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RESEARCH ARTICLE

Traces of Inflammation in Acute Appendicitis, Cholecystitis, and Diverticulitis: The Role of Biomarkers in Diagnosis

Serap Ulusoy,[1] Furkan Savas.[1]
[1]General Surgery, Ankara Bilkent City Hospital, Ankara, Turkiye

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ORCIDs of the authors:
SU :0000-0001-9014-7070
FS :0000-0002-3963-7784

Abstract

Introduction: Acute appendicitis, acute cholecystitis, and acute diverticulitis are among the most common causes of acute abdominal pain, requiring early diagnosis and rapid treatment. Although imaging modalities such as ultrasonography and computed tomography play a crucial role in diagnosis, access to these methods may be limited in certain situations. Inflammatory biomarkers, including C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), and delta neutrophil index (DNI), have been suggested as potential tools for differential diagnosis. This study aims to evaluate the diagnostic value of these biomarkers.

Methods: This retrospective study included 171 patients diagnosed with acute appendicitis (n=62), acute diverticulitis (n=56), and acute cholecystitis (n=53). White blood cell (WBC), neutrophil, lymphocyte, and eosinophil counts, as well as NLR, DNI, and CRP levels, were compared. Statistical analyses and ROC analysis were performed to assess the diagnostic performance of these biomarkers.

Results: CRP and lymphocyte levels were found to be significantly higher in the acute diverticulitis group ($p < 0.05$). Although DNI, NLR, WBC, and neutrophil levels were elevated in all three groups, no statistically significant difference was observed between them ($p > 0.05$). ROC analysis demonstrated that DNI has a moderate diagnostic potential for all three diseases, but none of the biomarkers provided high specificity.

Conclusion: Inflammatory biomarkers alone are not sufficient as a diagnostic tool for differentiating acute appendicitis, acute cholecystitis, and acute diverticulitis. However, CRP may be useful in assessing disease severity in patients with diverticulitis. Particularly in settings where access to imaging modalities is limited or unavailable, biomarkers such as CRP, DNI, and NLR may serve as supportive tools for diagnosis. Nevertheless, large-scale, multicenter studies are required to better define the role of inflammatory response and biomarkers in differential diagnosis and prognosis.

Correspondence Address: Üniversiteler Mahallesi 1604. Cadde No: 9 Çankaya Ankara - Türkiye
Phone: +90 532 226 88 78 / **e-mail:** serapulusoy13@gmail.com

Introduction

Acute abdominal pain is a common clinical presentation that accounts for a significant proportion of emergency department visits and requires prompt diagnosis and management.[1] The most important cause of acute abdominal pain in the emergency setting is intra-abdominal infections. The term "intra-abdominal infections" encompasses a wide range of pathological conditions, from uncomplicated appendicitis to widespread fecal peritonitis.[2] The most common cause of intra-abdominal infections is acute appendicitis, followed by acute cholecystitis and acute diverticulitis.[3] These three conditions may present with similar clinical manifestations; however, due to differences in their pathophysiological mechanisms, the severity of inflammation and its systemic effects may vary.

Acute appendicitis is characterized by bacterial proliferation, mucosal ischemia, and transmural inflammation following obstruction of the appendiceal lümen.[4] Acute cholecystitis typically begins with edema and inflammation due to cystic duct obstruction and may progress to necrosis and suppuration in advanced stages.[5] Acute diverticulitis is a clinical condition triggered by fecal stasis and mucosal inflammation, often accompanied by micro- or macro-perforation and abscess formation.[6] In advanced stages of these diseases, necrosis, perforation, and peritonitis may develop, leading to an exacerbation of systemic inflammatory response and serious complications.

These three conditions can generally be distinguished through clinical findings and imaging modalities; however, diagnosis may be challenging in some cases. Atypical symptoms, inflammation occurring outside classical anatomical locations, and presentations in special patient groups such as the elderly, children, or pregnant individuals can complicate differential diagnosis. Ultrasonography (USG) and contrast-enhanced computed tomography (CT) are the most frequently used imaging techniques for definitive diagnosis. CT is generally considered the most reliable modality; however, it may not be feasible in cases where radiation exposure or contrast administration is contraindicated, such as in patients with renal failure, contrast allergies, pregnancy, or pediatric patients. USG, on the other hand, may be limited by bowel gas interference, obesity, operator dependency, and technical inadequacies, making it less reliable in some cases. Additionally, limited access to advanced imaging techniques in peripheral hospitals may delay diagnosis.[7] Under such circumstances, the use of inflammatory biomarkers in clinical evaluation and diagnostic processes becomes increasingly important.

Hematological and biochemical markers such as C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), and delta neutrophil index (DNI) are widely used parameters for assessing systemic inflammatory response. CRP is an acute-phase reactant secreted by hepatocytes in response to pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), and it serves as a crucial indicator of disease severity.[8] NLR reflects the ratio between neutrophil elevation and lymphocyte reduction during inflammation, thereby providing insights into the severity of the inflammatory process.[9] DNI quantifies the proportion of circulating immature granulocytes, aiding in the detection of bacterial infections and assessment of the degree of inflammation.[10]

The use of inflammatory biomarkers not only supports diagnosis but also provides valuable information regarding disease prognosis and treatment decision-making. However, the extent to which these biomarkers differentiate between acute appendicitis, acute cholecystitis, and acute diverticulitis, and their reliability in diagnosis and differential diagnosis, remains unclear.

In this study, we aimed to compare the inflammatory response among patients with acute appendicitis, acute cholecystitis, and acute diverticulitis to evaluate the potential role of biomarkers in differential diagnosis. Furthermore, we sought to investigate the utility of these biomarkers in predicting disease prognosis and guiding clinical decision-making, particularly in settings with limited imaging availability, to determine whether they contribute to the diagnostic and therapeutic process.

Material and Methods

This retrospective study was conducted with adults aged ≥18 years who were treated in the general surgery clinic with a diagnosis of acute appendicitis, acute cholecystitis, or acute colonic diverticulitis between February 2019 and November 2020. A total of 1.198 case files were retrospectively screened. Patients younger than 18 years, those with diabetes mellitus, malignancies, immunodeficiency, severe heart failure, liver or kidney failure, a history of or-

gan transplantation, absence of a radiologically confirmed diagnosis, or cases where study criteria were not assessed at the time of presentation were excluded from the study.

The total white blood cell (WBC) count, neutrophil count, lymphocyte count, eosinophil count, neutrophil-to-lymphocyte ratio (NLR), delta neutrophil index (DNI), and C-reactive protein (CRP) levels were compared among the three groups. These parameters were assessed using the initial blood samples obtained in the emergency department. Hematological parameters were measured with the Siemens ADVIA 2120i Hematology Analyzer (Ireland, Dublin,2019). Leukocytosis and leukopenia were defined as WBC > 10.6 × 10^9/L and WBC < 3.5 × 10^9/L, respectively, based on the reference values provided by the laboratory medicine department of our hospital. The reference values of neutrophil, lymphocyte and eosinophil were taken as 1.5-7.7 (× 10 ^ 9)/L, 1.1-4 (× 10 ^ 9)/L and 0.02-0.5 (× 10 ^ 9)/L, respectively. CRP was measured using the Siemens Adria Chemistry XPT (Japan, Tokyo, 2018) device, taking 0-5 mg/dl as reference. The neutrophil-to-lymphocyte ratio (NLR) was automatically calculated as the ratio of the neutrophil count to the lymphocyte count using the ADVIA 2120i Hematology Analyzer.

Statistical Analysis

The patients' characteristics were summarized using descriptive statistics. Numerical parameters were presented as mean, standard deviation, minimum, and maximum values, with 95% confidence intervals provided where applicable. Non-numerical parameters were reported as frequencies and percentages. For secondary analyses, the Kolmogorov-Smirnov test was employed to assess the distribution of all variable groups. Parametric tests were applied to normally distributed variables, while non-parametric tests were used for variables with non-normal distributions. Analysis of variance (ANOVA) was performed for parameters with a normal distribution. The threshold for statistical significance (p-value) was set at 0.05. All statistical analyses were carried out using SPSS version 22.0.

Parameters that did not show normal distribution were compared using the Kruskal-Wallis test. Significant results from these analyses were further investigated using the Mann-Whitney U test. The chi-square test was employed for the comparison of categorical data. It was observed that age, WBC and neutrophil values showed normal distribution while the other values did not show normal distribution. Finally, receiver operating characteristic (ROC) analysis was conducted to determine the sensitivity, specificity, and recommended cut-off value of DNI for each group. For this analysis, DNI values from 51 cases with a homogeneous age and gender distribution, consisting of healthy individuals who visited the check-up outpatient clinic of our hospital, were utilized.

Results

A total of 1.198 case files were screened, and 62 appendicitis, 56 colonic diverticulitis and 53 calculus cholecystitis cases were included in the study. All pathologies had been radiologically confirmed by ultrasonography or computed tomography. The general datas of the study are given tables 1.

Table 1: General data of the patient groups

Parameter	Acute appendicitis	Acute diverticulitis	Acute cholecystitis	p	
WBC	12.290.48±4.475.40	13.117.50±3.933.07	12.995.85±5.443.67	0.577	*
Neutrophil count	9.739.52±4.107.08	10,223.75±3,770.14	10.386.60±4.893.01	0.695	*
Lymphocyte count	1.555 (400-5070)	1,920 (220-4,420)	1390 (220-4.420)	0.024	**
Eosinophil count	95 (10-460)	115 (10-470)	90 (0-950)	0.187	**
NLR	6.06 (1.40-30.27)	5.82 (1.32-26.41)	6.07 (1.71-30.84)	0.614	**
DNI	0.09 (0.01-11.7)	0.08 (0.01-7.8)	0.09 (0.01-13.5)	0.833	**
CRP	38.9 (2-258)	75.75 (6.25-303)	48 (2-354)	0.011	**

*ANOVA **Kruskal-Wallis test

WBC :White blood cell, NLR: Neutrophil Lymphocyte Ratio, DNI:Delta neutrophil index, CRP:C-reactive protein

The mean WBC and neutrophil counts were elevated in all three groups, although no statistically significant differences were observed between them. The mean lymphocyte counts fell within the reference ranges for all three groups; however, a significant difference was noted in the diverticulitis group (appendicitis-diverticulitis, p = 0.037; cholecystitis-diverticulitis, p = 0.011). No statistically significant differences were found in the mean eosinophil values among the three groups. The NLR and DNI were elevated in all three groups, but no statistically significant differences were observed.

The DNI values for all three groups were evaluated using ROC analysis. For acute appendicitis, the area under the curve (AUC) was calculated

as 0.771 ($p < 0.01$), with a DNI cut-off value of 1 yielding a sensitivity of 0.532 and a specificity of 0.925. For acute diverticulitis, the AUC was 0.742 ($p < 0.01$), with a sensitivity of 0.589 and specificity of 0.81 for a DNI cut-off value of 1. For acute cholecystitis, the AUC was calculated as 0.758 ($p < 0.01$), and a DNI value of 1 demonstrated a sensitivity of 0.547 and specificity of 0.929 (Figure 1).

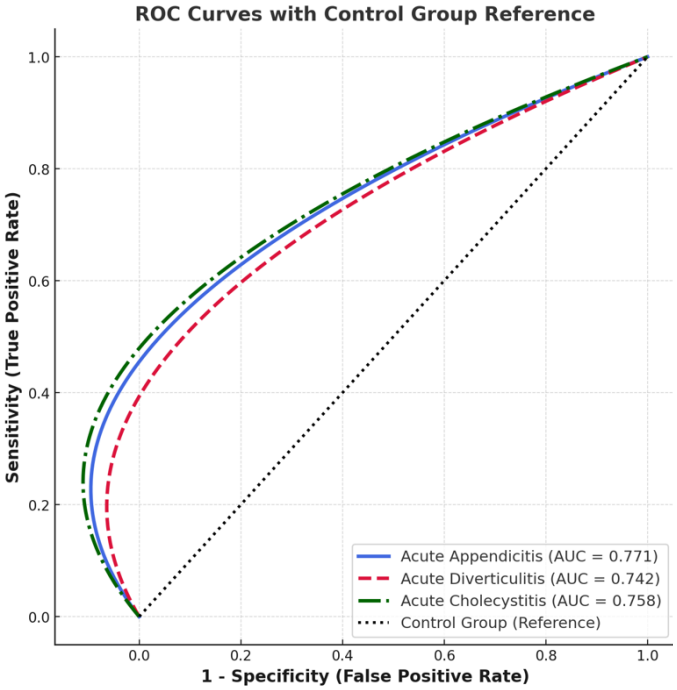

Figure 1: DNI ROC curves values for the three diagnoses

A significant difference was observed among the groups in terms of CRP and lymphocyte values, as determined by the Kruskal-Wallis test ($p < 0.05$). The Mann-Whitney U test, used to identify the group(s) responsible for the significant difference, revealed that the difference in CRP was attributed to the acute diverticulitis group (appendicitis vs diverticulitis, $p = 0.004$; cholecystitis vs diverticulitis, $p = 0.022$). Both CRP and lymphocyte values were significantly higher in the acute diverticulitis group.

The mean age of patients in the appendicitis group was statistically lower than that of the other two groups (appendicitis vs diverticulitis, $p = 0.012$; appendicitis vs cholecystitis, $p < 0.001$) (Table 2). No statistically significant differences were observed between the three groups regarding gender distribution (Table 3).

Table 2: Age distribution of the cases

Parameter	Acute appendicitis	Acute diverticlitis	Acute cholecystitis	p
Age	45.85±11.08	53.35±16.22	57.49±14.79	<0.001

Table 3: Gender distribution of the cases

Group		Female	Male	p
Acute appendicitis	Count	23	39	0.165
	% within the group	62.9%	37.1%	
Acute diverticulitis	Count	30	26	
	% within the group	53.6%	46.4%	
Acute cholecystitis	Count	24	29	
	% within the group	45.3%	54.7%	

Discussion

In this study, we aimed to investigate how the acute inflammatory response differs among patients with acute appendicitis, acute cholecystitis, and acute diverticulitis, as well as the role of inflammatory biomarkers in differential diagnosis. Our findings indicate that CRP and lymphocyte levels were significantly higher in the acute diverticulitis group ($p<0.05$), whereas DNI, NLR, WBC, and neutrophil levels were elevated in all three patient groups but did not show significant differences between them ($p>0.05$).

These differences suggest that the inflammatory process varies depending on the pathophysiological mechanisms of each disease, and the severity and systemic implications of inflammation may differ accordingly. The significantly higher CRP levels in acute diverticulitis patients may indicate that this condition is associated with more severe or prolonged inflammation. The elevated lymphocyte levels in this group may be related to the chronic inflammatory component of acute diverticulitis.

The observed increases in CRP and lymphocyte levels should not be regarded as specific tools for differential diagnosis; rather, they should be considered supportive parameters that may contribute to the diagnostic process when evaluated together with clinical and other laboratory findings.

CRP is a crucial component of the systemic response to acute inflammation and is secreted by hepatocytes in response to pro-inflammatory cytokines such as IL-6, IL-1, and TNF-α.[11–13] In our study, CRP levels were significantly higher in the acute diverticulitis group compared to the acute appendicitis and acute cholecystitis groups.

This finding is consistent with some studies in the literature. A review including 21 studies on diver-

ticulitis reported that CRP levels were significantly elevated in patients with complicated diverticulitis, and CRP levels above 150–200 mg/L were helpful in predicting perforation and the need for surgical intervention.[14–15] Additionally, CRP levels below 50 mg/L were associated with a lower likelihood of perforation, highlighting CRP as a potential marker for risk stratification.

A recent meta-analysis of 17 studies identified CRP as the most important laboratory biomarker for diagnosing diverticulitis, with particularly high negative predictive value.[16] These findings suggest that the inflammatory response in acute diverticulitis may be more severe or prolonged due to the nature of colonic pathology, delayed presentation, or microbial composition.

The neutrophil-to-lymphocyte ratio (NLR) is a hematological biomarker that reflects the dynamic balance between innate immunity (neutrophils) and adaptive immunity (lymphocytes). It is widely used in the assessment of inflammation, infection, stress, and cancer prognosis.[17] Clinical studies have shown that NLR has high sensitivity in diagnosing and classifying systemic infections, sepsis, and bacteremia, making it a valuable prognostic marker.[18]

A study involving 799 patients with histologically confirmed appendicitis found that NLR was significantly higher in cases of complicated appendicitis, with an area under the curve (AUC) value of 0.727 and a cutoff value of 6.96, suggesting its potential use as a biomarker for disease severity.[19]

In our study, NLR levels were found to be elevated in patients with acute appendicitis, acute cholecystitis, and acute diverticulitis; however, no statistically significant differences were observed between the groups. This suggests that while NLR is a sensitive marker for intra-abdominal inflammation, it may not be sufficiently specific for differential diagnosis.
DNI, which measures the proportion of immature granulocytes in peripheral circulation, is gaining increasing attention as a marker of infection severity.[20] It has been reported to be associated with sepsis, bacterial infections, and acute inflammatory conditions.[21–22]

Our ROC analysis demonstrated that DNI values were significantly elevated across all patient groups, with strong diagnostic potential as indicated by AUC values.However, no significant differences were found between the disease groups. This suggests that although DNI is a reliable marker for detecting acute inflammation, it has limited specificity in distinguishing between appendicitis, diverticulitis, and cholecystitis.

In our study, WBC and neutrophil levels were elevated in all three patient groups, but no significant differences were observed between them. This finding indicates that while these parameters are useful in identifying the inflammatory process, they are not sufficient for differentiating between different etiologies.[23–25]

The results of this study suggest that inflammatory biomarkers alone are not sufficient for differential diagnosis but are effective in identifying intra-abdominal infections. Particularly in peripheral hospitals or settings with limited imaging availability, inflammatory biomarkers may contribute to diagnosis and assist in patient management.

This study has certain limitations. Being a single-center, retrospective study may limit the generalizability of the results. Additionally, the relatively small sample size may have prevented the identification of potential differences between inflammatory biomarkers in a larger cohort. The study only evaluated biomarker levels at the time of presentation, without assessing changes over time. Moreover, precise diagnostic cutoff values for these biomarkers were not determined, and their correlations with imaging modalities were not analyzed in detail.

Intra-abdominal infections have distinct pathophysiological mechanisms, making it natural for inflammatory biomarkers to exhibit disease-specific variability. A better understanding of these mechanisms may enhance the role of inflammatory biomarkers in clinical evaluation. Our findings should be validated in larger patient cohorts through prospective studies, and further research should explore the effectiveness of combining inflammatory biomarkers in the diagnostic process.

Conclusion

This study aimed to evaluate the differences in inflammatory responses among patients with acute appendicitis, acute cholecystitis, and acute diverticulitis, as well as the potential role of biomarkers in differential diagnosis. Our findings indicate that CRP and lymphocyte levels were significantly elevated in patients with acute diverticulitis. However, while DNI, NLR, WBC, and neutrophil levels were elevated in all three groups, no statistically significant differences were observed between them.

The markedly higher CRP levels in diverticulitis suggest that the inflammatory process in this condi-

tion may be more prolonged and pronounced. However, despite the increased levels of biomarkers such as DNI and NLR across all patient groups, they were not sufficiently specific for differential diagnosis.

These results indicate that inflammatory biomarkers may be valuable in detecting intra-abdominal infections but may not be sufficient for definitive diagnosis on their own. Particularly in settings with limited imaging availability, these biomarkers may contribute to clinical assessment and serve as supportive diagnostic tools.

Nevertheless, further large-scale, prospective, and multicenter studies are required to enhance our understanding of inflammatory processes in these conditions. In particular, the mechanisms underlying the significant increase in CRP levels in diverticulitis and its potential diagnostic and prognostic implications should be explored in greater detail.

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