




Osmangazi Journal of Medicine

e-ISSN: 2587-1579

Could Simple Laboratory Parameters Calculated from Blood Tests Be Predictive of Complicated Acute Appendicitis in The Pediatric Emergency Department?

Çocuk Acilde Hemogramdan Hesaplanan Basit Laboratuvar Parametreleri, Komplike Akut Apandisitinin Öngörülmesinde Kullanılabilir mi?

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Received 08.01.2026

Accepted : 19.02.2026

Abstract: We aimed to determine the importance of systemic immune-inflammation index (SII), CRP (C-Reactive Protein), neutrophil-lymphocyte ratio (NLR), plateletcrit (PCT), platelet-lymphocyte ratio (PLR) in the diagnosis of complicated acute appendicitis in children. The study included patients who presented to the pediatric emergency department and underwent surgery with a diagnosis of acute appendicitis. After surgery, patients were divided into two groups: uncomplicated appendicitis and complicated appendicitis based on histopathologic and radiologic findings. The groups were compared based on age, sex, systemic immune-inflammation index (SII), neutrophil-lymphocyte ratio (NLR), plateletcrit (PCT), platelet-lymphocyte ratio (PLR), and C-reactive protein (CRP). Total of 287 patients were included in our study. While 197 patients were in the uncomplicated acute appendicitis (UA) group, 90 patients were included in the complicated acute appendicitis (CA) group. When the two groups were compared, CRP (p=0.001), NLR (p=0.001) and PLR (p=0.01) were significantly higher in the CA group. No difference was found in gender, white blood cell count, neutrophil count, SII and PCT. Computed tomography was performed at a higher rate in the CA group. CRP, neutrophil/lymphocyte ratio, and platelet/lymphocyte ratio are open laboratory parameters that can assist in differentiating between complicated and uncomplicated appendicitis in children. These universal parameters may inform the treatment plan and decision to operate on a challenging-to-diagnose population.

Keywords: Systemic immune-inflammation index, acute appendicitis, pediatrics, CRP

Ethics Committee Approval: The study was approved by the Ethics Committee of Mardin Artuklu University (decision date:19.09.2023, number:2023/9-1).

Informed Consent: As this was a retrospective study based on anonymized patient data, informed consent was not required according to institutional ethical guidelines.

Authorship Contributions: EG, ÖO: Data curation, Investigation. ÖO, SB: Data curation, Investigation. EG, ÖO: Methodology. ÖO,SB: Formal Analysis. EG: Writing – original draft. ÖO, SB Project administration, Validation. EG: Supervision

Copyright Transfer Form: Copyright Transfer Form was signed by all authors.

Peer-review: Internally peer-reviewed.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

Acknowledgements: We extend our gratitude to all healthcare professionals with whom we have worked and who dedicate their lives to patients.

Özet: Bu çalışmada, sistemik immün-inflamasyon indeksi, C-reaktif protein, nötrofil-lenfosit oranı, plateletkrit ve trombosit-lenfosit oranının çocuklarda komplike akut apandisit tanısındaki önemini belirlemeyi amaçladık. Çalışmaya, çocuk acil servise başvuran ve akut apandisit tanısıyla cerrahi tedavi uygulanan hastalar dahil edildi. Ameliyat sonrası, hastalar histopatolojik ve radyolojik bulgulara göre iki gruba ayrıldı: Komplike olmayan apandisit ve komplike apandisit. Gruplar yaş, cinsiyet, sistemik immün-inflamasyon indeksi, nötrofil-lenfosit oranı, plateletkrit, trombosit-lenfosit oranı (PLR) ve C-reaktif protein düzeyleri açısından karşılaştırıldı. Toplamda 287 hasta çalışmaya alındı; 197'si komplike olmayan apandisit grubunda, 90'ı ise komplike apandisit grubunda yer aldı. Komplike apandisit grubunda CRP (p=0,001), NLR (p=0,001) ve PLR (p=0,01) düzeyleri anlamlı olarak daha yüksek bulundu. Cinsiyet, lökosit sayısı, nötrofil sayısı, SII ve PCT açısından gruplar arasında anlamlı bir fark saptanmadı. Ayrıca, komplike apandisit grubunda ortalama yaş ve bilgisayarlı tomografi çekilme oranının daha yüksek olduğu gözlemlendi. CRP, nötrofil/lenfosit oranı ve trombosit/lenfosit oranı, çocuklarda komplike ve komplike olmayan apandisit ayırt etmede yardımcı olabilecek laboratuvar parametreleridir. Bu evrensel parametreler, zor tanı konulan hasta grubunda tedavi planlamasına ve cerrahi karar sürecine katkı sağlayabilir.

Anahtar Kelimeler: Sistemik immün-inflamasyon indeksi, akut apandisit, pediatri, CRP

How to cite/ Atf için: Gungor E , Orhan O,Bayram S, Could Simple Laboratory Parameters Calculated from Blood Tests Be Predictive of Complicated Acute Appendicitis in The Pediatric Emergency Department?, Osmangazi Journal of Medicine, 2026;48(3):471-476

1. Introduction

Acute appendicitis (AA) is one of the most common surgical emergencies in the world, especially children (1). In childhood, especially in young infants and children, it is very difficult to make an accurate diagnosis due to differential diagnoses such as acute testicular torsion, ovarian torsion or even acute gastroenteritis. The underlying cause remains elusive, despite limited progress in recent decades. Achieving a definitive preoperative diagnosis remains challenging, given that appendicitis must be considered in any patient with acute abdominal symptoms. Although laboratory parameters and imaging modalities aid in the diagnosis, physical examination and clinical evaluation are the most important guides. Although AA patients are divided into complicated and uncomplicated, the most difficult dilemma for many patients is still an uncertain diagnosis and a difficult diagnostic process (1, 2). Especially in patients who are uncertain about diagnosis, clinical scoring systems together with clinical findings and imaging modalities can distinguish between uncomplicated and complicated appendicitis and eliminate the possibility of complicated appendicitis (3). However, making a differential diagnosis in children is quite difficult. In contrast to adults, USG is the first imaging modality in the differential diagnosis of AA in children and adolescents. (4). However, it is not always easy to diagnose complicated and uncomplicated AA. Diagnosis of complicated AA is usually made with computed tomography (CT). CT is generally readily available at pediatric emergency departments, but it involves exposure to radiation and may require the use of an intravenous contrast agent or sedation(4). Complicated acute appendicitis in children carries the risk of rapid intrabdominal sepsis. Identification of high-risk patient groups and rapid decision-making for surgery are very important (5). Therefore, more noninvasive methods need to be developed to help differentiate for complicated AA. In this context, the most commonly utilized diagnostic tools are C-reactive protein (CRP) level, white blood cell (WBC) count, neutrophil-to-lymphocyte ratio (NLR), serum sodium level, and platelet-to-lymphocyte ratio (PLR) , plateletcrit (PCT) and Systemic Immune-Inflammation Index(SII)(6, 7). SII is an index used to assess inflammation based on neutrophil, lymphocyte, and platelet counts. It more objectively reflects changes in the level of inflammation in the body(7).The calculation formula is as follows: $SII = \text{platelet count} \times \text{neutrophil count} / \text{lymphocyte count}$ (7, 8).

Our study aimed to evaluate the diagnostic value of CRP, WBC, NLR, PLT, PLR, PCT and SII levels for prediction of complicated AA at pediatric population.

2. Materials and Methods

Patients who presented to Artuklu University, Mardin Training and Research Hospital the Pediatric Emergency Department between 1/06/2023 and 31/05/2024 and were operated with a diagnosis of acute appendicitis were included in our study. This study was approved by the Ethics Committee of the Mardin Artuklu University (2023/9-1) and was conducted in accordance with the Declaration of Helsinki. The study was retrospective in nature and was conducted at a single center. Histopathological confirmed AA diagnosis was considered the gold standard. Patients without pathology confirmation even if operated were excluded from the study. The medical records of the patients were retrospectively reviewed in terms of two subgroups as non-complicated appendicitis and complicated appendicitis according to surgical findings and final pathology reports. Perforated appendicitis, acute phlegmonous appendicitis, acute gangrenous appendicitis, and abscess were considered complicated appendicitis, whereas patients diagnosed with AA were considered uncomplicated appendicitis and computed tomography examinations were interpreted and reported by radiologists in routine clinical practice. The groups were compared for age, gender, WBC, neutrophil, lymphocyte, and platelet count, NLR, PLR, PTC, SII, CRP levels and imaging modalities at the time of admission were considered. NLR, PLR, PTC and SII were calculated based on routine blood examination results at admission. $SII = \text{platelets} \times \text{neutrophils} / \text{lymphocytes}$, $LMR = \text{lymphocytes} / \text{monocytes}$ and $PLR = \text{platelets} / \text{lymphocytes}$.

The analysis of the data was made with descriptive statistical methods. Normality tests including Kolmogorov-Smirnov and Shapiro-Wilk tests, was preferred in determining the data distribution. Normally distributed data were expressed as mean±standard deviation, and not normally distributed data were expressed as median (interquartile range). Categorical variables were specified as percentage (%) and number (n). While comparing the numerical data between the groups, the appropriate one among the Mann-Whitney U test, Independent Samples T test, Kruskal-Wallis

and ANOVA tests was selected and used. Chi-square and Fisher's test were used for categorical variables. The receiver operating characteristic (ROC) curve analysis was used to determine the sensitivity and specificity values. Statistical Package for Social Sciences (SPSS) Windows software (ver. 26; IBM SPSS, Chicago, USA) was used for all statistical analyses. P value less than 0.05 was considered as statistically significant.

3. Results

Total of 287 patients were included in our study. While 197 patients were in the uncomplicated AA

group, 90 patients were included in the complicated AA group. Comparative analysis was conducted between patients with uncomplicated appendicitis (n=197) and those with complicated appendicitis (n=90). The gender distribution was 33.5% and 42.2% female, respectively, with no statistically significant difference (p=0.155). The mean age was 11.7 ± 3.2 years in the uncomplicated appendicitis group and 10.7 ± 3.7 years in the complicated appendicitis group. There was no statistically significant difference in WBC (p=0.33), neutrophil (p=0.856), or platelet counts (p=0.325) between the two groups (Table 1).

Table 1. Demographic characteristics and laboratory findings Between Complicated and Uncomplicated Appendicitis

	Uncomplicate Appendicitis n=197	Complicated Appendicitis n=90	P
Gender / Female	66(33.5)	38(42.2)	0.155
Age	11.7±3,2	10.7±3,7	0.024
WBC (10 ³ / μL)	13.8 (7.5)	15.3(8)	0.33
Neutrophil (10 ³ / μL)	11(7.5)	12.6(2.2)	0.856
Lymphocyte (10 ³ / μL)	1.8(1.2)	1.6(1.1)	0.031
Platelet (10 ³ / μL)	294.7±81.4	308.5±120.7	0.325
Hemoglobin	13.2(1.6)	12.7(2.2)	0.107
PTC	0.29±0.06	0.30±0.09	0.186
CRP (mg/L)	28.8±19.8	128.4±100.4	0.0001
NLR	7.6±6.2	10.5±6.7	0.0001
PLR	192.6±122.4	235.5±146.1	0.01
SII	2637.7(2370.1)	3201.4(2828.6)	0.190

Computed Tomography

24/197 (%12.1)

30/90(33.3)

0.001

Abbreviations: WBC, white blood cell; PTC, NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio, SII, systemic immune-inflammation index. Note: Parameters were expressed as n (%), mean±standard deviation, and median (interquartile range).

However, lymphocyte counts were found to be lower in the complicated appendicitis group (p=0.031). The levels of C-reactive protein (CRP) (p=0.0001), neutrophil-to-lymphocyte ratio (NLR) (p=0.0001) and platelet-to-lymphocyte ratio (PLR) (p=0.01) were found to be statistically significantly higher in patients with complicated AA. There was no difference in the systemic immune-inflammation index (SII) (p=0.190). The computed tomography (CT) scan was performed in 12.1% (24/197) of the uncomplicated appendicitis group and 33.3% (30/90) of the complicated appendicitis group. This difference was statistically significant (p=0.001).

and Table 2. The NLR achieved an AUC value of 0.653 (95% CI: 0.587-0.720) with an optimal cut-off value of 6.46. The NLR demonstrated a sensitivity of 73.3%, specificity of 54.3%, and a significant p-value of 0.001. CRP exhibited an AUC of 0.843 (95% CI: 0.760-0.896) with a cut-off value of 28.3 mg/L, showing 81.1% sensitivity, 72.1% specificity, and a p-value of 0.001. The AUC for PLR was 0.616 (95% CI: 0.546-0.686) with a cut-off value of 145.8, yielding a sensitivity of 75.1% and a specificity of 45.2%. Notably, these results suggest that CRP has superior diagnostic accuracy compared to NLR and PLR.

The diagnostic performance of NLR, CRP, and PLR was evaluated with the findings presented in figure 1

Table 2. Predictive power of the NLR, CRP and PLR Between Complicated and Uncomplicated Appendicitis

	Auc (95% Ci)	Cut-Off Value	P	Sensitivity (%)	Specificity (%)
NLR	0.653(0.587-0.720)	6.46	0.001	73.3	54.3
CRP (mg/L)	0.843(0.760-0.896)	28.3	0.001	81.1	72.1
PLR	0.616(0.546-0.686)	145.8	0.002	75.1	45.2

4. Discussion

Our study showed that CRP, NLR and PLR values were significantly increased in patients with complicated appendicitis compared to patients with uncomplicated appendicitis. Our study has shown that CRP, NLR, and PLR could be used to distinguish uncomplicated from complicated acute appendicitis with a statistically significant difference. Therefore, in this challenging patient group, where physical examination is unreliable, clinicians need to rely more on laboratory results and imaging. To avoid misdiagnosis and mismanagement, it is crucial to understand which signs, symptoms, imaging and laboratory tests are most reliable and cost-effective, both individually and in combination.

Differentiating complicated from uncomplicated acute appendicitis is more difficult in children (9). The difficulty in performing an accurate abdominal examination of the child is compounded by the fact that the symptoms of acute appendicitis in childhood are non-specific and can be confused with those of numerous diseases that are specific to children (10). In this context, differentiating between complicated and uncomplicated appendicitis is a challenging task. Our objective was to demonstrate the contribution of simple, rapid, and accessible laboratory parameters to the diagnosis. In line with the findings of our study, we believe that CRP, NLR, and PLR can assist clinicians in diagnosing complicated AA.

Acute appendicitis is one of the most common pathologies in children with abdominal pain. (11). Although imaging modalities are becoming more widespread, USG is still the preferred method to protect children from the effects of ionizing radiation. The main limitation of USG is its practitioner-dependency and the difficulty of always having a radiologist with appropriate experience in USG and CT interpretation available. In addition, the rate of correct diagnosis decreases with age and the rate of complicated AA increases. (10). In infants, there is a greater necessity for laboratory parameters that can corroborate the diagnostic scoring systems. (12). In this context, a complete blood count and CRP are typically obtained from nearly all patients with AA. The WBC, CRP, NLR, PLR, PTC and SII values that can be obtained from routine examinations without any additional procedure in children can serve as a basis for guidance for the clinician and may facilitate the decision to perform emergency surgery in this patient group. (7). There is a limited number of studies examining these parameters in children, and

our study contributes to this area of research. In the pediatric population, AA is more likely to present with complications, particularly as age decreases, with an increased incidence of complicated AA observed in children under five years of age (10). In our study, although the age of patients in the complicated group was lower, it should not be overlooked that the likelihood of misdiagnosis and missed acute appendicitis (AA) increases as age decreases. Furthermore, it should be noted that the risk of complicated appendicitis in younger children is five times higher. (13).

We also explored the potential value of commonly utilized biomarkers, such as white blood cell count (WBC) and C-reactive protein (CRP). WBC and CRP are among the primary parameters considered in cases of inflammation. While WBC tends to rise earlier within the first 24 hours of acute appendicitis (AA), CRP becomes more effective in indicating ongoing inflammation after the 24-hour mark. (14). A comprehensive meta-analysis has indicated that $WBC > 10,000/\mu L$ and $CRP > 50 \text{ mg/dL}$ are valuable markers for acute appendicitis (AA). However, their diagnostic utility in distinguishing complicated cases appears to be limited, as setting a definitive threshold for such cases remains challenging. (15). In fact, in our study, the WBC count was above $10,000/\mu L$ in both groups, and no significant difference was found between them. While elevated WBC levels are seen in life-threatening conditions such as infection, sepsis, and acute appendicitis (AA), its ability to differentiate between complicated and uncomplicated AA remains limited. The WBC level is useful for clinical decision-making tools, such as the pediatric appendicitis score and the Alvarado score, which assist in the differential diagnosis of AA from other conditions.

CRP, with its early rise in inflammation, widespread use, cost-effectiveness, and utility in differentiating non-specific abdominal pain in children, is a valuable marker for differential diagnosis. (16). Although it significantly increases in cases of acute appendicitis (AA), its diagnostic utility for complicated acute appendicitis (CAA) in pediatric patients remains controversial. (17). In our study, CRP levels were found to be significantly higher in the CAA group. The area under the curve (AUC), along with sensitivity and specificity, suggests that CRP may serve as a useful indicator for clinicians in distinguishing complicated AA. Notably, as age increases, CRP appears to have a greater ability to differentiate perforated AA (18). It has been shown

that children diagnosed with acute appendicitis (AA) who have elevated CRP levels are at increased risk of perforation. Considering these findings, it is important to highlight that elevated CRP levels were also identified in the complicated acute appendicitis cohort during our study (19).

The NLR could serve as a simple parameter to assess the inflammatory status in adults, according to the results of the studies conducted to date. (20) In a comprehensive review and meta-analysis, it was noted that the calculation of the neutrophil-to-lymphocyte ratio (NLR) in adult patients may serve as a sensitive parameter for the preoperative prediction of acute appendicitis (AA), potentially preventing negative appendectomies due to its predictive value. Reports indicate that an NLR greater than 4.7 is associated with higher specificity and sensitivity. Furthermore, an NLR exceeding 4.7 has been identified as an independent predictor of acute appendicitis, while an NLR greater than 8.8 is considered an independent predictor of complicated appendicitis (21). In our study, we identified a neutrophil-to-lymphocyte ratio (NLR) threshold of 6.46 as a potential alerting marker for clinicians in cases of complicated appendicitis. We believe that NLR can be particularly useful in settings with limited resources and where rapid action is necessary.

Additionally, the platelet-to-lymphocyte ratio (PLR) may serve as another indicator of inflammation. We found PLR to be a reliable parameter for distinguishing complicated acute appendicitis (CAA) when its value exceeded 145.8 in children. The area under the curve (AUC) was 0.616, and we found that it had similar diagnostic accuracy to studies conducted in both adults and children, with a sensitivity of 75.1%. (22, 23). In another study conducted on preoperative adult patients, a platelet-to-lymphocyte ratio (PLR) greater than 163.27 demonstrated a sensitivity of 64.3% and a specificity of 67.5% in differentiating complicated appendicitis from uncomplicated appendicitis. (24). While PLR shows promise in the context of acute appendicitis, it is important to note that there are significant variations in measurement levels and units within the literature. Therefore, PLR can be a valuable tool in the diagnostic workup of acute appendicitis,

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especially when used in conjunction with other clinical and laboratory findings. However, it should be considered as part of a comprehensive diagnostic strategy rather than as a stand-alone test.

Both NLR and PLR are promising markers for predicting the diagnosis and severity of appendicitis in children. When interpreted together, they may provide acceptable sensitivity and specificity. Our data support the use of NLR and PLR to stratify risk in children with clinically confirmed appendicitis, particularly in resource-limited settings with limited operating room facilities or when repeat imaging is not readily available. In addition, these markers have the potential to provide reassurance and confidence to healthcare professionals managing pediatric patients with appendicitis non-operatively. Further studies are needed to determine whether the combination of NLR and PLR with other markers, such as CRP, would improve the predictive value.

The main limitations of our study are its single-center design and retrospective cross-sectional nature with limited data, but we think it's important to take a practical approach to interpreting results. While further stratifying patients based on the onset of symptoms could be useful for research, it might not be as helpful in real-world clinical settings. The second limitation is that CT scans were only performed on a subset of patients, and findings were not standardized across all cases, making it impossible to perform a robust correlation analysis between specific CT pathologies and inflammatory indices.

5. Conclusion

CRP, NLR, and PLR can be used to identify suitable cases and support patient selection. Parameters such as NLR and PLR can enable us to optimally utilize surgical resources. This allows us to provide efficient, safe patient care that meets modern standards. The use of CT imaging is increasingly important in the investigation of acute right iliac fossa pain and in the diagnosis of AA. However, in certain populations, the risk of ionizing radiation from CT is difficult to justify. In these patients, NLR and PLR can inform decision-making and plan management.

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