



Research Article

THE ROLE OF INFLAMMATORY PARAMETERS AND SCORING SYSTEMS IN PREDICTING COMPLICATED ACUTE APPENDICITIS

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ABSTRACT

Aim: To assess the complications associated with acute appendicitis (AA) and to evaluate how specific routine patient parameters influence disease severity.

Materials and Methods: A retrospective study was carried out on patients diagnosed with AA who presented to the emergency department (ED) between January 1, 2019, and December 31, 2020. Data collected included demographic details, blood test results, and specific scoring systems utilized in the ED. Results: Of the 223 patients studied, 63.7% were male with a mean age of 37.5 \pm 16.8 years. Patients with complicated appendicitis (CA) showed significantly elevated hematological parameters such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), C-reactive protein (CRP), systemic immune inflammation index (SII), white blood cell count (WBC), and neutrophil levels. Conversely, decreased lymphocyte/C-reactive protein ratio (LCRP) and lymphocyte levels were noted. Furthermore, CA cases exhibited significantly greater Appendicitis Inflammatory Response (AIR) and Alvarado scores. In the context of diagnosing CA, the AIR score had a sensitivity of 85.9% and a specificity of 47.9% with a cut-off value of ≥6 (95% CI 0.675-0.821, Area Under the Curve (AUC): 0.748; p<0.01). The Alvarado score showed a sensitivity of 80.6% and a specificity of 44.5%, using a cut-off value of ≥6 (95% CI 0.527-0.683, AUC: 0.605; p=0.10).

Conclusion: Our study determined that inflammatory markers such as LCRP, SII, NLR, and PLR serve as significant indicators for distinguishing between CA and its NCA.

Keywords: Acute appendicitis, Appendicitis inflammatory response score, Alvarado score, Emergency department, Complicated appendicitis, Non-complicated appendicitis

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INTRODUCTION

Approximately 5% to 10% of patients presenting to the Emergency Department (ED) report abdominal pain (1). Given the frequent occurrence of this problem and its varied etiologies, there is a growing interest in imaging and laboratory methods to aid differential diagnosis (2). Acute appendicitis (AA) stands out as the predominant abdominal surgical condition encountered globally. Its prevalence is approximately 8.6% in males and 6.9% in females (3). The significance of early diagnosis in AA cannot be overstated. The risk of perforation, for instance, ranges from 16% to 36% within the initial 36 hours of abdominal pain onset, and sees an additional increase of 5% every subsequent 12 hours (4). This is concerning, especially since perforation stands as the most common complication of AA, contributing substantially to increased mortality and morbidity (5). Thus, timely intervention and early diagnosis in patients susceptible to complications are paramount. Notably, the challenge persists in identifying a universally acknowledged gold standard for diagnosing AA. Even with assessments from seasoned radiologists, imaging techniques like ultrasonography (USG) and computed tomography (CT) haven't met the expected diagnostic precision, prompting continuous research into alternative diagnostic methodologies (6).

The primary objective of this study is to determine the discriminatory power of laboratory values, imaging results, and appendicitis scoring systems in distinguishing between complicated appendicitis (CA) and non-complicated appendicitis (NCA) by comparing them with pathology reports.

MATERIALS AND METHODS

Study Design and Setting

This retrospective, single-center, observational, cross-sectional study was conducted in the ED of a university-affiliated training and research hospital in Muğla, Turkey. Data were collected from consecutive patients admitted to the ED between January 1, 2019, and December 31, 2021, who were subsequently diagnosed with concomitant acute appendicitis. Ethical approval for the study was obtained from the local ethics committee (Reference Number: 7), and the research was performed in accordance with the Principles of the Declaration of Helsinki (1975), as revised in 1983. Due to the retrospective nature of the study, the necessity for written informed consent was waived.

Definitions and Clinical Scoring Systems

AA refers to the inflammation of the appendix, which is a blind-ended pouch located in the lower right abdomen. When patients present with abdominal pain in the ED, a diagnosis of AA is established through the patient's history, physical examination, laboratory tests, clinical scoring systems, and imaging methods.

Patients in the study were categorized into two groups: those with CA and NCA. The identification of CA was based on surgical and pathological findings, with the aim to ascertain the prevalence of CA. Specifically, surgical and/or pathological reports that described conditions as gangrenous/necrotizing, abscessed, or perforated were classified under CA. All other diagnostic outcomes were categorized as NCA.

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To evaluate the severity of AA, we utilized both the Appendicitis Inflammatory Response (AIR) score and Alvarado score.

Outcome Measures

The differentiation between CA and NCA is important to assess the severity of the health issue and determine the appropriate treatment method. CA indicates advanced stages of appendicitis. In cases of CA, there may be perforation of the appendix or other serious complications. Perforation, spreading of inflammation to surrounding tissues, or other appendicitis-related complications can pose a significant risk to the patient's outcome. Early diagnosis and treatment can reduce the risk of such complications.

On the other hand, in NCA cases, patients may experience a quicker recovery process, and their length of stay (LOS) hospital stay may be shorter. In contrast, in cases of CA, the recovery process can be more prolonged and complex.

CA cases can lead to more complex surgical interventions and an increased risk of surgical complications. Therefore, it is essential to differentiate between CA and NCA to manage patients effectively and prevent complications. Consequently, clinical, laboratory, imaging results and scoring systems can be used to make this distinction.

Patient Selection

Our study primarily encompassed 223 patients who were aged 18 years and above, had been diagnosed with AA in the ED, and had operated by the general surgery team. However, certain groups were excluded to maintain the study's integrity. These included 85 patients under 18 years, those with incomplete data or a recent hospitalization history within the last 14 days, 5 pregnant individuals, 2 immunosuppressed patients, 3 patients diagnosed with hematological or liver diseases, and 10 patients underwent an appendectomy for reasons other than AA.

Data Collection

Patient records were retrieved via archival research, utilizing the HIMS for laboratory result extraction. For every patient satisfying the study's inclusion criteria, a dedicated form was developed. This form encapsulated various parameters: demographic details (age and gender), laboratory results, C-reactive protein (CRP), White blood cell count (WBC), Platelet (PLT), Neutrophil (NEU), Lymphocyte (LYM), Neutrophil-to-Lymphocyte ratio (NLR), Platelet-to-Lymphocyte ratio [PLR], Systemic Immune-Inflammation Index (SII), and Lymphocyte to CRP ratio (LCRP)], length of stay (LOS) hospital, CT scan outcomes, the patient group



diagnosed with CA, AIR and Alvarado scores from the ED, and admission year (2019-2020). The initial Alvarado score, and AIR score were systematically calculated for each patient.

Statistical Analysis

Whether the continuous variables conformed to a normal distribution was assessed using the Kolmogorov-Smirnov test. Descriptive statistics were reported as mean ± standard deviation for continuous and discrete numerical variables, while for categorical variables, the number of cases and percentage (%) were provided. For parameters showing a normal distribution, Student t-test was employed for comparisons, while the Mann–Whitney U test was used for comparisons between two different groups for parameters that did not display a normal distribution. Sensitivity, specificity, the positive predictive value (PPV) and the negative predictive value (NPV) were evaluated for parameters used in distinguishing between the groups. Receiver Operating Characteristic (ROC) analysis was performed to determine the appropriate cutoff value along with specificity and sensitivity values. Results obtained with p<0.05 were considered statistically significant. Statistical analyses were performed using the SPSS software package, version 22 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Between January 1, 2019, and December 31, 2020, a total of 328 patients were diagnosed with AA at the Emergency Department of Muğla Training and Research Hospital and subsequently underwent surgery in the hospital's General Surgery Department. Following the application of the exclusion criteria), the study focused on a final sample of 223 patients.

The patient cohort exhibited a mean age of 37.5 ± 16.8 years, encompassing a range of 18-90 years, with males constituting 63.7% of the population. Central tendency and variability in laboratory results were noted as follows: a median WBC count of 12.61 (3,30-24,96), mean NEU count of $9.83\pm3,70$, median NLR of 7.25 (0,67-40,39), median PLR of 172,31(50,11-780,65), median LCRP of 0,40 (0,00-4,72), and median SII of 1816,99(158,03-10828,33). Tables 1 provide an in-depth view of the patients' laboratory results. Furthermore, significant differences were identified in several laboratory parameters between CA and NCA, specifically in WBC, NLR, PLR, LCRP and SII. (P = 0.045, P < 0.001, P = 0.010, P < 0.001 and P = < 0.001, respectively).



Table 1. Comparison of age, hemogram and crp values in the differentiation of complicated appendicitis

	Complicated Appendicitis (n= 57)	Non-complicated appendicitis (n= 166)	Total (n=223)	P Value
Age	41.00 (19.00-90.00)	30.00 (18.00-85.00)	37.54 (18-90)	<0.001
WBC(10³/μg)	13.35 (6.90-24.96)	12.18 (3.30-20.02)	12.61(3.30-24.96)	0.045
PLT (10³/μg)	239 (147.00-365.00)	242.5 (101.00-611.00)	252.35(101.00-611.00)	0.693
NEU (10³/μg)	10.99 ±3.63	9.43 ±3.65	9.83±3.70	0.006
LYM (10 ³ /μg)	1.36 (0.41-3.41)	1.80 (0.31-4.44)	1.79(0.31-4.44)	0.002
NLR	8.20 (1.94-29.75)	5.18 (0.67-40.39)	7.25(0.67-40.39)	<0.001
PLR	203.17 (78.42-715.60)	161.72 (50.11-780.65)	172.31(50.11-780.65)	0.010
CRP(mg/L)	51.78 (3.73-599.00)	9.90 (0.60-303.92)	47.40(0.60-599.00)	< 0.001
LCRP	0.07(0.00-0.48)	0.51(0.00-4.72)	0.40(0.00-4.72)	< 0.001
SII	2316.05(488.75-10828.33)	1645.63(158.03-9773.68)	1816.99(158.03- 10828.33)	<0.001

Note: Data showing parametric distribution is presented as Mean ± Standard Deviation, while data that does not show parametric distribution is presented as Median (minimum-maximum). *WBC: White Blood Cell, PLT: Platelet, NLR: Neutrophil / Lymphocyte Ratio, PLR: Platelet / Lymphocyte Ratio, CRP: C-Reactive Protein, LCRP: Lymphocyte / C-Reactive Protein Ratio, SII: Systemic Immune Inflammation Index

According to the data presented in Table 1 when patients were divided into two groups as AA and CA, in CA cases, NLR, PLR, CRP, SII, WBC levels were found to be statistically significantly higher, while LCRP and lymphocyte values were lower. Additionally, it was determined that CA cases were significantly older.

As shown in Table 2, when comparing the CA and NCA patient groups in terms of gender ratio, no statistically significant difference was obtained. However, among 105 patients who presented in 2019, KA was detected in 27 (25.7%), while among 118 patients who presented in 2020, KA was identified in 30 (23%). The mean length of hospital stay (LOS) was 2 (1-12) days, and it was determined that CA cases stayed in the hospital for a longer period.

A total of 179 patients underwent CT scans, and of these patients, 16 had CT reports consistent with CA. Additionally, Table 3 shows that the median AIR and Alvarado scores were 6. When NCA and CA cases were compared based on this value, it was determined that the appendicitis scores of CA cases were statistically significantly higher.



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		Complicated Appendicitis (n: 57)	Non Complicated Appendicitis (n: 166)	P Value	
	Male n(%)	41 (71.9)	101 (60.8)	0.180	
Gender	Female n(%)	16 (28.1)	65 (39.2)		
Length of Stay n(min-max)		3 (1-12)	2 (1-12)	<0.001	
Application	2019	27	78	0.060	
Year	2020	30	88	0.960	

The initial AIR score of the CA was significantly higher than NCA (8, [range, 3–10] vs. 6 [range, 1–10], P < .001). The initial Alvarado score of the CA was significantly higher than NCA (6, [range, 2-9] vs. 6 [range, 1–10], P = 0.017).

Table 3. Comparison of clinical scoring in the differentiation of complicated appendicitis

	Complicated Appendicitis (n: 57)	Non Complicated Appendicitis (n: 166)	P Value
AIR Score	8 (3-10)	6 (1-10)	<0.001
Alvarado Score	6 (2-9)	6 (1-10)	0.017

In Table 4, when the cutoff values for diagnostic tests to determine whether cases are CA or not are provided, the sensitivity of CT is 30.7%, the specificity is 96.9%, and the accuracy rate is 77.6%. These rates, when an AIR score of \geq 6 is considered, are 85.9%, 47.9%, and 57.5%, respectively. When an Alvarado score of \geq 6 is considered, these rates are 80.6%, 44.5%, and 54.9%, respectively. When LCRP is \leq 0.1, these rates are 78.9%, 89.7%, and 87%, respectively. When NLR is \geq 8.2, these rates are 64.9%, 77.1%, and 73.9%, respectively.

In ROC curve analysis, the closer the area under the curve (AUC) of a tested parameter is to 1, the more important the marker is in predicting the complication. In this study, for predicting complications, the AUC of LCRP was 0.782 (95% CI, 0.711-0.847, p: 0.00), the AUC value of CRP was 0.765 (95% CI 0.697-0.833; p: 0.00), the AUC value of AIR score was 0.748 (95% CI, 0.675-0.821; p: 0.00), the AUC value of NLR was 0.664 (95% CI, 0.585-0.743, p: 0.01), the AUC value of SII was 0.644 (95% CI, 0.565-0.723; p: 0.00) and the AUC value of Alvarado score was 0.605 (95% CI, 0.527-0.683; p: 0.1). This is shown in Figure 1



Table 4. Diagnostic effectiveness of parameters in the differentiation of complicated appendicitis

СТ	Complicatio n Present	No Complication	Sensitivity	Specificity	Accuracy	PPV	NPV
Positive	16	4	30.7%	96.9%	77.6%	80%	77.3%
Negative	36	123					
AIR Score ≥6	Complicatio n Present	No Complication	Sensitivity	Specificity	Accuracy	PPV	NPV
Positive	49	87	85.9%	47.9%	57.5%	36%	90.9%
Negative	8	80					
Alvarado Score ≥6	Complicatio n Present	No Complication	Sensitivity	Specificity	Accuracy	PPD	NPV
Positive	44	92	80.6%	44.5%	54.9%	36.9%	85%
Negative	13	74					
LCRP ≤0.1	Complicatio n Present	No Complication	Sensitivity	Specificity	Accuracy	PPV	NPV
Positive	45	17	78.9%	89.7%	87.0%	72.5%	92.5%
Negative	12	149					
SII ≥2300	Complicatio n Present	No Complication	Sensitivity	Specificity	Accuracy	PPV	NPV
Positive	23	36	40.3%	78.3%	68.6%	38.9%	79.2%
Negative	34	130					
NLR ≥8.2	Complicatio n Present	No Complication	Sensitivity	Specificity	Accuracy	PPV	NPV
Positive	37	38	64.9%	77.1%	73.9%	49.3%	86.4%
Negative	20	128					
PLR ≥182	Complicatio n Present	No Complication	Sensitivity	Specificity	Accuracy	PPV	NPV
Positive	24	45	42.1%	72.8%	65.0%	34.7%	78.5%
Negative	33	121					

^{*}CT: Computed Tomography, AIR score: Appendicitis Inflammatory Response Score, LCRP: Lymphocyte / C-Reactive Protein Ratio, SII: Systemic Immune Inflammation Index, NLR: Neutrophil / Lymphocyte Ratio, PLR: Platelet / Lymphocyte Ratio



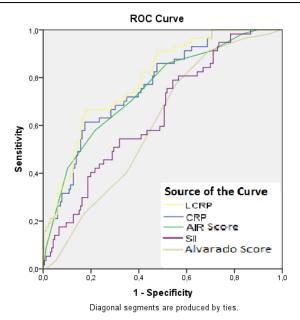


Figure 1. ROC Analysis Showing the Relationship Between AIR and Alvarado Scores, CRP, LCRP and SII Values And Complicated Appendicitis.

DISCUSSION

The aim of this study is to identify parameters that could help distinguish between CA and NCA in patients undergoing surgery in the ED with a diagnosis of acute AA. According to the results obtained from the study, WBC, NLR, PLR, LCRP, and SII were found to be statistically significant in determining the differences between CA and NCA in patients diagnosed with AA in the ED. The specificity of CT was 97%, the sensitivity of the AIR score was 86%, the sensitivity of the Alvarado score was 81%, the specificity of LCRP was 90%, the specificity of SII was 78%, the specificity of NLR was 77%, and the specificity of PLR was 73%. Additionally, while the AIR score was identified as the most sensitive indicator, CT was found to be the most specific screening tool for distinguishing between CA and NCA.

When the literature is reviewed, it is observed that CA cases are more frequently encountered in pediatric, elderly, and male patient groups (7; 8). Similarly, in this study, it was found that the majority of CA cases were male, and the average age was significantly higher compared to the NCA group, which is consistent with the literature. This situation is thought to be related to delayed diagnosis in the elderly patient group due to atypical presentation and less pronounced clinical symptoms, which may lead to more frequent complications.

In a study conducted in 2022 covering 449 patients, it was determined that the CA group had a LOS hospital stay duration 6 times longer (9). Similarly, in this study, it was found that the LOS hospital in CA



cases was longer compared to NCA cases. The reason for this could be the possibility of pathogens to contaminate the surgical area.

There are numerous studies that have demonstrated the relationship between hematologic parameters in patients with AA and underlying inflammatory or infectious processes (8; 10). The elevation of WBC counts in AA cases has thoroughly studied. While an increase in WBC count is commonly encountered in the diagnosis of AA, it has low diagnostic value when used alone. Additionally, other inflammatory conditions may also lead to elevated WBC counts in differential diagnosis (11). In cases without complications such as perforation and periappendicular abscess, the WBC count typically ranges between 10,000 and 18,000 (12). Left shift, often accompanied by leukocytosis, is present in approximately 80-90% of cases. In NCA cases, the WBC count is not expected to be above 18,000 (13). Yang et al. (10) have noted that the increase in leukocytes and the percentage of neutrophils are related to the degree of appendix inflammation. In a study conducted in 2018 with 576 patients, it was found that the WBC value is a useful parameter for distinguishing between CA and NCA patient groups (8). Similarly, in this study, it was found that there was a statistically significant difference in the averages of WBC and neutrophil values in the distinguishing between CA and NCA.

Kahramanca et al. (14) reported that NLR is a valuable parameter for both diagnosing AA and distinguishing between CA and NCA. In a meta-analysis that examined the role of NLR in the differentiation of AA, CA, and NCA in 8914 patients, a threshold value of 8.8 yielded 76.9% sensitivity and an AUC of 0.91 with 100% specificity for CA (15). In this study as well, the mean NLR of CA patients was significantly higher than that of the NCA group. NLR with a cutoff value of 8.2 was found to have 64.9% sensitivity and 77.1% specificity. The increase in WBC and neutrophil values and the decrease in lymphocyte values were found to be significant. It is suggested that evaluating NLR would be more useful in distinguishing between CA and NCA rather than considering only WBC or neutrophil values.

The PLR value, calculated by dividing the platelet count by the lymphocyte count, is reported to be a potential important marker in determining the diagnosis of CA (16). In a study covering 334 pediatric patients diagnosed with AA and undergoing surgery, the group of patients with a higher PLR ratio was found to have a higher likelihood of developing complications, and PLR was found to have a sensitivity of 42% and a specificity of 86% (17). In this study as well, for a PLR value \geq 182, the sensitivity was 42.1% and the specificity was 72.8%. The mean PLR in CA cases was found to be significantly higher than in NCA cases.

CRP, first defined in 1930, was later recognized as an acute-phase protein serving as an early indicator of inflammatory processes (18). In their research conducted in 2021, Fujiwara et al. (19) found that high serum CRP levels were significantly associated with CA. In this study as well, a statistically significant difference in CRP, a valuable acute-phase reactant, was obtained between the CA and NCA groups.

The LCRP value, obtained by dividing the lymphocyte count by the CRP value, and SII are considered parameters that increase in many inflammatory and infectious disease processes and play a role in



determining disease severity and predicting mortality (20). Acar et al. (21), in their study on patients diagnosed with community-acquired pneumonia, found a threshold of 4 for LCRP to predict 28-day mortality, with a sensitivity of 89% and specificity of 73%. They also determined a threshold of >3551 for the SII parameter, which yielded 63.8% sensitivity and 68.1% specificity in predicting mortality and considered them valuable markers in assessing disease severity. In this study, when the cutoff value for LCRP was set at 0.1 in CA cases, it resulted in 78.9% sensitivity and 89.7% specificity. When a cutoff of 2300 or higher was used for SII in distinguishing between CA and NCA cases, it resulted in 40.3% sensitivity and 78.3% specificity. Decreased LCRP and increased SII were found meaningful. There is no known study in the literature that has examined this aspect of the topic. Therefore, further research to support the findings would be beneficial.

During the COVID-19 pandemic, it has been reported that there is a higher rate of CA due to delays in the time between the onset of symptoms and presentation to the ED (22). Wang et al. (23) in their research reported that patients could delay seeking medical attention for COVID-19 due to the fear of transmission, and as a result, there could be an increase in the number of CA cases. However, in this study, there was a slight increase in the number of CA cases during the pandemic period, but no statistically significant difference was observed. This may be attributed to the perception of abdominal pain as a serious condition in our country and early presentation to the ED.

The diagnosis of AA is subjective as it is associated with multiple parameters, and clinical scoring systems can make the diagnostic process more objective. AIR and Alvarado are among these scoring systems (7). In a study conducted with 578 patients in 2018, the AIR and Alvarado scoring systems were compared for distinguishing between CA and NCA, and the AIR score was found to be more significant in predicting CA and appendix diameter (24). In a retrospective analysis of two cohorts from referral centers in Switzerland and Germany, it was stated that the highest Alvarado and AIR scores with >90% sensitivity for detecting CA were \geq 5 and \geq 3, respectively (25). In this study, when the total scores were \geq 6, the AIR score had a sensitivity of 85.9% and specificity of 47.9%, while the Alvarado score had a sensitivity of 80.6% and specificity of 44.5%. Additionally, both AIR and Alvarado scoring systems were found to significantly distinguish between CA and NCA cases.

It has been reported that CT, one of the imaging methods used for the diagnosis of AA, has a sensitivity of 98% and a specificity of 98% (24). Tsuboi et al. (26) found a sensitivity of 95% and a specificity of 97% for CT in detecting perforated appendicitis. In this study, the sensitivity of CT in detecting perforated appendicitis was found to be 31%, while the specificity was 97%. This is attributed to radiologists interpreting CT scans focusing more on the diagnosis of AA rather than complications.

Limitations

The study is designed retrospectively, and has some limitations. Since it's a single-center study, further research is needed to apply the results to the general population. Information about the time interval between

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patients being diagnosed with acute appendicitis (AA) and their presentation to the emergency department, followed by surgery, is not available. During this elapsed time, the possibility of complications should be considered. Therefore, it cannot be predicted at which stage of inflammation the detection occurred.

CONCLUSION

Many factors influence the differentiation between CA and NCA. Inflammatory markers are important parameters in distinguishing between CA and NCA. This study has shown that values such as LCRP, SII, NLR, and PLR may be useful markers in differentiating CA from NCA. Additionally, it has been concluded that the diagnostic process can be strengthened by using AIR and Alvarado scores and CT in addition to these markers.

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This study represents the transformed version of researcher's thesis.

Authorship contributions

All authors contributed equally to the writing of this paper.

Data availibity statement

Data available on request.

Declaration of competing interest

All authors declare no potential conflicts of interest in this study.

Ethics

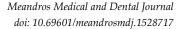
The ethics committee approval for the study was obtained Mugla Sitki Kocman University Clinical Research Ethics Committee (30/11/2021).

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