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The Diagnostic Value of Systemic Inflammatory Markers in Acute Appendicitis

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Abstract

Background: Early diagnosis of Acute Appendicitis (AA)can be challenging because it relies on the patient's signs and symptoms, which often mimic other abdominal pathologies.

Objectives: The study aimed to assess the importance of systemic inflammatory response parameters in contrast with the Alvarado scoring system.

Methods: This cross-sectional study was conducted on 300 patients diagnosed with AA who underwent an appendectomy. Demographic data, medical history, physical examination findings, Alvarado score, complete blood count (CBC), and pathology results of the appendix were documented.

Results: In a study involving 300 patients, 53.7% were male. The mean age of the patients was 37.24 ± 14.79 years. The number of females with a negative appendectomy was 2.45 times higher than that of males. Most patients with appendicitis were male, while most with RLH (reactive lymphoid hyperplasia) and normal appendices were female. For diagnosing AA, the following thresholds were established: NLR (neutrophil-to-lymphocyte ratio) >2.93 with 90.08% sensitivity and 76.32% specificity, PLR (platelet-to-lymphocyte ratio) >117.8 with 70.61% sensitivity and 65.79% specificity. The sensitivity of the Alvarado scoring system was 79.8%, and its specificity was 81.6% at >6 cut-off value.

Conclusion: NLR, PLR, CRP (C-reactive protein), SII (systemic immune inflammation index), and Alvarado scoring showed great potential in diagnosing appendicitis with acceptable sensitivity and specificity.

Keywords: Acute Appendicitis, Appendectomy, Alvarado scoring system, Neutrophil-to-Lymphocyte Ratio, Platelet-to-Lymphocyte Ratio.

1. Background

Acute appendicitis (AA) is among the most common causes of abdominal pain requiring emergency surgery (1). The lifetime incidence of AA is about 8.6% for men and 6.7% for women, and the rate of perforation is up to 20% (2,3). Early diagnosis of AA can be quite challenging due to relying on the patient's signs and symptoms that often mimic other abdominal pathologies. However, the perforation rate increases over time, increasing the death rate. The definitive diagnosis of appendicitis requires pathological investigations. Imaging methods increase diagnostic accuracy but may not be readily available in all areas. So, various techniques, such as scoring systems, are used to identify vague cases and decrease the rate of negative appendectomy (4,5). The Alvarado scoring system is commonly used in Western

countries, but very low sensitivity and specificity have been reported (6). A retrospective study has shown that it is insufficient for the accurate diagnosis of AA (7).

There is no specific laboratory parameter to diagnose AA. White blood cells (WBC) and C-reactive protein (CRP) have been commonly used to indicate AA. Among these parameters, CRP had the highest sensitivity and the lowest specificity due to increased levels in all acute inflammatory processes (8,9). Recently, the predictive value of hematological indexes, such as the Neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) in diagnosing AA, has been investigated (10). In a recent systematic review, Hajibandeh et al. reported that the NLR demonstrated high performance in diagnosing AA (11). Complete blood count is inexpensive and easy to interpret. It has valuable information about cell types and morphological parameters. In addition, the combination of these parameters is helpful in the diagnosis and progression of many diseases (12).

2. Objectives

The study aimed to assess the importance of systemic inflammatory response parameters in contrast with the Alvarado scoring system. Evaluating parameters such as NLR, PLR, CRP level, and neutrophil percentage may prevent unnecessary appendectomy.

3. Methods

3.1. study design and setting

This cross-sectional study was conducted on 300 patients diagnosed with AA in the emergency department who underwent an appendectomy in Mashhad, Iran, in 2023. Patients were divided into four groups according to their surgical findings and histopathological examination. Group 1 included patients without appendicitis, Group 2 included patients with uncomplicated acute appendicitis, and Group 3 included patients with complicated appendicitis, which is defined as perforated or gangrenous appendicitis, and cases with abscess or generalized peritonitis. Group 4 consisted of patients with reactive lymphoid hyperplasia (RLH). RLH is a cellular response developing against viral infection anywhere in the body. It also increases the appendix's outer diameter to 6 cm or more in ultrasonography. Such a situation can be mistaken for acute appendicitis, leading to a high rate of unnecessary appendectomies (13). This research was approved by the Ethics Committee of Mashhad University of Medical Sciences (IR.MUMS.REC.1401.105).

3.2. Participants

All patients older than 18 years were included. Pregnant patients, patients who underwent appendicectomy during surgery for other indications, and those with a known history of hematologic malignancy or any viral, bacterial, or parasitic infections were excluded from this study because of the potential effect of these conditions on hemogram values.

3.3. Data gathering

Demographic data of the patients, complaints at the time of admission, examination findings, results of imaging tests, lymphocyte count, neutrophil percentage, CRP level, NLR, PLR, SII (systemic immune inflammation index), and appendix pathology were recorded. SII is calculated by (NxP)/L, where N, P, and L represent neutrophil, platelet, and lymphocyte count respectively (14). Patient's preoperative diagnoses were established based on their clinical history, physical examination, laboratory tests such as a hemogram, CRP level, ultrasonography (USG) findings, and the results of advanced imaging modalities such as computed tomography (CT) in patients in whom a diagnosis could not be achieved using a USG. We used the Alvarado scoring system in the physical examination. Those with a score of 7-8 were considered probable AA, and those with a 9-10 were regarded as definite AA.

3.4. Statistical analysis

We analyzed two comparisons in this study: appendicitis versus no appendicitis and uncomplicated versus complicated appendicitis. Data were analyzed using SPSS v.25. Categorical variables (sex and age) were expressed as numbers of patients (n) and percentages (%). Numerical data were expressed as mean, standard deviation, minimum, maximum, and median values. ANOVA and Student's t-test were used in data analysis. Intergroup comparisons were conducted using Tukey's test. A P-value of <0.05 was considered statistically significant. The diagnostic values of NLR, PLR, SII, CRP, and Alvarado scoring system were determined by receiver operating characteristic (ROC) analysis. Cut-off values were calculated for each biomarker using the ROC curve and the Youden index. The sensitivity, specificity, and the likelihood ratio were also calculated.

4. Results

Among the 300 patients included in the study, 139 (46.3%) were female and 161 (53.7%) were male. The age range of the patients was between 18 and 79 years, with an average of 37.24 ± 14.79 years. Of the 300 patients, 38 (12.67%) patients were diagnosed with a normal appendix, 185 (61.67%) were diagnosed with uncomplicated appendicitis, 50 (16.67%) patients were diagnosed with complicated appendicitis, and 27 (9.00%) patients were diagnosed with RLH. Age distribution according to pathology results is presented in Table 1. No significant difference was found between these groups based on age (P-Value = 0.086). The distribution of sex based on pathology results is shown in Table 1. There is a significant difference between the two groups based on pathology results (P-Value=0.001). The number of females with a negative appendectomy was 2.45 times higher than that of males with a negative appendectomy. Most of the patients with both complicated and uncomplicated appendicitis were male, while most of the patients with RLH were female. As depicted in Table 1, the mean of inflammatory markers and Alvarado score were calculated and compared between the groups. The highest and lowest mean was in Group 3 (complicated appendicitis) and Group 1 (normal appendix), respectively, which was a statistically significant difference. The mean of these markers in Group 4 (RLH) was higher than Group 1 and lower than Group 2 (uncomplicated appendicitis).

Table 1. Sociodemographic and clinical profiles of the study population according to pathology results

Variable		G1 (N=38)	G2 (N=185)	G3 (N=50)	G4 (N=27)	Test Statistic (P-Value)
Age	Mean (SD) Range	36.47 (17.12) 18-75	36.97 (13.83) 18-78	41.32 (17.20) 18-79	32.63 (11.50) 19-68	P = 0.086* F = 2.22
Gender	Male female	11 (6.8%) 27 (19.4%)	106 (65.8%) 79 (56.8%)	33 (20.5%) 17 (12.2%)	11 (6.8%) 16 (11.5%)	P = 0.001** Likelihood Ratio = 15.34
NLR	Mean SD	2.97 3.81	7.49 4.94	11.95 10.27	5.73 3.85	F = 17.31, P = 0.0001* P^{23}, P^{12}, P^{34}, P^{13}<0.05
PLR	Mean SD	121.46 76.70	170.74 101.15	230.21 116.83	159.98 75.87	F = 9.13, P = 0.0001* P^{23}, P^{12}, P^{34}, P^{13}<0.05
CRP (mg/l)	Mean SD	20.77 43.35	34.11 34.72	91.16 104.40	23.91 21.14	F = 11.68, P = 0.0001* P^{23}, P^{34}, P^{13} <0.05
SII	Mean SD	719.69 885.60	1804.85 1313.62	2800.37 2101.96	1445.67 861.91	F = 16.57, P = 0.0001* P^{23}, P^{12}, P^{34}, P^{13}<0.05
Alvarado	Mean SD	5.08 1.79	7.59 1.67	7.78 1.59	7.52 1.70	F = 25.76, P = 0.0001* P^{12}, P^{13}, P^{14}<0.05

Group 1 (G1): normal appendix; Group 2 (G2): uncomplicated appendicitis; Group 3 (G3): complicated appendicitis; Group 4 (G4): reactive lymphoid hyperplasia; SD: standard deviation

*A one-way ANOVA test was applied

**Chi-squared test

Alvarado score was calculated for each patient. Accordingly, the sensitivity and specificity were calculated for diagnosing AA and distinguishing uncomplicated and complicated appendicitis. The sensitivity of the Alvarado scoring system was 79.8%, and its specificity was 81.6% at >6 cut-off value. We found that the score of 9-10 had 44% sensitivity and 67% specificity in distinguishing uncomplicated and complicated appendicitis. The study computed and compared NLR, PLR, CRP, and SII values across different groups. Table 2 in the document presents AUR (area under the receiver operating characteristic curves), sensitivity, and specificity. For diagnosing AA, the following thresholds were established: NLR >2.93 with 90.08% sensitivity and 76.32% specificity, PLR >117.8 with 70.61% sensitivity and 65.79% specificity, CRP level >16.97 mg/L with 73% sensitivity and 75% specificity, and SII >746.31 with 86.3% sensitivity and 78.9% specificity.

Table 2.Comparisons of inflammatory markers in identifying the patient with AA and distinguishing uncomplicated and complicated appendicitis

Variable	AUC	SE	Cut off	Sensitivity (%)	Specificity (%)
Uncomplicated appendicitis					
NLR	**0.88**	**0.038**	**2.93**	**90.08**	**76.32**
PLR	**0.72**	**0.041**	**117.8**	**70.61**	**65.79**
CRP	**0.76**	**0.055**	**16.97**	**73**	**75**
SII	**0.87**	**0.38**	**746.31**	**86.3**	**78.9**
Complicated appendicitis					
NLR	**0.68**	**0.040**	**8.48**	**62**	**69.73**
PLR	**0.67**	**0.045**	**221.3**	**52**	**78.92**
CRP	**0.71**	**0.050**	**33.5**	**78.1**	**56.1**
SII	**0.66**	**0.043**	**2386.08**	**50**	**80**

AUC: Area under the receiver operating characteristic curve; SE: Standard Error; CRP: C-Reactive Protein; NLR: Neutrophil-to-Lymphocyte ratio; PLR: Platelet-to-Lymphocyte ratio; SII: Systemic Immune Inflammatory Index.

Figures 1 and 2 show the AUC, sensitivity, and specificity of NLR, PLR, CRP, and SII in predicting the diagnosis of AA. According to the ROC analyses, a PLR greater than 221.3 had a sensitivity of 52% and a specificity of 78.92%. Similarly, a CRP level greater than 33.5 mg/L had a sensitivity of 78.1% and a specificity of 56.1%, and an SII greater than 2386.08 had a sensitivity of 50% and a specificity of 80% for distinguishing between uncomplicated and complicated appendicitis.

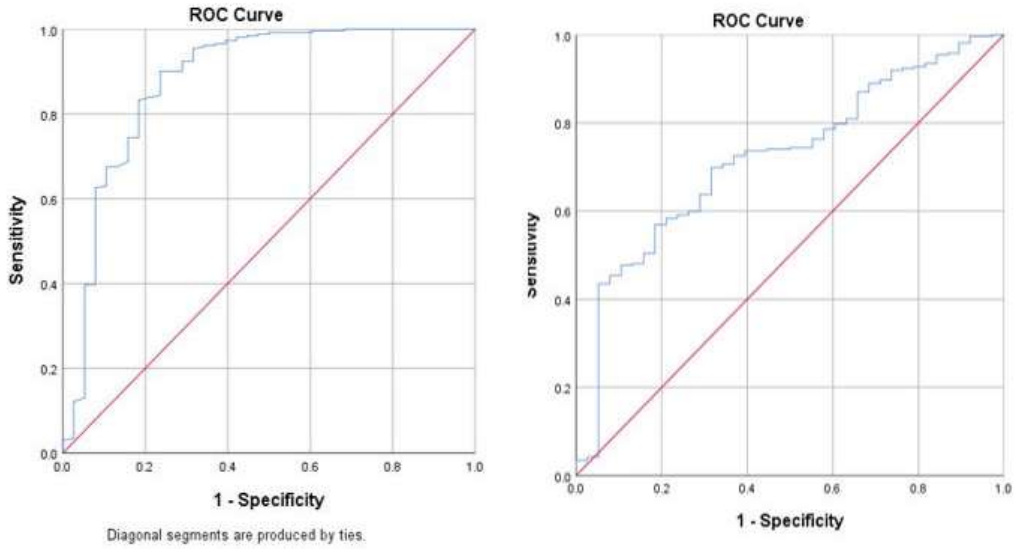

Figure 1. AUC of NLR (Right) and PLR (Left) in predicting the diagnosis of AA.

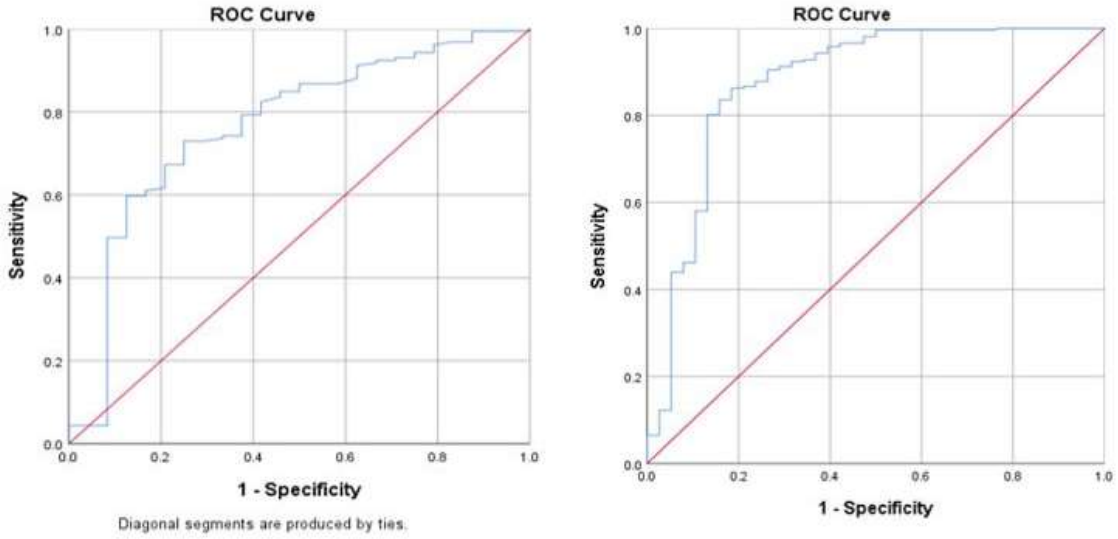

Figure 2. AUC of CRP (Right) and SII (Left) in predicting the diagnosis of AA.

5. Discussion

According to the results of this study, NLR, PLR, CRP, SII, and Alvarado scoring showed great potential in diagnosing appendicitis with acceptable sensitivity and specificity. They also could help distinguish uncomplicated and complicated appendicitis. Diagnosis of AA can be challenging, and choosing between observation or early operation represents a serious dilemma for a surgeon. Therefore, surgeons still need an accurate and inexpensive diagnostic test to diagnose AA (15). Standard imaging, such as ultrasound and CT scan, can be helpful, but diagnostic work-ups for AA remain challenging. Hospitals, particularly in rural areas, may not be equipped with such imaging facilities (16,17). This study aimed to assess the use of NLR, PLR, CRP, SII, and Alvarado scores to facilitate accurate diagnosis of AA and differentiate uncomplicated from complicated AA.

The incidence of AA in our study was higher in the third decade of life. In addition, there was no significant difference in age between the groups. The mean age of group 3 (complicated appendicitis) was higher than that of the other groups, but it was not statistically significant. Based on the histopathological examination of the patient's appendix, there was a statistically significant difference in gender proportion between the groups. The majority of patients in the uncomplicated and complicated groups were male.

In contrast, most of the patients in both normal appendix and RLH groups were female, and the rate of negative appendectomy was higher in females. According to previous studies, male patients tend to have a higher threshold of pain and present late to the hospital compared to females (16-18). Thus, they tend toward complicated appendicitis. On the other hand, females may have higher rates of negative appendectomy due to gynecological conditions mimicking appendicitis. As a result, diagnosis of appendicitis is more challenging in females, and it needs better clinical examination. Inflammatory markers such as NLR and SII may help improve diagnostic accuracy.

Scoring systems such as Alvarado provide an accurate diagnosis of AA in the fastest and cheapest status. In contrast to our findings, Tabibzadeh Dezfuli et al. have shown that Alvarado's scoring has low sensitivity (53.95%) and specificity (70.18%) (4). The

results of our study showed that sensitivity and specificity in Alvarado's scoring were 79.8% and 81.6%, respectively. Taking history and clinical examinations is essential in diagnosing AA, but designing new scoring systems, especially with new inflammatory markers such as NLR and SII, could improve diagnostic accuracy.

Our study has shown that serum markers such as NLR, PLR, SII, and CRP could be used in diagnosing AA with a statistically significant difference. Among these markers, NLR and SII had the highest sensitivity and specificity in diagnosing AA. Based on the recent metanalysis by Hajibande et al. NLR>4.8 independently predicts AA with a sensitivity of 88.89% and specificity of 90.91%, and NLR>8.8 predicts complicated acute appendicitis with a sensitivity of 76.92% and specificity of 100% (11). Our cut-off value for NLR in diagnosing AA was lower than 4.8. However, our cut-off value of 6.96 remains statically significant with a P-value of <0.05. According to the results, NLR has a great potential to predict appendicitis and distinguish between complicated and uncomplicated appendicitis. It could be helpful to prioritize the cases waiting for emergency appendectomy in busy General surgical settings. Another retrospective study by Fatma Özcan Siki et al., which examined 1265 patients, aimed at determining the diagnostic role of SII and SIRI (systemic inflammation response index) in children who underwent appendectomy and concluded that high SII and SIRI value support the diagnosis of AA at a rate of 95% (12). It showed that a combination of these inflammatory markers may improve the accuracy of diagnosing AA. Further studies are required to assess the combination of these markers in predicting both the diagnosis and severity of AA.

It is essential to differentiate between complicated and uncomplicated appendicitis, as recent studies have reported that conservative therapy can be a treatment option in patients with uncomplicated appendicitis (19). In our study, 185 (61.67%) patients had uncomplicated appendicitis, and 50 (16.67%) had complicated appendicitis. The complicated appendicitis group showed a significantly higher mean compared to other groups. This means that these markers increase as the inflammation progresses. Thus, they can be used to determine the severity of acute appendicitis. In a retrospective study of 212 adult patients with acute appendicitis, Secil Yesilalioglu et al. categorized the patients into two groups (Group I, uncomplicated acute appendicitis; Group II, complicated appendicitis) according to their surgical findings and histopathological examination. The study indicated that NLR, MER, and CRP could not predict complicated appendicitis. However, a PLR value ≥133.73 was found to be the cut-off with 60% sensitivity and 58.4% specificity in identifying complicated appendicitis (20). In our study, a CRP level greater than 33.5 mg/L had the highest sensitivity (78.1%) in identifying complex appendicitis among these inflammatory markers, and a PLR greater than 221.3 had a sensitivity of 52% and a specificity of 78.92%.

As far as we know, few studies investigate combinations of these marker values by comparing uncomplicated and complicated appendicitis and other conditions mimicking appendicitis, such as RLH. Most previous studies were retrospective, and the patients suspected of appendicitis were omitted.

6. Conclusion

According to the results of this study, NLR, PLR, CRP, SII, and Alvarado scoring showed great potential in diagnosing appendicitis with acceptable sensitivity and specificity. They also could help distinguish uncomplicated and complicated appendicitis. NLR and SII had the highest sensitivity in diagnosing appendicitis, and CRP had the highest sensitivity in distinguishing uncomplicated and complicated appendicitis.

These markers are simple measurements, low cost, and available tools to predict both diagnosis and severity of appendicitis with acceptable accuracy, particularly in resource-limited settings. They can provide valuable information to clinicians when combined with scoring systems and imaging studies, potentially leading to more accurate diagnosis and better management of acute appendicitis.

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Availability of data and materials: All data generated or analysed during this study are included in this published article.

Conflicts of interests: All authors declared that they have no competing interests.

Consent for publication: Written informed consent was obtained from all participants included in the study.

Ethics approval and consent to participate: The present study has a code of ethics with an ID number (IR.MUMS.REC.1401.105). The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

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Author contributions: Conceptualization: TZ and MRT - Methodology and Formal analysis: YR and MM- Investigation, Data curation: MRT, TZ, YA and, AD - Writing- Original draft: MRT- Writing - review & editing: TZ.

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