ORIGINAL ARTICLE

Diagnostic value of basic laboratory parameters for simple and perforated acute appendicitis: an analysis of 3392 cases

Mert Mahsuni Sevinç, M.D., Erdem Kınacı, M.D., Ekrem Çakar, M.D., Savaş Bayrak, M.D., Abdulkerim Özakay, M.D., Acar Aren, M.D., Serkan Sarı, M.D.

Department of General Surgery, İstanbul Training and Research Hospital, İstanbul-*Turkey*

ABSTRACT

BACKGROUND: The aim of the present study was to examine the efficacy of simple laboratory parameters including neutrophil-to-lymphocyte ratio (NLR), platelet count (PLT), mean platelet volume (MPV), and serum bilirubin level in the diagnosis of acute appendicitis and recognition of perforated appendicitis.

METHODS: Records of 3392 patients who underwent appendectomy in a 10-year period were reviewed retrospectively. Patients were divided into 2 groups according to histopathological examination results: Group 1 had normal appendix, Group 2 had acute appendicitis. Patients with acute appendicitis were divided into subgroups: Group 2A had simple acute appendicitis, while Group 2B had perforated appendicitis. Efficacy of the aforementioned laboratory parameters was evaluated in the diagnosis of acute appendicitis and recognition of perforated appendicitis. Independent variables were determined by univariate analysis and multivariate analysis was performed. Receiver operating characteristic (ROC) curve analysis was used to identify significant parameters in multivariate analysis. Cut-off values, sensitivity, specificity, and accuracy calculations performed for parameters with area under curve (AUC) >0.600 were accepted as "significant parameters."

RESULTS: White cell count (WCC), bilirubin, and NLR were significant parameters for the diagnosis of acute appendicitis. Cut-off values were 11900/mm^3 for WCC (sensitivity: 71.2%; specificity: 67.2%; OR: 5.13), 1.0 mg/dl for bilirubin (sensitivity: 19.1%; specificity: 92.4%; OR: 2.96), and 3.0 for NLR (sensitivity: 81.2%; specificity: 53.1%; OR: 4.27). Serum bilirubin and NLR were independent variables for the diagnosis of perforated appendicitis. Cut-off values were 1.0 mg/dl for bilirubin (sensitivity: 78.4%; specificity: 41.7%; OR: 2.6) and 4.8 for NLR (sensitivity: 81.2%; specificity: 53.1%; OR: 2.6).

CONCLUSION: Presence of at least 1 of the following findings in a patient suspected of having acute appendicitis was significantly associated with a definite diagnosis: WCC >11.900 mm^3, serum bilirubin >1.0 mg/dl, NLR >3.0. In patients with acute appendicitis, serum bilirubin >1.0 mg/dl or NLR >4.8 were significantly associated with the presence of perforation. While WCC is a significant parameter for diagnosis of acute appendicitis, no significant association with perforated appendicitis was found. PLT and MPV were not useful parameters when diagnosing acute appendicitis.

Keywords: Appendicitis; bilirubin; mean platelet volume; neutrophil-to-lymphocyte ratio; platelet count.

INTRODUCTION

In addition to so-called "leukocytosis," many laboratory parameters have been used to diagnose or determine severity of infectious or inflammatory diseases such as acute appendicitis. As diversity of such parameters increases, attendant problems arise, including availability, accuracy, intelligibility, time-effectiveness, and cost-effectiveness. When the relatively high incidence of acute appendicitis is considered, these problems take on great importance. Radiological modalities, particularly ultrasonography and computed tomography, have been widely and successfully used in the diagnosis of acute appendicitis and its complications.[1,2] However, because these modalities require special equipment and experienced radiologists, surgeons seek simpler means of definitive diagnosis. In the last decade, simple parameters included in a standard complete blood count and routine preoperative tests, including neutrophil count, neutrophil ratio,[3] neutrophil-to-lymphocyte ratio (NLR),[4–7] platelet count (PLT),[8,9] mean platelet volume (MPV),[8–13] and serum bilirubin level,[14–20] have been studied for potential value in diagnosis of acute appendicitis

Address for correspondence: Mert Mahsuni Sevinç, M.D.
İstanbul Eğitim ve Araştırma Hastanesi, Genel Cerrahi Kliniği,
34098 Fatih, İstanbul, Turkey
Tel: +90 212 - 459 60 00 E-mail: mertsevinc34@gmail.com

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and prediction of possible complications. However, reported results widely vary, and the number of patients studied has been relatively small. The aim of the present study was to evaluate the predictive value of simple laboratory parameters including white cell count (WCC), NLR, PLT, MPV, and serum bilirubin level in the diagnosis of acute appendicitis and its complications in a very large case series.

MATERIALS AND METHODS

Records of patients who underwent open or laparoscopic appendectomy between March 2005 and December 2014 were reviewed retrospectively. Demography, recorded anamneses, histopathological diagnoses, and preoperative laboratory findings including WCC, neutrophil count, lymphocyte count, PLT, MPV, and serum bilirubin level were reviewed, and NLR was calculated.

Patients were divided into 2 groups according to histopathological evaluation. Group 1 included patients with normal appendix, and Group 2 included patients with acute appendicitis. Group 2 patients were divided into subgroups: Group 2A included patients with simple acute appendicitis according to histopathological examination, Group 2B included patients with perforated appendicitis. Basic demographic data (age, gender) and preoperative laboratory findings were compared between Groups 1 and 2, and between Groups 2A and 2B, providing reliable results regarding the diagnosis of acute appendicitis and the prediction of perforation, respectively.

Exclusion criteria were age younger than 15 years, presence of malignant diseases, current course of chemotherapy or radiotherapy, pregnancy, intraoperative diagnosis of intraabdominal pathology other than appendicitis, and presence of known liver diseases. Clinically insignificant causes of hyperbilirubinemia, including hereditary enzyme deficiency syndromes such as Gilbert's syndrome, could not be determined due to the retrospective nature of the study.

Statistical Analysis

SPSS software (version 20.0; SPSS Inc., Chicago, IL, USA) was used for statistical analysis. In univariate analysis, normally distributed continuous variables were expressed as mean±SD 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 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

A total of 3392 patients who underwent appendectomy between March 2005 and December 2014 were included. Median age was 32 (range: 16–95) years, and the majority of patients were male (59.2% male, 40.8% female).

Negative laparotomy was more common in females. WCC, MPV, serum bilirubin, and NLR values were significantly different between Groups 1 and 2 in univariate analyses. These parameters were independent variables for the diagnosis of

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	531	2861							
Age (years)†	33 (16–95)	32 (16-91)	0.000						
Gender (n)			0.000						
Male (%)	205 (39%)	1803 (63%)							
Female (%)	326 (61%)	1058 (37%)							
WCC (x10³/mm³)‡	10.8±3.8	14.3±4.2	0.000	1.23	1.20–1.27	0.000	0.748	0.725–0.771	0.000
PLT (x10³/mm³)‡	251±70	254±72	0.296						
MPV (fL)‡	8.5±1.2	8.3±1.1	0.001	0.89	0.82–0.97	0.011	0.543	0.517–0.570	0.002
Bilirubin (mg/dl)†	0.6 (0.1–2.1)	0.6 (0.1–9.0)	0.000	4.27	2.78–6.57	0.000	0.621	0.596–0.646	0.000
NLR†	3.0 (0.1–72.0)	5.7 (0.2–150)	0.000	1.03	1.00–1.06	0.007	0.692	0.667–0.717	0.000

†Median (range); ‡Mean (±standard deviation). OR: Odds ratio; AUC: Area under the curve; WCC: White cell count; PLT: Platelet count; MPV: Mean platelet volume; NLR: Neutrophil-to-lymphocyte ratio.

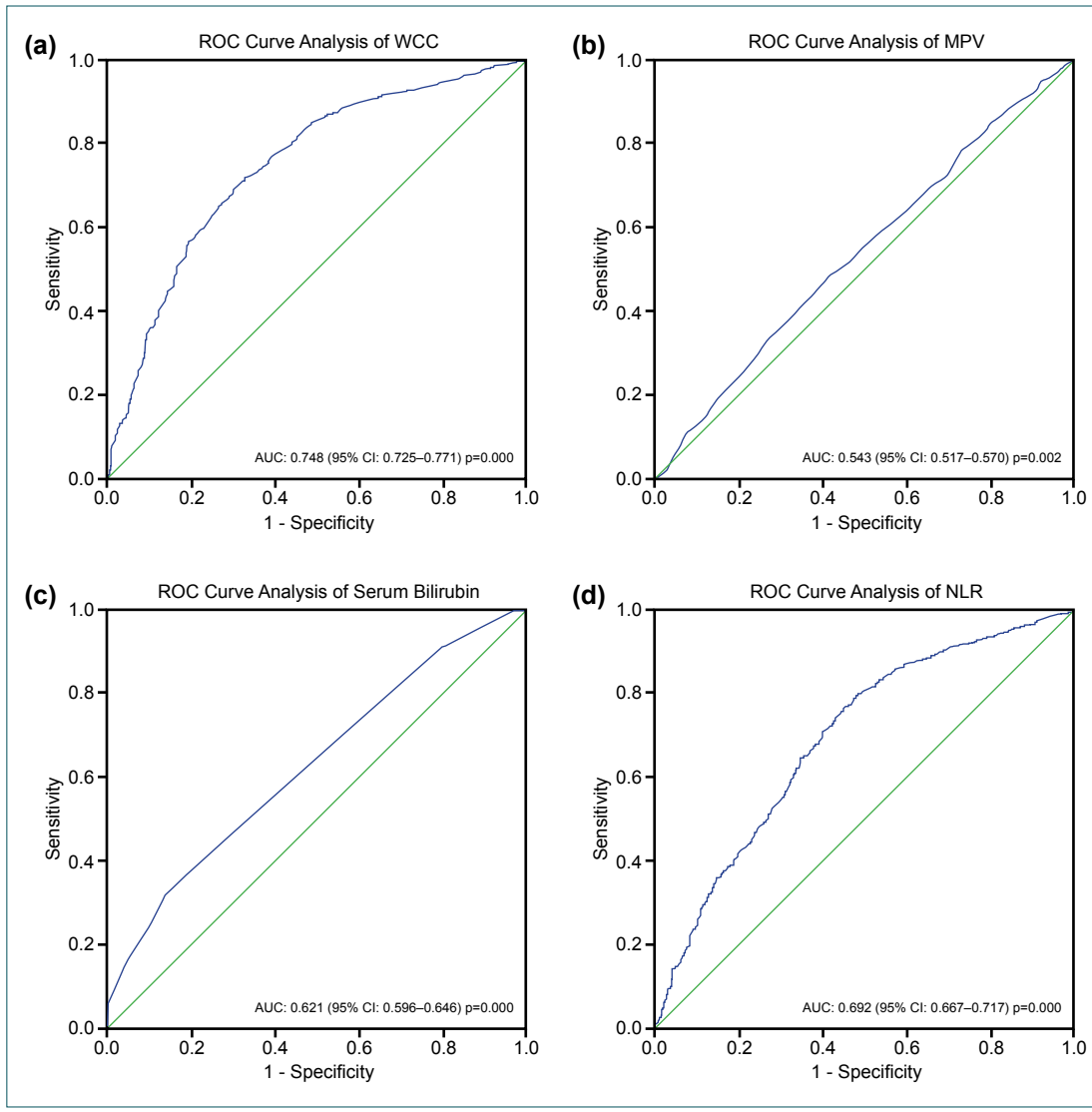

Figure 1. Receiver operating characteristic (ROC) curve analyses of significant parameters for the diagnosis of acute appendicitis: **(a)** white cell count (WCC), **(b)** mean platelet volume (MPV), **(c)** serum bilirubin, **(d)** neutrophil-to-lymphocyte ratio (NLR).

acute appendicitis 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, bilirubin, and NLR (Figure 1). Proposed cut-off values and performance characteristics for these variables are shown in Table 2.

Each parameter considered (WCC, PLT, MPV, bilirubin, and NLR) were significantly different between patients with simple (Group 2A) and perforated (Group 2B) appendicitis. Each parameter was an independent variable for recognition of perforated appendicitis in multivariate logistic regression analysis. Comparison of Groups 2A and 2B is detailed in Ta-

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 (/mm³)	11,900	71.2	67.2	0.92	0.30	5.13	2.15	0.43	0.748
Bilirubin (mg/dl)	1.0	19.1	92.4	0.93	0.17	2.96	2.5	0.87	0.621
NLR	3.0	81.2	53.1	0.89	0.36	4.87	1.72	0.35	0.692

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	2675	186							
Age (years)‡	33.9±12.2	38.7±15.8	0.000						
Gender (n)			0.388						
Male (%)	1680 (63%)	123 (66%)							
Female (%)	995 (37%)	63 (34%)							
WCC (x10³/mm³)‡	14.2±4.1	15.8±4.9	0.000	1.06	1.02–1.10	0.001	0.596	0.554–0.638	0.000
PLT (x10³/mm³)‡	253±70	278±98	0.001	1.00	1.00–1.01	0.000	0.570	0.525–0.615	0.001
MPV (fL)‡	8.3±1.1	8.0±1.1	0.001	0.83	0.72–0.95	0.008	0.588	0.546–0.630	0.000
Bilirubin (mg/dl)†	0.6 (0.1–9.0)	0.7 (0.2–3.4)	0.000	1.43	1.16–1.76	0.001	0.602	0.563–0.639	0.000
NLR†	5.5 (0.2–150)	7.8 (0.4–58.6)	0.000	1.02	1.00–1.04	0.018	0.624	0.584–0.665	0.000

†Median (range); ‡Mean (±standard deviation). OR: Odds ratio; AUC: Area under the curve; WCC: White cell count; PLT: Platelet count; MPV: Mean platelet volume; NLR: Neutrophil-to-lymphocyte ratio.

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

	Cut-off value	Sensitivity (%)	Specificity (%)	PPV	NPV	OR	pLLR	nLLR	AUC
Bilirubin (mg/dl)	1.0	34.4	81.4	0.11	0.94	2.6	1.84	0.80	0.594
NLR	4.8	78.4	41.7	0.08	0.96	2.6	1.34	0.51	0.624

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.

ble 3. In ROC curve analyses of these independent variables, AUC above 0.600 was found only in bilirubin and NLR (Figure 2). Proposed cut-off values and performance characteristics for these 2 variables are shown in Table 4.

DISCUSSION

Acute appendicitis is one of the most common causes of emergency surgery. Diagnosis is based on physical examination and presence of specific anamnesis. With technological advances in radiological modalities, successful diagnosis is more easily achieved.[1,2] However, availability, intelligibility, time-effectiveness, and cost-effectiveness of these modalities remain disadvantageous, particularly to relatively small hospitals. Thus the potential of simple laboratory parameters to aid in diagnosis of acute appendicitis 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.

Moderate leukocytosis is an expected laboratory finding in cases of acute appendicitis.[15] According to the present results, WCC is a significant parameter for the diagnosis of acute appendicitis. However, it is not a perfect indicator, due to relatively low sensitivity and specificity. With a cut-off value of 11900/mm³, 71% sensitivity and 68% specificity were found. In a recent study, Rafiq et al.[21] reported very high sensitivity and specificity (87% and 92%, respectively) with the same cut-off value. Nevertheless, in previous studies, sensitivity and specificity of WCC have been reported between 67%–87% and 43%–81%, respectively.[3,22] While accuracy of the test remains controversial, the significant positive correlation between WCC and diagnosis of acute appendicitis can be agreed upon. As the present study included a very large number of participants, the authors believe the results are comprehensive. Regarding recognition of complicated cases, results were similar to the diagnosis of acute appendicitis. While a significant difference between patients with and without perforation was found in univariate analysis, WCC did not greatly aid in determining it (OR: 1.06; AUC: 0.596). However, Atema et al.[1] suggested WCC >13000/mm³ as a component of a scoring system for differential diagnosis of non-complicated and complicated appendicitis. Due to the lower AUC level, the present authors did not create a cut-off value for WCC in predicting perforation. While WCC alone may not efficiently predict incidence of perforation, it may prove valuable when used in conjunction with other parameters.

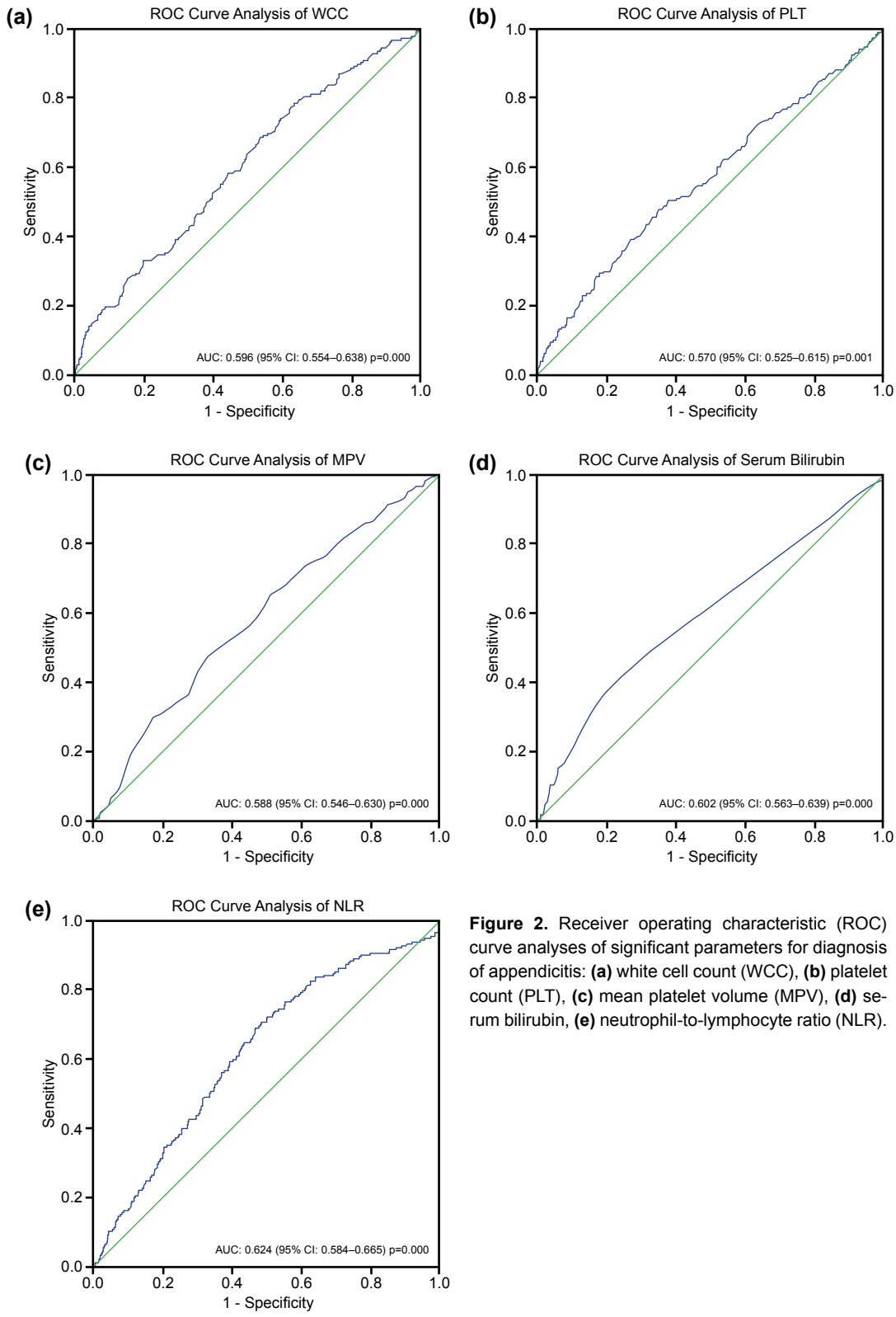

Figure 2. Receiver operating characteristic (ROC) curve analyses of significant parameters for diagnosis of appendicitis: **(a)** white cell count (WCC), **(b)** platelet count (PLT), **(c)** mean platelet volume (MPV), **(d)** serum bilirubin, **(e)** neutrophil-to-lymphocyte ratio (NLR).

Neutrophilia and lymphocytopenia are components of the cellular response in systemic inflammation.[23] Increase in the difference between neutrophil and lymphocyte counts reflects severity of inflammatory response. Hence, neutrophil-to-lymphocyte ratio has long been used as a marker for many pathologies, including malignancies, chronic inflammatory diseases, and postoperative complications.[23,24] Use of NLR for diagnosis of acute appendicitis is not a new idea.

The argument that NLR is a more sensitive parameter than the number of leukocytes was put forth 20 years earlier by Goodman et al.[25] Four studies have been published in the last 5 years regarding this issue.[4–7] Shimizu et al.[7] suggest a NLR cut-off value of 5.0 for the diagnosis of acute appendicitis, with 44% sensitivity and 22% specificity. Ishizuka et al.[5] determined a cut-off value of 8.0 for NLR to differentiate gangrenous appendicitis from catarrhal appendicitis, with 73% sensitivity and 39% specificity. Kahramanca et al.[6] reported 2 NLR cut-off values of 4.68 (65% sensitivity, 55% specificity) and 5.74 (71% sensitivity, 49% specificity) to distinguish acute appendicitis from normal appendix, and complicated appendicitis from non-complicated appendicitis, respectively. According to the present results, NLR cut-off values were 3.0 (81% sensitivity, 53% specificity) and 5.5 (78.4% sensitivity, 41.7% specificity) for the diagnosis of acute appendicitis and perforated appendicitis, respectively (Tables 2 and 4). In spite of conflicting suggestions regarding cut-off values, the authors believe that NLR is a significant parameter for diagnosing acute appendicitis and differentiating complicated cases.

According to the present results, PLT was not a useful indicator. However, it was significantly higher in patients with perforated appendicitis, compared to simple appendicitis. Platelet count is a well-known indicator of the severity of systemic infections.[26] However, data regarding the diagnostic value of PLT for acute appendicitis remains limited. Two recent studies that each included fewer than 260 patients similarly found that PLT had no diagnostic value for acute appendicitis.[8,9] According to the present results, neither was PLT a reliable indicator of perforation (OR: 1.0; AUC: 0.570).

Platelet size is at least as important as platelet number. According to present results, MPV was significantly lower in cases of appendicitis, compared to normal appendix. In addition, MPV was significantly lower in patients with complicated appendicitis. Conflicting results have been reported regarding the relationship between MPV and active inflammatory processes. Kim et al.[27] defined an increase in MPV from baseline as an independent risk factor for mortality in patients with sepsis, while decreases in MPV have been associated with activation of rheumatologic diseases, including rheumatoid arthritis, systemic lupus erythematosus, and ankylosing spondylitis.[28] Five of 6 studies to address the relationship between MPV and acute appendicitis reported results consistent with those of the present study.[8–12] However, in the sixth study, conflicting results were reported.[13] Reported MPV cut-off values in the 5 studies with similar results were between 7.3 and 7.95 fL.[8–12] However, in the present study, the AUC was 0.543. Thus, in spite of significant differences between groups, a reliable cut-off value for MPV was not suggested in the present study. In addition, differences in MPV values between groups were very small in each of these studies, including the present. Therefore, the authors believe that MPV is not a useful parameter for daily clinical practice. Likewise, Leader et al.[29] concluded in a review that MPV has limited value for clinical use, in spite of statistically significant differences.

It was confirmed in the present study that serum bilirubin level above 1 mg/dl has a highly specific significant relationship with diagnoses of acute appendicitis (92.4% specificity) and perforated appendicitis (81.4% specificity). However, the sensitivity of this test was quite low (19% for acute appendicitis, 34% for perforated appendicitis). In 3 previous studies, reported sensitivities and specificities of serum bilirubin level of 1.0 mg/dl for diagnosis of appendicitis were 27%–96%,[14] 30%–88%,[20] and 69%–56%,[15] respectively. For prediction of perforation, reported sensitivities were between 38% and 77%, and specificities were between 66% and 87%.[14–20] In the present results, ORs were 2.5 and 3.0 for simple and perforated appendicitis, respectively, while very high values (including some above 10) have been reported.[14] Correlation of hyperbilirubinemia and severe appendicitis has long been known.[30] However, the measure is not widely used in daily clinical practice, possibly due to the very low sensitivity of this test. Nevertheless, the present authors suggest that surgeons consider total serum bilirubin level when attempting to rule out diagnosis of acute appendicitis or predict perforation.

The primary limitation of the present study was its retrospective nature. Only patients who underwent appendectomy were included; data did not reflect patients suspected of having acute appendicitis who did not undergo surgery. However, the patient population was very large, and the authors believe that comprehensive data is provided regarding diagnostic accuracy of simple laboratory parameters in cases of suspected acute appendicitis. An additional limitation was lack of data regarding patients with suspicious abdominal findings who did not undergo surgery. However, the authors believe that in spite of these limitations, the present study provides comprehensive results and contributes valuable reference data.

In conclusion, it was demonstrated that no simple yet perfect test currently exists for diagnosing acute appendicitis and recognizing perforation. However, increases in WCC, serum bilirubin level, and NLR can be considered moderately reliable indicators for the diagnosis of acute appendicitis. Serum bilirubin level and NLR are useful indicators for the recognition of perforated appendicitis. Although MPV was an independent variable for diagnosis, differences between groups were minimal, rendering this test impossible to use in daily clinical practice. Neither is PLT a reliable indicator of acute appendicitis or perforation.

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Conflict of interest: None declared.

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ORİJİNAL ÇALIŞMA - *ÖZET*

Basit ve perfore apandisitlerde temel laboratuvar testlerinin tanısal değeri: 3392 olgu analizi

Dr. Mert Mahsuni Sevinç, Dr. Erdem Kınacı, Dr. Ekrem Çakar, Dr. Savaş Bayrak, Dr. Abdulkerim Özakay, Dr. Acar Aren, Dr. Serkan Sarı

İstanbul Eğitim ve Araştırma Hastanesi, Genel Cerrahi Kliniği, İstanbul

AMAÇ: Bu çalışmada ameliyat öncesi lökosit (WCC), nötrofil/lenfosit oranı (NLR), trombosit (PLT), ortalama-trombosit-hacmi (MPV) ve serum bilirubin düzeyleri gibi basit laboratuvar incelemelerinin akut apandisit tanısı koymakta veya perfore olguların basit apandisitlerden ayırmını yapmaktaki etkinliğini ortaya koymayı amaçladık.

GEREÇ VE YÖNTEM: Apendektomi ameliyatı uygulanmış 3392 hasta geriye dönük olarak değerlendirildi. Hastalar histopatolojik tanılarına göre öncelikle iki gruba ayrıldı. Normal appendiks bulguları olan olgular (Grup 1) ve akut apandisit olan olgular (Grup 2). Daha sonra ikinci gruptaki olgular basit akut apandisit olguları (Grup 2A) ve perfore apandisit olguları (Grup 2B) olarak alt gruplara ayrıldı. Gruplar arasında ameliyat öncesi WCC, NLR, PLT, MPV ve serum bilirubin düzeyleri karşılaştırıldı. Önce univariate analiz ile bağımsız değişkenler saptandı, daha sonra bunlardan çok değişkenli analizde p değeri 0.05'den küçük olanlara ROC eğrisi analizi uygulandı. Eğrinin altında kalan alan 0.600'den büyük olan parametreler anlamlı paremtetre olarak kabul edilerek eşik değer hesaplandı.

BULGULAR: WCC, bilirubin ve NLR, akut apandisit tanısında klinik kullanımda anlamlı parametreler olarak saptandı. Lökositoz için eşik değer 11.900/mm3 (sensitivite %71.2, spesifisite %67.2, OR: 5.13), bilirubin için 1.0 mg/dl (sensitivite %19.1, spesifisite %92.4, OR: 2.96) ve NLR için 3.0 (sensitivite %81.2, spesifisite %53.1, OR: 4.27) idi. Bilirubin ve NLR, perfore apandisit olgularının ayırımında anlamlı parametrelerdi. Bilirubin için eşik değer 1.0 mg/dl (sensitivite %78.4, spesifisite %41.7, OR: 2.6) ve NLR için 4.8 (sensitivite %81.2, spesifisite %53.1, OR: 2.6) idi.

TARTIŞMA: Akut apandisit şüphesi oluşturan bulgularla gelen bir olguda serum lökosit değerinin 11.900/mm^3'den, bilirubin değerinin 1.0 mg/dl'den, veya nötrofil/lenfosit oranının 3.0'den fazla olması akut apandisit tanısı destekler. Akut apandisit düşünülen bir olguda ise bilirubin değerinin 1.0 mg/dl'den veya nötrofil/lenfosit oranının 4.8'den büyük olması olguda perforasyon geliştiğini destekler verilerdir. WCC, akut apandisit tanısında anlamlı olmasına rağmen, perfore olguların tanınmasında güçlü bir parametre değildir. PLT ve MPV akut apandisit şüpheli olgularda tanısal anlam taşımamaktadırlar.

Anahtar sözcükler: Apandisit; bilirubin; nötrofil/lenfosit oranı; ortalama trombosit hacmi; trombosit sayısı.

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