ORIGINAL ARTICLE

Role of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in identifying complicated appendicitis in the pediatric emergency department

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ABSTRACT

BACKGROUND: The objective of this research was to evaluate the potential clinical utility of baseline hematological parameters measured on admission as adjuncts in the identification of complicated and uncomplicated appendicitis in children.

METHODS: The records of a total of 334 pediatric patients who underwent curative surgery for acute appendicitis (AA) between 2015 and 2016 were retrospectively investigated. The patients were categorized as complicated or uncomplicated appendicitis based on the histopathological reports. The clinical features and baseline hematological parameters of leukocyte count, neutrophil percentage, thrombocyte count, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), mean platelet volume (MPV), red cell distribution width (RDW), and platelet distribution width (PDW) of the groups were compared.

RESULTS: Complicated AA was determined in 36 (10.8%) patients. The white blood cell count (WBC) ($p<.001$), neutrophil percentage ($p<.001$), NLR ($p<.001$), and PLR ($p=.004$) were higher in the complicated appendicitis group compared with the uncomplicated group, while the RDW, MPV, and PDW levels were uninformative. Analysis of receiver operating characteristic curves yielded the cut-off values of 14.870 cell/mm^3 for WBC (area under the curve [AUC]: 0.675; sensitivity: 86.1%; specificity: 41.6%), 10.4 for NLR (AUC: 0.717; sensitivity: 61.1%; specificity: 73.2%), and 284 for PLR (AUC: 0.647; sensitivity: 42%; specificity: 86%) were found to be the best predictive values for the determination of complicated acute appendicitis.

CONCLUSION: The present study demonstrated that AA patients with higher NLR and PLR levels might be more likely to develop a complication. The NLR and PLR values combined with a physical examination, imaging studies, and other laboratory tests may help clinicians to identify high-risk AA patients in the emergency department.

Keywords: Acute appendicitis; complicated; neutrophil-to-lymphocyte ratio; pediatrics; platelet-to-lymphocyte ratio.

INTRODUCTION

Acute appendicitis (AA) is a common surgical disease which occurs in almost all age groups, and especially in childhood. A clinical history and physical examination remain the basis of the diagnosis. Other diagnostic tools, such as inflammatory markers and imaging studies, including ultrasonography (US) and computed tomography (CT), are of significant help in the diagnostic process.[1]

Despite the development of diagnostic advances, approximately 30% of patients, in particular children under the age of 5 years, are revealed to have perforation at diagnosis, and 28% to 57% of older children present with missed and de-

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layed diagnosis.[2,3] An initial misdiagnosis can be the result of nonspecific presenting symptoms or a difficult physical examination due to an anxious or distressed child. Another challenge is the variability in appendicular location, such as a hidden or retrocecal appendicitis, which may not exhibit enough peritoneal signs to support the diagnosis of AA.[3,4] Delay in the diagnosis and surgery for AA may lead to complications associated with perforation, gangrene, and intraabdominal abscess formation.[3,5] Optimal treatment depends on early diagnosis followed by rapid intervention.

A number of inflammatory markers have long been proposed as a tool to support the clinical data in the decision-making process to determine AA.[6,7] The most studied and used in clinical practice include the measurement of white blood cell count (WBC), absolute neutrophil count, and C-reactive protein.[8–18] Recently, other potential markers of appendicitis have been evaluated and reported as potential predictors. such as procalcitonin,[10] bilirubin,[19] calprotectin,[20] interlekin-6,[21] and fibrinogen.[22,23] However, these tests require special equipment and may not be available in some hospitals. The complete blood count (CBC) is the most frequently used and easily found baseline hematological parameter in clinical laboratories. The parameters of leukocyte count, neutrophil percentage, thrombocyte count, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), mean platelet volume (MPV), red cell distribution width (RDW), and platelet distribution width (PDW) have been studied for use in the diagnosis and prediction of complicated AA.[24–31] However, their role in the diagnosis of appendicitis has yielded diverse and controversial results.[5–10,32]

Therefore, the aim of this study was to assess the potential use of basic laboratory parameters of the CBC: leukocyte count, neutrophil percentage, thrombocyte count, NLR, PLR, MPV, RDW, and PDW, in the diagnosis of AA and determining complicated appendicitis on admission in pediatric patients.

MATERIALS AND METHODS

The medical records of 334 pediatric patients at a single institution who underwent appendectomy between January 2015 and December 2016 and had histopathological findings consistent with AA were retrospectively analyzed. The preoperative clinical diagnosis was AA in all patients. For each patient, the age; sex; presenting symptoms; laboratory values of WBC, neutrophil percentage, thrombocyte count, NLR, PLR, MPV, RDW, and PDW; abdominal US (appendiceal diameter); contrast-enhanced CT; and pathological findings were investigated.

The CBC was measured at admission with an automated hematology analyzer (LH 780 analyzer; Beckman Coulter, Inc., Brea, CA, USA). The markers recorded were WBC, neutrophils, lymphocytes, platelets, RDW, MPV, and PDW. The NLR and PLR were calculated using the neutrophil, platelet, and lymphocyte counts as part of the routine preoperative workup. The normal WBC value was accepted as $4.5–11\times10^3/mm^3$.

The pathological diagnosis of AA was based on intraoperative findings combined with a macroscopic and histological examination of the resected appendix. Patients were classified into 2 groups according to the intraoperative findings and pathology reports: complicated (gangrenous, perforated, or abcess) and uncomplicated AA (suppurative appendicitis). The patients included in this study had a pathological confirmation of acute appendicitis.

This study was approved by the Clinical Research Ethics Committee of Kayseri Research and Training Hospital (12.06.2017/05).

Statistical Analysis

Analyses were performed using SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). The compatibility of variables were investigated using the Shapiro-Wilks test. The characteristics of patients were expressed using descriptive statistics. Parameters compatible with normal distribution were described as mean±SD, and parameters that did not fit normal distribution were described with the median and distribution (lower-upper limit). The comparisons of proportions were performed with a chi-square test. For comparisons between the uncomplicated and the complicated groups, an independent samples t-test was used for the parameters with normal distribution and the Mann-Whitney U test was used for the parameters with non-normal distribution. A summary receiver operating characteristic (sROC) curve was utilized to characterize and compare the accuracy of the hematological ratios. An sROC curve is a graphical representation of sensitivity (x-axis) plotted against 1 – specificity (y-axis). The area under the curve (AUC) represented the accuracy of the marker in distinguishing between complicated and uncomplicated AA. Cut-off values were calculated for each biomarker using Youden's index. Sensitivity and specificity with 95% confidence intervals and the likelihood ratio (LR) were also calculated. $P<0.05$ was considered to be statistically significant.

RESULTS

A total of 334 patients underwent an appendectomy at the institution during the study period. The median age of the study group was 11 years (range: 3–16 years). In all, 210 (62.9%) were male and 124 (37.1%) were female. Non-complicated appendicitis was found in 298 (89.2%) patients while 36 (10.8 %) patients had complicated appendicitis. No significant differences were found between the uncomplicated and complicated group in terms of age or gender (p=0.091, p=0.219, respectively).

Table 1. Baseline clinical characteristics of the study cohort

Variables		Pathologically confirmed appendicitis		p*
	Study population (n=334)	Uncomplicated (n=298, %)	Complicated (n=36, %)	
Age (years)	11 (3–16)	11 (3–16)	10 (3–16)	0.091
Gender, male, n (%)	210 (62.9)	184 (61.7)	26 (72.2)	0.219
Clinical findings, n (%)				
Fever	10 (3)	8 (2.7)	2 (5.6)	0.271
Abdominal pain	333 (99.7)	298 (100)	35 (97.2)	0.004
Vomiting	186 (55.7)	160 (53.7)	26 (72.2)	0.013
Diarrhea	23 (6.9)	20 (6.7)	3 (8.3)	0.639
Baseline laboratory findings, n (%)				
Leukocyte count (cell/mm^3)	16.511±4864	16.170±4805	19.330±4472	<0.001
Neutrophils (%)	82 (43–95)	81 (43–95)	85 (66–93)	<0.001
Thrombocyte count (cell/mm^3)	299.500 (156.000–552.000)	298.000 (156.000–552.000)	309.000 (167.000–532.000)	0.610
NLR	7.4 (0.85–56.8)	6.9 (0.85–56.8)	12.7 (3.19–30)	<0.001
PLR	161.7 (26.39–870)	156.2 (26.4–870)	234 (68–629)	0.004
RDW	13.3 (11.3–17.8)	13.3 (11.3–17.8)	13.7 (11.9–16)	0.207
MPV	9.49±1.08	9.47±1.074	9.66±1.141	0.304
PDW	15.4 (8–17.80)	15.4 (8–17.8)	15.5 (8.7–17.7)	0.161
Individual US findings (appendiceal diameter), n (%)				
Appendix not visualized	25 (7.5)	20 (6.7)	5 (13.9)	<0.001
<6 mm	13 (3.9)	11 (3.7)	2 (5.6)	
6–8 mm	139 (41.6)	136 (45.6)	3 (8.3)	
>8 mm	137 (41)	128 (43)	9 (25)	
Perforated	16 (4.8)	3 (1)	13 (36.1)	
Abscess	4 (1.2)	0 (0)	4 (11.1)	
Individual CT findings, n (%)				
Appendicitis	11 (3)	9 (3)	2 (5.6)	0.070
Perforation/abscess	1/1	0 (0)s	1 (2.8)/1 (2.8)	

Data are presented as mean±SD or as median with range. P<0.05 was considered significant.
MPV: Mean platelet volume; NLR: Neutrophil-to-lymphocyte ratio; PDW: Platelet distribution volume; PLR: Platelet-to-lymphocyte ratio; RDW: Red cell distribution volume.

The most frequently observed symptoms were abdominal pain (99.7%) and vomiting (55.7%). These findings were significantly different in the complicated group compared with the uncomplicated group (p=0.004, p=0.013, respectively). The laboratory results of the study group and comparisons between the 2 groups are shown in Table 1.

There was a significant difference in the WBC, neutrophil percentage, NLR, and PLR results between the complicated group and the uncomplicated group. The mean WBC count in the complicated group was 19.330±4472 cell/mm^3, and it was significantly higher than that of the uncomplicated AA group (p<0.001). The median neutrophil percentage, NLR, and PLR in the complicated AA group was 85%, 12,7 and 234, respectively and these values were significantly higher in the complicated AA group (p<0.00, p<0.001, p=0.004, respectively). Figure 1 illustrates the distribution of the parameters in the complicated and uncomplicated AA groups. There was no significant difference between the complicated and uncomplicated AA groups in the median thrombocyte count, RDW, MPV, or PDW (p=0.610, p=0.207, p=0.304, p=0.161, respectively).

Based on the US findings, a total of 309 (92.5%) patients had a visualized appendix. The most frequent appendix diameter was 6–8 mm (139 patients, 41.6%), followed by a diameter

Table 2. Receiver operating characteristic curve results of hematological indices for discrimination of complicated from uncomplicated appendicitis

Predictors	Complicated and uncomplicated acute appendicitis						
	AUC	p	Cutoff	Sensitivity (95% CI)	Specificity (95% CI)	LR+	LR-
Leukocyte count (cell/mm^3)	0.675	0.001	14.870	86.1 (71–95.3)	41.6 (36–47.4)	1.48	0.33
Neutrophil %	0.678	<0.001	76	97.2 (85.5–99.9)	32.2 (27–38)	1.43	0.09
NLR	0.717	<0.001	10.4	61.1 (44–77)	73.2 (68–78)	2.28	0.53
PLR	0.647	0.004	284	42 (26–60)	86 (81–89)	2.89	0.68

AUC: Area under the curve; LR+: Likelihood ratio positive; LR-: Likelihood ratio negative; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio.

of >8 mm (137 patients, 41%). Perforated appendicitis was seen in 16 (4.8 %) patients, 13 of whom were in complicated group. All 4 (1.2%) patients with an abscess were in the complicated group. These findings represented a significant difference between the complicated group and the uncomplicated group (p<0.001). Abdominal CT was performed for 13 patients with a diagnosis of perforation, and CT revealed an abcess in 1 patient (Table 1).

An sROC curve was employed to evaluate the accuracy of hematological indices in distinguishing between complicated and uncomplicated AA. The AUC reflects marker accuracy and p values reflect statistical significance for the given population. Curves representing each hematological index were plotted and compared. WBC (AUC: 0.675; p=0.001), neutrophil percentage (AUC: 0.678; p<0.001), NLR (AUC: 0.717; p<0.001), and PLR (AUC: 0.647; p=0.004) were the most accurate markers in distinguishing the 2 groups (complicated vs. uncomplicated; Table 2, Fig. 2). Utilizing WBC >14.87 cell/mm^3 as a predictor of complicated AA, the cutoff point had a sensitivity of 86.1% and a specificity of 41.6%. A neutrophil percentage of >76% had a sensitivity of 97.2% and a specificity of 32.2% for determining complicated AA. Utilizing a NLR >10.4 as a predictor of complicated AA, the cutoff point

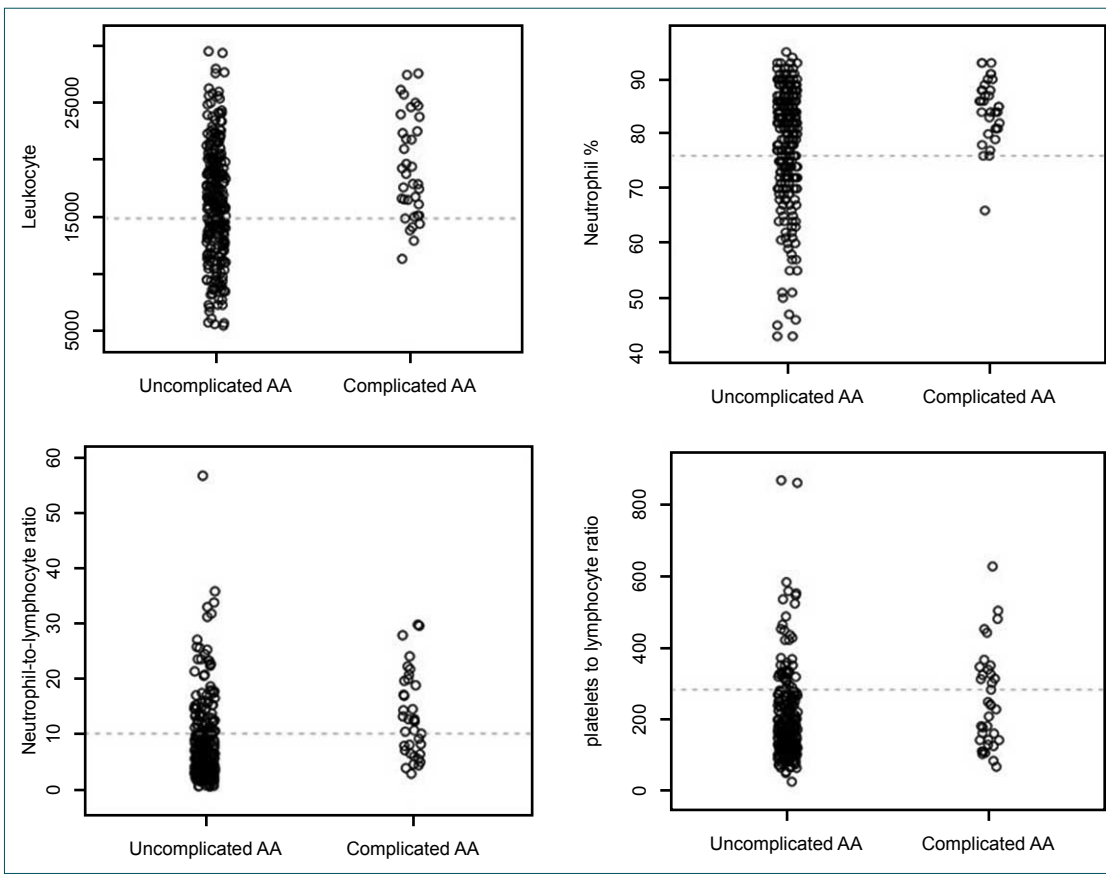

Figure 1. Distiribution graph of the hematologic indices (leukocyte, neutrophil percentage, NLR, PLR) in complicated and uncomplicated AA. AA: Acute appendicitis; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio.

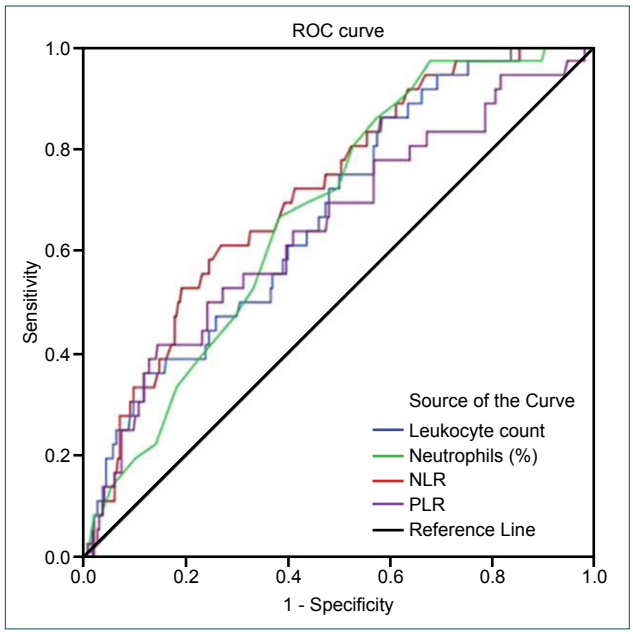

Figure 2. ROC curves for leukocyte, neutrophil percentage, NLR, and PLR to discriminate complicated appendicitis from uncomplicated appendicitis. NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; ROC: Receiver operating characteristic.

had a sensitivity of 61.1% and a specificity of 73.2%. A cutoff value of 284 for the PLR had a sensitivity of 86% and a specificity of only 41% (Table 2, Fig. 2). The test performance of the PLR was maximal (LR+ of 2.89), while for the neutrophil percentage, WBC count, and NLR, it provided a LR of 1.43, 1.48, and 2.28, respectively (Table 2).

DISCUSSION

AA is the one of the most common childhood surgical emergencies of the abdomen. Severe phlegmonous or gangrenous appendiceal inflammation can easily lead to peritonitis if perforation occurs.[1–3,6,7] Therefore, correct evaluation of the severity and discrimination between uncomplicated and complicated appendicitis provides valuable information to surgeons. Non-operative management with antibiotics alone may be an option for patients with uncomplicated appendicitis; however, surgery is still the first choice for complicated AA, and especially gangrenous appendicitis. Early detection of cases of complicated appendicitis and timely therapeutic intervention can reduce the risks of postoperative complications, such as intra-abdominal abscess or life-threatening peritonitis, which are more common when the appendix is perforated.[1–3,5,13,25,33]

Understanding whether a child is experiencing simple or complicated appendicitis is still a diagnostic challenge for the clinician. Although a thorough assessment of clinical symptoms, use of a scoring system, and imaging methods are important in the general diagnosis of appendicitis, these evaluations provide only some hints in establishing the severity of appendicitis.[7,12,15,32,33]

In this study, the focus was to determine the predictive significance for complicated AA of markers of inflammation in the CBC. WBC, neutrophil percentage, thrombocyte count, NLR, PLR, MPV, RDW, PDW were assessed. To best of our knowledge, this is the first study to utilize CBC parameters with the intent of evaluating the ability to differentiate complicated AA from uncomplicated AA in the pediatric age group. We found that admission values of WBC, neutrophil percentage, NLR, and PLR were all significantly increased in patients with complicated appendicitis compared with patients suffering from uncomplicated AA.

Previous studies have revealed conflicting and varying information of traditional biomarkers such as the WBC count in the diagnosis of AA.[6,10] An increase in WBC concentration has been reported as the earliest sign of appendiceal inflammation. Part of the difficulty in drawing exact conclusions from the studies is that there is wide variability in the WBC concentration sensitivity, specificity, LR, and accuracy.[10] A WBC cutoff of greater than 10–12,000 cell/mm^3 yielded a range of sensitivity between 65% and 85% and a specificity between 32% and 82%.[6,10–18] A 2003 meta-analysis of 14 studies (3382 patients) likely gives a representative approximation of the true sensitivity and specificity of a WBC >10,000 cell/mm^3 measured at 83% and 67%, respectively, with a positive and negative LR of 2.52 and 0.26.6 Our findings are supported by prior research that found a sensitivity and specificity of the WBC count of 86.1% and 41.6%, respectively, and an AUC of 0.675. However, the presence of a WBC count >14,870 cell/mm^3 provided a LR of 1.48, which has limited clinical significance. The limited utility of a WBC concentration should not be surprising, as appendicitis is a dynamic, changing process, for which variations in levels might be assumed. The neutrophil percentage >75% was a discriminator of AA, but had limited clinical significance due to a sensitivity of 66% to 87% and a specificitiy of 33% to 84%.[6,12,15,17] Again, the LR was not high enough to significantly change the probability of appendicitis. Similar to previous reports, our study found that a neutrophil percentage >76% had a total sensitivity of 97.2% and a specificity 32.2%. Here, the LR was 1.43.

Systemic inflammatory response can also cause neutrophilia and lymphocytopenia, resulting in an increase in the NLR and PLR, a sign of inflammation in AA.[24,25,33,34] It has also been reported that changes in platelet indices are involved in inflammatory processes.[35] The NLR and PLR are a simple, non-invasive, and cost-effective inflammatory markers, which can easily be calculated from the blood count in the emergency department. However, the role of these parameters in AA has only been investigated in a few studies.[24,25,33,34,36–38] A study conducted by Yazici et al.[24] showed that a NLR over 3.5 in a pediatric patient group had maximum sensitivity and more sensitivity than the WBC count. Another study by Ishizuka et al.[25] revealed that an NLR >8 had a significant association with gangrenous appendicitis in patients undergoing appendectomy. Markar et al.[36] assessed 1117 pediatric

patients who underwent appendectomy and determined that the NLR appeared to be of greater diagnostic accuracy than the total WBC count.

In our study, significant differences were not detected between the complicated and uncomplicated AA patients in the platelet count, MPV, or PDW, wheares a higher NLR and PLR were reported in complicated AA patients. The NLR had a higher AUC value than the other diagnostic factors, and an NLR cutoff of 10.4 demonstrated acceptable specificity and sensitivity. We found that NLR had a better AUC (0.717) compared with PLR (AUC: 0.647), neutrophil percentage (AUC: 0.678) or WBC (AUC: 0.675) for predicting complicated/severe appendicitis and a reasonable sensitivity and specificity. This suggests that NLR is a superior marker of acute phase response inflammatory processes. We think that these findings may be particularly important when clinical fndings and WBC are not adequate to safely distinguish complicated AA from uncomplicated AA. However, we concluded that the diagnostic value of these parameters alone was low and the positive or negative LR of NLR and PLR were unacceptably poor for use as a stand-alone rule-in or rule-out tool.

There are limitations to this study, beginning with the retrospective design. In addition, the data were only collected for a 1-year period, which may not show the real potential of NLR and PLR in the discrimination of complicated AA in pediatric patients. In all, 36 complicated AA patients were included in the study with 298 uncomplicated AA patients, which may affect the statistical significance determined. We attempted to limit selection bias by including only patients who had histological evidence of appendicitis. Finally, we did not ask or record when the pain began, so we could not consider the effect of time on the parameters studied. Compared with other studies in this area, because of the large sample size we had a large amount of patient data.

In conclusion, our study revealed that high NLR and PLR levels might help identify those who are more likely to develop complications in patients with AA. Moreover, these parameters are not expensive to measure, are easily available, and the short time required for analysis is valuable in the emergency department.

We recommend that clinicians use the NLR and PLR values combined with the results of a physical examination, imaging studies, and other laboratory tests to help identify high-risk AA patients in the emergency department.

Conflict of interest: None declared.

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ORİJİNAL ÇALIŞMA - *ÖZET*

Pediatrik acil serviste komplike apandisitin belirlenmesinde nötrofil-lenfosit oranı ve trombosit-lenfosit oranının rolü

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AMAÇ: Çocuklarda komplike ve komplike olmayan apandisitin saptanmasında yardımcı olarak başlangıç hematolojik parametrelerin olası klinik faydalarını değerlendirmek amaçlandı.
GEREÇ VE YÖNTEM: 2015'ten 2016'ya kadar akut apandisit için küratif cerrahi geçiren 334 pediatrik hasta geriye dönük olarak incelendi. Hastalar histopatolojik raporlara dayanarak komplike veya komplike olmayan apandisit olarak sınıflandırıldı. Klinik bulgular ve temel hematolojik parametrelerden lökosit sayısı, nötrofil yüzdesi, trombosit sayısı, nötrofil-lenfosit oranı (NLR), trombosit-lenfosit oranı (PLR), ortalama trombosit hacmi, kırmızı hücre dağılım genişliği, trombosit dağılım genişliği gruplar arasında karşılaştırıldı.
BULGULAR: Komplike akut apandisit 36 (%10.8) hastada bulundu. Komplike apandisitte WBC ($p<0.001$), nötrofil yüzdesi ($p<0.001$), NLR ($p<0.001$), PLR ($p=.004$) komplike olmayan gruba göre daha yüksek iken, RDW, MPV, PDW düzeyleri anlamlı fark bulunmadı. ROC eğrilerinin analizi, WBC için 14.870 hücre/mm^3 (eğri altındaki alan [AUC], 0.675; duyarlılık, %86.1; özgüllük, %41.6), NLR için 10.4 (AUC, 0.717; duyarlılık, %61.1, özgüllük, %73.2), PLR için 284 (AUC, 0.647; duyarlılık, %42; özgüllük, %86) komplike akut apandisitin belirlenmesinde en iyi kestirim değerler olarak bulundu.
TARTIŞMA: Bu çalışma, daha yüksek NLR ve PLR düzeylerine sahip akut apandisitli hastalarda komplikasyon gelişme olasılığının daha yüksek olabileceğini göstermiştir. Klinisyenlerin acil servisteki yüksek riskli akut apandisit hastalarını tespit etmelerine yardımcı olmak için fizik muayene, görüntüleme çalışmaları ve diğer laboratuvar testleri ile birlikte NLR ve PLR kullanılmasını öneririz.
Anahtar sözcükler: Akut apandisit; komplike; nötrofil-lenfosit oranı; pediatri; platelet-lenfosit oranı.

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