory indices[39]. In a meta-analysis including eleven studies containing 1804 patients, Yang et al. concluded that high peripheral blood NLR suggested poor prognosis for patients with pancreatic cancer[40]. Yildirim et al. used NLR as a diagnostic tool to predict a tubo-ovarian abscess (TOA) preoperatively and they conclude that preoperative NLR improve the predictive value of serum markers for the presence of TOA[41].

Contrary to descriptive and comparing statistical methods, analysis of ROC curves allows the estimation and verification of diagnostic suitability of diagnostic para- meters. The ROC curves provide an alternative to sensitivity and specificity that

allows the examination of a test's ability to discriminate between two populations regardless the cut-off level selected[42]. Therefore, we included this analysis to assess the overall diagnostic value of selected parameters in clinical practice.

The results of the present study suggested that NLR leads to precise the prediction of AA. Although all the statistical results of the comparison of three groups were significant, it has limited effects on discriminating the patients with uninflamed appendix and complicated AA according to the AUC, sensitivity and specificity values.

The main limitation of this study is that it is retrospective so there is biases in inclusion criteria of the patients which included all patients who underwent appendectomy, another prospective study containing all patients with abdominal pain with suspicion of AA must be made.

In conclusion, we think that although NLR is a nonspecific inflammatory marker in most of patient groups with inflammatory diseases, it is helpful in diagnosing and exclusion of AA but it has limited effects on discriminate complicated AA from uncomplicated AA and uninflamed appendix.

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