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Original Article

Diagnostic value of presepsin in predicting a complicated acute appendicitis

Sinan Binboga[1], Nilgun Isiksacan[2], Pinar Kasapoglu Atar[2], Elif Binboga[3], Mehmet Karabulut[1], Halil Alis[4]

[1]Bakirkoy Dr. Sadi Konuk Education and Research Hospital, Clinic of General Surgery, Istanbul, Turkey
[2]Bakirkoy Dr. Sadi Konuk Education and Research Hospital, Clinic of Biochemistry, Istanbul, Turkey
[3]Bakirkoy Dr. Sadi Konuk Education and Research Hospital, Clinic of Anesthesiology and Reanimation, Istanbul, Turkey
[4]Istanbul Aydin University, VM Medical Park Florya Hospital, Department of General Surgery, Istanbul, Turkey

Abstract

Aim: There is a growing body of evidence suggesting that the concentration of presepsin in serum was found to be increased in patients with sepsis compared to healthy individuals, but the clinical significance of presepsin in the diagnosis of complicated acute appendicitis remains unclear. The purpose of this study was investigation of the diagnostic value of presepsin in complicated acute appendicitis.

Material and Methods: This clinical prospective single-center study was conducted between May and August 2018, and comprised 120 patients with definitive diagnosis of acute appendicitis and 30 individuals as control group. White blood cell count (WBC), C-reactive protein (CRP), neutrophil/lymphocyte ratio (NLR) and presepsin levels were measured from venous blood samples. A receiver operating characteristic (ROC) curve was constructed to assess sensitivity and specificity as well as optimal cut points for each presepsin to diagnose acute appendicitis.

Results: Serum levels of CRP, WBC, NLR and presepsin were higher in complicated group compared with uncomplicated ($p<0.0001$, $p=0.01$, $p=0.034$ and $p<0.0001$, respectively). The time of hospitalization, the rate of postoperative infection, intraabdominal abscess and re-hospitalization were significantly higher in complicated group ($p<0.0001$, $p=0.0009$, $p=0.0073$ and $p=0.0073$, respectively). Comparing the diagnostic test results with ROC analysis, variable WBC (AUC=0.646, $p=0.0052$), CRP (AUC=0.807, $p<0.001$), NLR (AUC=0.620, $p=0.0305$) and presepsin (AUC=0.965, $p<0.001$) were significant parameters in predicting the presence of complicated acute appendicitis. Cut-off points of CRP, WBC, NLR and presepsin were calculated as 13.5 mg/dL, 1.4 x10^3/uL, 4.79 and 272 pg/ml. AUC of presepsin was larger than AUCs of WBC, CRP and NLR, suggesting the highest predicting power of presepsin among other parameters.

Conclusion: Plasma presepsin level with CRP, WBC and NLR are valuable diagnostic parameters to predict complicated acute appendicitis.

Keywords: Acute appendicitis; C-reactive protein; presepsin; ROC analysis; white blood cell count

INTRODUCTION

Appendicitis is caused by an inflammation or infection of appendix therefore it becomes one of the most common diseases which necessitate an emergency intervention by surgery (1). Appendectomy is first preference with low morbidity and mortality. Complications such as perforation with abscess formation and localized or four-quadrant peritonitis occur in about 15% of patients (2). There are several indications for the diagnosis of acute appendicitis which is divided into two types as complicated (advanced/perforated) and uncomplicated (phlegmonous/non-perforated)appendicitis. Complicated acute appendicitis progresses to gangrene and perforation while uncomplicated one resolves spontaneously (1). When an appendix were perforated, intensifies of the abdominal pain was increased with more diffuse character, with a possible development of rigidity, tachycardia and temperature was minimum 38°C. The pain may occasionally improve somewhat after rupture of the appendix because of relief of visceral distension, but it does not disappear (1). The diagnosis can be supported by adding laboratory investigations. Inflammatory variables (temperature, white blood cell (WBC) counts, C-reactive protein (CRP), neutrophil/lymphocyte ration (NLR) have been shown to be as crucial as clinical findings (direct and rebound abdominal tenderness and guarding), especially in cases with complicated appendicitis (3). However,

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Corresponding Author: Sinan Binboga, Bakirkoy Dr. Sadi Konuk Education and Research Hospital, Clinic of General Surgery, Istanbul, Turkey **E-mail:** dr.binboga@hotmail.com

these indications are not specific to any inflammatory disease, and in many of them, the blood WBC and CRP levels are found to be high. Today, although it is used in the diagnosis of acute appendicitis, sensitivity and specificity are low without the support of physical examination and imaging techniques (4).

Requirement of urgent intervention to acute appendicitis and usually being vital is related to its complicated or non-complicated. This distinction is often a process that requires time and effort. Radiological evaluation, biochemical test results and the presence of different medical conditions affect the process. In addition, demographic distributions such as age, gender, etc. affect the reference ranges of the diagnostic parameters. Thus, it may contribute to the literature and routine to investigate new markers in different subgroups, since acting with a limited number of general test results in an emergency can lead to a wrong decision.

The biological role of presepsin has not been totally elucidated, yet. It is a modulatory factor which has the capacity to regulate the cellular and humoral immune responses by interacting directly with T and B cells. One of the production pathways of presepsin is related to the phagocytosis process in response to bacterial infection and cleavage of membrane cluster of differentiation 14 (CD14) with lysosomal enzymes of granulocytes (5). There is a growing body of evidence suggesting that the serum levels of presepsin may be altered in patients with sepsis compared to healthy individuals, however, the clinical significance of presepsin in the diagnosis of complicated acute appendicitis remains unclear (6,7). Therefore, the purpose of this prospective single-center study was to assess the diagnostic capacity of serum presepsin levels in the patients with acute appendicitis. Additionally, the accuracy of presepsin as a predictor of the severity of appendicitis was assessed.

MATERIAL and METHODS

Setting and design

One hundred twenty patients with acute appendicitis, with an American Society of Anesthesiologists (ASA) score of I–III, who underwent laparoscopic appendectomy in our general surgery clinic between May 2018 and August 2018, were selected for the study. The control group consisted of 30 patients, which were selected from the patients admitted to our outpatient clinics were included to study. For acute appendicitis group, the patients without an appendicitis diagnosis, deficiencies in the tests, histopathologically confirmed as negative cases of appendectomy and those who did not agree to have surgery were excluded along with subjects who were alcoholic, smokers, had obesity, malignant diseases, and systemic inflammatory diseases. Moreover, subjects who were pregnant, appendicitis-operated, taking vitamins or antioxidant supplements were also excluded.

To patients, who presented with abdominal pain, a physical examination, laboratory tests and abdominal ultrasonography (USG) and computerized tomography (CT) were performed. Final diagnoses were confirmed by surgeon intraoperatively.

Study population and data collection

This prospective study was conducted with 120 acute appendicitis patients and 30 control patients from our department. To determine the sample size and to conduct power analysis for the predictive value of presepsin, GPower analysis was used. The effect size for presepsin values was determined as 1.043 from pilot application. With 0.05 Type I error rate, 1.043 effect size and %80 power, the minimum needed numbers of cases were determined as 12 for the control group and 24 for acute appendicitis group.

Laboratory Tests

Venous blood sampling were performed preoperatively and before any medical treatment by venipuncture into ethylenediaminetetraacetic acid (EDTA) blood collection tubes and immediately centrifuged at 2500 rpm for 10 minutes. After centrifugation, plasma samples were stored at -80 ºC until analysis (maximum, 3 months). The samples were allowed to thaw only once after that they did not used. Standardized reference values of our hospitals' biochemistry laboratory for the normal CRP (0.01 to 0.5 mg/dL), WBC (4 to 11x10^3/uL) and NLR values were accepted for study design. Plasma presepsin levels were determined using the chemiluminescent enzyme immunoassay method according to the manufacturer's recommendations with the PATHFAST® immunoassay analytical system (PROGEN Biotechnik GmbH, Germany; Mitsubishi Chemical Medience Corporation, Japan). Presepsin levels were reported as pg/ml.

Presepsin was measured in blood samples obtained from both the acute appendicitis and control groups. The detection limit for presepsin, according to literature described as 60.1-365 pg/mL (8).

Surgery

The abdominal cavity exploration was performed to patients during the laparoscopic appendectomy. Only the patients who have not any additional intra-abdominal inflammatory pathologies were included the study. Uncomplicated acute appendicitis was defined as catarrhal and phlegmonous appendicitis while complicated acute appendicitis was defined as acute appendicitis in which perforation, gangrenous or an intra-abdominal abscess (9).

Statistical Analysis

The data were examined for normality of distribution by the Kolmogorov Smirnov test. Data without normal distribution are expressed as median [minimum-maximum]. In case of rejection of normality, nonparametric Mann-Whitney U test was used to compare two independent variables and Kruskal Wallis H test for three group comparisons. Multiple comparisons were performed by Dunn's multiple

comparisons test with Bonferonni correction. Categorical variables were analysed by the Chi-Square test. A p value of <0.05 was considered as statistically significant.

A receiver operating characteristic (ROC) curve was constructed to assess sensitivity and specificity as well as optimal cut points for each presepsin to diagnose acute appendicitis. The changes in the related areas under curve (AUC) were tested by using the DeLong test (10).

Statistical analyses were performed using NCSS 11 (Number Cruncher Statistical System, 2017 Statistical Software) and MedCalc Statistical Software version 18 (MedCalc Software bvba, Ostend, Belgium). Power analysis was performed by G*Power 3.1.9.2 (11).

Ethical considerations

The study was approved by the local ethics committee of the Bakirkoy Dr Sadi Konuk Training and Research Hospital (2018/171). This study was performed in accordance with the declaration of Helsinki, International Conference on Harmonization (ICH) and the Good Clinical Practice (GCP) guidelines. Written informed consent was obtained and confidentiality ensured.

RESULTS

There were 150 subjects divided into two groups as control group (n=30) and acute appendicitis group (n=120). Of the patients, 43 (35.8%) were female and 77 (64.2%) were male with a median [range] age of 29.0 [16-18] (Table 1). The control group included 14 (46.7%) females and 16 (53.3%) males with a median [range] age of 37.5 [16-75] years (Table 1). There were no significant difference in the age and gender among groups. As it is expected, patients with acute appendicitis had significantly higher levels of CRP,

Table 1. Characteristics and clinical parameters of the patients with or without acute appendicitis

		Control Group (n=30)	Acute Appendicitis (n=120)	P value
Age (years)	Median (Min-Max)	37.5 (16-75)	29.0 (16-78)	NS
Gender N %	Male	16 (53.3)	77 (64.2)	NS
	Female	14 (46.7)	43 (35.8)	
CRP (mg/dL)	Median (Min-Max)	0.8 (0.06 -1.9)	1.97 (0.04 -42.88)	0.0002
WBC (x10^3/uL)	Median (Min-Max)	8.47 ± 1.96	13.52 ± 4.56	<0.0001
NLR	Median (Min-Max)	3.15 (1.3-5.3)	5.87 (1.1-48.0)	<0.0001
PRE (pg/ml)	Median (Min-Max)	20.0 (7.0-122.0)	133.5 (3.0- 1310.0)	<0.0001

Categorical data were compared by the Chi-square test and continuous data by the Mann–Whitney test, p<0.05.
NS: Non significant, CRP: C-reactive protein, WBC: white blood cell, NLR: Neutrophil/Lymphocyte ratio, PRE: Presepsin

Table 2. Comparison of the clinical parameters of the patients with uncomplicated and complicated acute appendicitis

		Uncomplicated (n=81)	Complicated (n=39)	P value
CRP (mg/dL)	Median (Min-Max)	1.04 (0.04-19.83)	10.62 (0.08-42.88)	<0.0001
WBC (x10^3/uL)	Median (Min-Max)	12.66 (4.92-26.42)	14.64 (5.96-21.2)	0.010
NLR	Median (Min-Max)	5.56 (1.31-48.0)	6.58 (1.11-23.58)	0.034
PRE (pg/ml)	Median (Min-Max)	40 (3 - 400)	472 (28 - 1310)	<0.0001
USG				
Diameter (mm)	Median (Min-Max)	8.0 (6.0-14.0)	10.0 (7.0-12.0)	0.0092
Presence of PF	N (%)	10 (12.35)	23 (58.97)	<0.0001
Hypertension	N (%)	4 (4.94)	6 (15.38)	NS
Diabetes	N (%)	3 (3.70)	4 (10.26)	NS
Respiratory Disorders	N (%)	6 (7.41)	1 (2.56)	NS
ASA grade				
I		67 (82.72)	31 (79.49)	
II	N (%)	14 (17.28)	7 (17.95)	NS
III		0 (0)	1 (2.56)	

Categorical data were compared by the Chi-square test and continuous data by the Mann–Whitney test, p<0.05.NS: Non significant,
CRP: C-reactive protein, WBC: white blood cell, NLR: Neutrophil/Lymphocyte ratio, PRE: Presepsin, USG: Ultrasonography PF: Periappendiceal Fluid

WBC and NLR compared to the control group (p<0.0001). Interestingly, serum levels of presepsin in patients was approximately seven times higher than control group and the difference was statistically significant (p<0.0001).

Comparing the clinical parameters of uncomplicated with complicated acute appendicitis patients (Table 2), serum levels of CRP, WBC, NLR and presepsin were statistically higher in complicated group (p<0.0001, p=0.01, p=0.034 and p<0.0001, respectively). Expectedly, USG showed significantly larger diameter of appendix (p=0.0092), and the majority (58.97%) of patients in the complicated acute appendicitis group had a periappendiceal fluid while minority in uncomplicated group had the fluid (p<0.0001). In terms of the presence of hypertension, diabetes, respiratory disorders, and of ASA scores, there were no significant difference between the uncomplicated and complicated groups.

Table 3 shows the comparisons of the postoperative parameters of the patients with uncomplicated and complicated acute appendicitis. The time of hospitalization, the rate of postoperative infection, intraabdominal abscess and re-hospitalization were significantly higher in complicated group (p<0.0001, p=0.0009, p=0.0073 and p=0.0073, respectively). However, there were no patients with postoperative fistula in uncomplicated group while only 2 patients (5.13%) had fistula in complicated group (p>0.05).

Comparing the diagnostic test results with ROC analysis (Table 4), variables of WBC (AUC=0.646, p=0.0052), CRP (AUC=0.807, p<0.001), NLR (AUC=0.620, p=0.0305) and presepsin (AUC=0.965, p<0.001) were significant parameters in predicting the presence of complicated acute appendicitis. Cut-off points of WBC, CRP, NLR and presepsin were calculated as 1.4 x10^3/uL, 13.5 mg/dL, 4.79 and 272 pg/ml, and the higher values than these cut-off points were correlated significantly with the presence of complicated acute appendicitis (p=0.0052, p<0.001, p=0.0305 and p<0.001, respectively). When AUCs of these biochemical parameters were compared (Figure 1), a significant difference was found in the predictive power of presepsin compared with WBC, CRP and NLR (p<0.0001 for all). AUC of presepsin was larger than AUCs of WBC, CRP and NLR, suggesting the highest predicting power of presepsin among other parameters.

Table 3. Comparison of the postoperative parameters of the patients with uncomplicated and complicated acute appendicitis

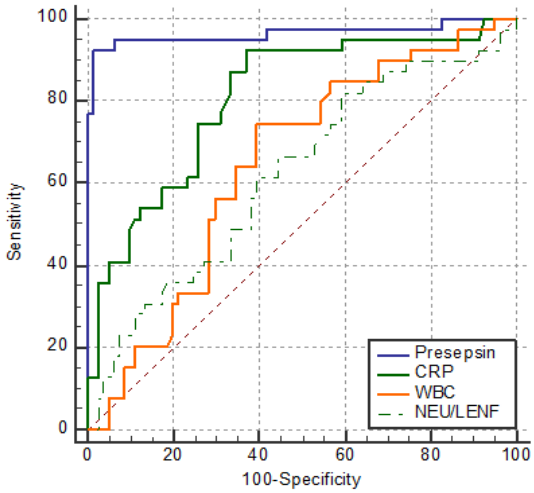
		Uncomplicated (n=81)	Complicated (n=39)	P value
Hospitalization (day)	Median (Min-Max]	1 (1-3)	3 (1-7)	<0.0001
Postop Infection	N (%)	3 (3.7)	10 (25.6)	0.0009
Postop Intraabdominal Abscess	N (%)	1 (1.23)	6 (15.38)	0.0073
Postop Fistula	N (%)	0 (0)	2 (5.13)	NS
Re-hospitalization	N (%)	1 (1.23)	6 (15.38)	0.0073

Categorical data were compared by the Chi-square test and continuous data by the Mann–Whitney test, p<0.05.
NS: Non significant

Table 4. Comparative diagnostic test results in predicting the complicated acute appendicitis

	Cut off	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)	P*
WBC	>13.5	74.36 (57.9-87.0)	60.49(49.0-71.2)	47.5 (39.5-55.7)	83.1 (73.6-89.6)	0.646 (0.55- 0.73)	0.0052
CRP	>1.4x10^3	92.31 (79.1-98.4)	62.96 (51.5-73.4)	54.5 (47.1-61.8)	94.4 (85.0-98.1)	0.807 (0.73- 0.87)	<0.0001
NLR	>4.79	82.05 (66.5-92.5)	40.74 (29.9 -52.2)	40.0 (34.6 - 45.7)	82.5 (69.6-90.6)	0.620 (0.53 - 0.71)	0.0305
PRE	>272	92.31 (79.1-98.4)	98.77 (93.3-100.0)	97.3 (83.7 - 99.6)	96.4 (90.0-98.8)	0.965(0.91 -0.99)	<0.001

***p<0.05**
ROC: Receiver operating characteristic, WBC: White blood cells, CRP: C-reactive protein, NLR: Neutrophil-Lymphocyte ratio, PRE: Presepsin, PPV: Positive Predictive Value, NPV: Negative Predictive Value, AUC: Area under ROC curve, CI: Confidence Interval



	ΔAUC	95% CI	P value
Presepsin ~ CRP	0.157	0.064 – 0.251	<0.0001
Presepsin ~ WBC	0.319	0.205 – 0.433	< 0.0001
Presepsin ~ NEU/LENF	0.344	0.225 – 0.464	< 0.0001

Figure 1. Receiver operating characteristic (ROC) curve analysis for the diagnosis of patients with complicated acute appendicitis using a presepsin, C-reactive protein (CRP), white blood cell count (WBC) and neutrophil/lymphocyte ratio (NEU/LENF)

DISCUSSION

While revealing many valuable early diagnosis markers such as presepsin, all necessary sensitive and confirmatory tests must be performed correctly. Carefully selected patient groups, their number and the first anamnesis in emergency admissions are of great importance. It takes great effort to discover and routinely applicable tests with proven accuracy, cost-effectiveness for early diagnosis and treatment.

In the present study, the diagnostic value of serum presepsin levels to predict both the presence of acute appendicitis and the discrimination of uncomplicated and complicated appendicitis was evaluated. Higher levels of presepsin were found in patients with the complicated acute appendicitis compared to the control and uncomplicated patients. Importantly, the diagnostic sensitivity and specificity of presepsin were higher than of WBC, CRP, NLR in predicting the complicated acute appendicitis (12).

Appendicitis is the most common reason of emergency cases including the abdominal surgeries (13). The diagnosis of the cases generally involves the patient history, clinical symptoms and the findings of physical examination and biochemical tests. As the atypical clinical symptoms are confused with other organ damages especially in women and children, the diagnostic accuracy becomes challenging and time-consuming. Although radiological analysis reduces the incidence of negative appendectomy, it may also be time-consuming and over costing in emergency cases (14). In addition to the need of appendectomy, acute appendicitis may give rise to a complicated appendicitis if the diagnosis period prolongs, leading to long duration of hospitalization and financial burden on both patient and social security institutions. Although there are many biochemical and inflammatory parameters such as WBC, CRP and NLR to detect the acute appendicitis, still, the ratio of false positivity in diagnosis was reported as 15% (15,16). A recent review stated that traditional biomarkers (such as WBC, CRP) had a moderate diagnostic accuracy (0.75) but lower costs in the diagnosis of acute appendicitis. Conversely, novel markers (pro-calcitonin, IL 6 and urinary 5-HIAA) were found to have high process-related costs including analytical times, but improved diagnostic accuracy (17). Therefore, new biomarkers have been investigated for an accurate and rapid diagnosis of the disease. That is to say that the aim of the current study was to reveal the predictive value of presepsin, which has been investigated in various inflammatory diseases, in the acute appendicitis.

Although so many different biomarkers have been used in the acute appendicitis, there is not yet a highly sensitive and specific marker. Ozer et al. are the first researchers who investigated presepsin levels in patients with acute appendicitis6. They found that the presepsin level was significantly higher in patients with acute appendicitis compared with the controls. However, they could not find a significant difference in presepsin levels between perforated and non-perforated appendicitis groups (6). This is probably due to the small size of group; even there was no power analysis to detect the effective sample size. In this study, we gave the effect size for presepsin values as 1.043 with 0.05 Type I error rate, and %80 power. As the minimum needed numbers of cases were determined as 12 for the control group and 24 for acute appendicitis group, we collected the data of 81 control cases, 81 cases of uncomplicated and 39 of complicated acute appendicitis. More interestingly, ROC analysis gave a highly significant diagnostic value of presepsin in predicting the disease, with a cut-off value as 272 pg/ml. Contrary to descriptive and comparative statistical methods, ROC curve analysis allows evaluation of appropriateness of diagnostic parameters and diagnostic accuracy, allowing to evaluate the likelihood that a case with a given test result has that disorder (14).

The most used laboratory markers for reinforcing the diagnosis of acute appendicitis are still WBC, CRP and NLR. High WBC, CRP and NLR levels have been reported to be associated with the other laboratory biomarkers and imaging modalities, hence, useful for the diagnosis of the complicated appendicitis (15,16,18). However, there are also controversy findings which failed to determine the difference between the uncomplicated and complicated appendicitis patients regarding WBC and CRP levels

(19; 6). Some studies claimed that CRP estimation does not improve accuracy in the diagnosis of acute appendicitis in pediatric patients (19). For a long time, blood WBC, CRP and NLR tests have been used for the diagnosis of appendicitis, but their sensitivities and specificities are varied. In literature, the sensitivity of WBC have been reported to vary between 19% and 90%, and the specificity between 44% and 100% (14,20). In the present study, we reported the sensitivity and specificity of WBC as 74.36% and 60.49%, which are obviously in the range of literature.

In acute appendicitis, migration of leukocytes to target tissues results in release of cytokines like CRP. The synthesis of CRP increases within 4–6 hours after acute tissue injury or onset of the inflammation and doubles every 8 hours thereafter peaking at nearly 36–50 hours. Since its half-life is only 4–7 hours, its concentration rapidly drops. Therefore, in patients whose symptoms manifest within less than 12 hours, it has a relatively lower sensitivity. The sensitivity and specificity of CRP have been shown to vary between 48% and 98.7% and 57% and 82%, respectively13. In the present study, we reported them as 92.31% and 62.96%, respectively, showing a consistency with the literature. Buyukbese Sarsu et al., suggested that combined use of cut-off values of WBC (≥13.1x10^3/μL) and CRP (≥1.17 mg/L) yields a higher sensitivity and NPV for the diagnosis of complicated appendicitis. In the present study, cut-off points of WBC and CRP were calculated as 1.4 x10^3/uL and 13.5 mg/dL, respectively. These differences are probably depending on the study population of Buyukbese Sarsu et al. consisted of the children aged between 6 and 17 years while our study had a larger range of age of adult patients.

A study by Kahramanca et al., showed that NLR of 5.74 was significantly associated with complicated acute appendicitis21. The sensitivity and specificity of NLR were 70.8% and 48.5%, respectively. In a similar manner, our ROC analysis gave a cut-off value of 4.79 with a 82.05% sensitivity and 40.74% specificity in predicting the complicated acute appendicitis. Although the size of population involved in the study by Kahramanca et al. was large, they did not give the effect size of population and samples (21).

Presepsin has three biological characteristics that differ from inflammatory markers such as CRP and interleukins. Firstly, it can be detected at an earlier stage in the onset of the infection. Secondly, levels are not affected by situations such as severe trauma, burns or invasive surgical intervention. Thirdly, it reflects the clinical course and severity of septic patients (22). The last characteristic was also related with the blood presepsin levels (23). Our study determined the predictive value of raftlin, presepsin as well as compared its diagnostic features with other biochemical parameters in complicated acute appendicitis. Being a single center study, however, it has some limitations as the patients who had negative appendectomy.

Complicated acute appendicitis is related to a variety of potentially serious complications like infection, intraabdominal abscess or fistula formation, small bowel obstruction, leading to re-hospitalization of the patient. In the present study, the patients of complicated acute appendicitis hospitalized longer than the patients with uncomplicated one. In addition, more incidences of postoperative infection, intraabdominal abscess and fistula formation and re-hospitalization were recorded in complicated group. Thus, early appendectomy remains the gold standard, and discrimination of complicated appendicitis from uncomplicated one is vital to avoid delays of essential operative procedures for these patients (24,25).

CONCLUSION

In this regard, we suggested that a diagnostic accuracy of the combination of WBC, CRP and NLR could be enhanced by the addition of serum presepsin levels in biochemical analysis of acute appendicitis. Further studies are needed to investigate new biomarkers and address concerns over bias, in order to improve the diagnosis of complicated acute appendicitis.

Competing interests: The authors declare that they have no competing interest.

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Ethical approval: The study was approved by the local ethics committee of the Bakirkoy Dr Sadi Konuk Training and Research Hospital (2018/171).

Sinan Binboga ORCID: 0000-0002-6923-7423
Nilgun Isiksacan ORCID: 0000-0002-0230-6500
Pinar Kasapoglu Atar ORCID: 0000-0003-1703-2204
Elif Binboga ORCID: 0000-0003-4068-2694
Mehmet Karabulut ORCID: 0000-0002-1889-5637
Halil Alis ORCID: 0000-0003-0907-6047

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