



Evaluation of Systemic Immune-Inflammation Index as Novel Marker in the Diagnosis of Acute Appendicitis in Children

Çocuklarda Akut Apendisit Tanısında Yeni Bir Belirteç Olarak Sistemik İmmün-İnflamasyon İndeksinin Değerlendirilmesi

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Abstract

Aim: The aim of this study was to determine the usefulness of systemic immune-inflammation index (SII) in the diagnosis of acute appendicitis (AA) in children

Material and Method: This study was done retrospectively, and two groups were formed as AA and control group. AA group was divided into two subgroups as nonperforated appendicitis and perforated appendicitis. The groups were compared for age, sex, WBC, neutrophil, lymphocyte and platelet count, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), C-reactive protein (CRP).

Results: The study included a total of 162 children. There were 81 children in the AA group and 81 in the control group. Of 81 patients included in the AA group, 31 were girls (38.3%) and 50 were boys (61.7%), and the median age of the patients was 11 (5) years. When the AA group and the control group were compared in terms of laboratory values. It was found that WBC count, neutrophil count, platelet count, NLR, PLR and SII in the AA group were significantly higher and lymphocyte count was significantly lower ($p<0.001$ for all). When nonperforated and perforated appendicitis groups were compared, there was a significant difference only in CRP value and the CRP value was significantly higher in the perforated appendicitis (groups $p<0.001$)

Conclusion: To the best of our knowledge, present study is the first report to demonstrate the diagnostic value of SII in children with AA. We think that SII can use as novel marker supporting AA diagnosis in children

Keywords: Acute appendicitis, children, systemic immune-inflammation index (SII)

Öz

Amaç: Bu çalışmanın amacı, çocuklarda akut apandisit (AA) tanısında sistemik immün inflamasyon indeksinin (SII) yararlılığını belirlemektir.

Gereç ve Yöntem: Bu çalışma retrospektif olarak yapıldı; AA ve kontrol grubu olmak üzere iki grup oluşturuldu. AA grubu nonperfore apandisit ve perfore apandisit olarak iki alt gruba ayrıldı. Gruplar yaş, cinsiyet, WBC, nötrofil, lenfosit ve trombosit sayısı, nötrofil-lenfosit oranı (NLR), trombosit-lenfosit oranı (PLR), sistemik immün inflamasyon indeksi (SII), C-reaktif protein (CRP) değerleri açısından karşılaştırıldı.

Bulgular: Çalışmaya toplam 162 çocuk dahil edildi. AA grubunda 81, kontrol grubunda 81 çocuk vardı. AA grubuna dahil edilen 81 hastanın 31'i kız (%38,3), 50'si erkek (%61,7) olup, hastaların ortanca yaşı 11 (5) yıl idi. AA grubu ve kontrol grubu laboratuvar değerleri açısından karşılaştırıldığında. AA grubunda WBC sayısı, nötrofil sayısı, trombosit sayısı, NLR, PLR ve SII'nin anlamlı derecede yüksek olduğu ve lenfosit sayısının anlamlı derecede düşük olduğu bulundu (tümü için $p<0,001$). Perfore olmayan ve perfore apandisit grupları karşılaştırıldığında, sadece CRP değerinde anlamlı fark vardı ve perfore apandisit gruplarında CRP değeri anlamlı olarak daha yüksekti ($p<0,001$)

Sonuç: Bilgilerimize göre bu çalışma, AA'lı çocuklarda SII'nin tanılabilirliğini gösteren ilk rapordur. SII'nin çocuklarda AA tanısını destekleyen yeni bir belirteç olarak kullanılabileceğini düşünüyoruz.

Anahtar Kelimeler: Akut apandisit, çocuklar, sistemik immün-inflamasyon indeksi (SII)



INTRODUCTION

Acute appendicitis (AA) is a common cause of abdominal pain in childhood that requires accurate diagnosis and prompt intervention. In a child with suspected AA, the diagnosis is usually made based on the child's physical examination findings and the story told by the family. However, in pediatric patients, it is difficult to take the full history and their compliance with the examination is poor, therefore the negative laparotomy ratio is higher than adults.^[1-4] In addition, non-surgical diseases that cause abdominal pain in children are very common.^[3,4] For this reason, delays in diagnosis may be experienced in pediatric patients, and this may increase mortality and morbidity by causing perforated appendicitis.^[3]

Some laboratory tests have long been used to support the diagnosis of AA. C-reactive protein (CRP) level, white blood cell (WBC) count, neutrophil percentage (NP) and are frequently preferred values.^[1,2,5] Recently it has been reported in many publications that measurements made from blood values are beneficial in the diagnosis of AA; Neutrophil-lymphocyte ratio (NLR), serum sodium level, mean platelet volume (MPV), platelet-lymphocyte ratio (PLR) are the most commonly used ones.^[1-6]

The systemic immune inflammation index (SII), which contains peripheral neutrophils, lymphocytes, and platelets, has recently been defined in some studies.^[7-9] It has been reported in some studies that elevated as an inflammation marker.^[8,10] However, it has been reported that SII may be more sensitive in predicting prognosis in certain cancer patients than current methods using only one or two cell subtypes.^[11-13] Considering that appendicitis is a disease that starts with the inflammation process, it should be expected to SII will have diagnostic value.

There is no study in the literature showing the effectiveness of SII as an inflammation index in the diagnosis of AA in pediatric patients. The aim of this study is to determine the usefulness of SII in the diagnosing of AA in children.

MATERIAL AND METHOD

This study was planned retrospectively and was carried out at Süleyman Demirel University, Faculty of Medicine, Department of Pediatric Surgery. This study was planned two groups were formed as AA and control group. AA group: 81 patients younger than 17 years of age who were operated with the diagnosis of AA between 2019-2021 and whose AA diagnosis was confirmed by the pathology report were included. The medical records of the patients were reviewed retrospectively in terms into two subgroups as nonperforated appendicitis and perforated appendicitis according to surgical findings and definitive pathology reports. Eighty-one children who were similar age and sex as the patient group and operated for circumcision, inguinal hernia, umbilical hernia, etc. were included in the

control group. In control group, cases with appendectomy, drug use and chronic disease were excluded from the study. All children in the control group were operated for non-inflammatory reasons. The cases who had incomplete medical records, appendiceal neoplasm, incidental appendectomy as a part of another procedure and recent history of antibiotic use were excluded from the study. The groups were compared for age, sex, WBC, neutrophil, lymphocyte, and platelet count, NLR, PLR, SII and CRP level. The SII was defined as follows: $SII = \frac{\text{neutrophil count} \times \text{platelet count}}{\text{lymphocyte count}}$ In both groups, hemogram parameters at the time of admission were considered.

The study was carried out with the permission of Süleyman Demirel University Ethics Committee (Date: 06.01.2022, Decision No: 11). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

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 of NLR, PLR and SII in diagnosis of acute appendicitis. Statistical Package for Social Sciences (SPSS) Windows software (ver. 22; IBM SPSS, Chicago, USA) was used for all statistical analyses. P value less than 0.05 was considered as statistically significant.

RESULTS

The study included a total of 162 children. There were 81 children in the AA group and 81 in the control group. Of 81 patients included in the AA group, 31 were girls (38.3%) and 50 were boys (61.7%), and the median age of the patients was 11 (5) years. 81 patients were included in the control group. 34 of these patients were girls (42%), 47 were boys (58%), and the median age of the patients was 12 (5) years. When the AA group and control groups were compared in terms of age and gender, there was no significant difference between them ($p > 0.05$ for all) (**Table 1**). When the AA group and the control group were compared in terms of laboratory values, there was no significant difference between platelet count alone ($p = 0.931$). A significant difference was found between other values (neutrophil, lymphocyte and WBC count, PLR, NLR, SII) as detailed in **Table 1**.

Table 1. The demographic characteristics and laboratory findings of acute appendicitis and control groups

	Acute appendicitis (n=81)	Control (n=81)	P value
Gender, n (%)			
Female	31 (38.3)	34 (42.0)	0.631
Male	50 (61.7)	47 (58.0)	
Age (year)	11.0 (5.0)	12.0 (5.0)	0.849
WBC (10 ³ /μL)	16.4 (7.5)	6.6 (1.6)	<0.001
Neutrophil (10 ³ /μL)	13.4±4.5	3.4±1.0	<0.001
Lymphocyte(10 ³ /μL)	1.5 (1.1)	2.7 (0.9)	<0.001
Platelet (10 ³ /μL)	296.0 (93.5)	280.0 (78.0)	0.931
NLR	9.0 (6.8)	1.2 (0.7)	<0.001
PLR	190.2 (135.0)	104.3 (27.7)	<0.001
SII	2597.3 (2241.5)	353.9 (174.9)	<0.001

Abbreviations: WBC, white blood cell; 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).

There were 55 patients in the nonperforated appendicitis group and 26 patients in the perforated appendicitis group. Of the 55 patients in the nonperforated appendicitis group, 21 were female (38.2%), 34 were male (61.8%), with a median age of 12 (5) years, 10 (38.5%) of the 26 patients in the perforated appendicitis group were girls and 16 (61.5%) were boys, and the median age of the patients was 10.5 (5.5) years. When the two groups were compared, no significant difference was found in terms of gender and age distribution (Table 2). Non-perforated and perforated appendicitis groups were compared; there was a significant difference only in CRP value between laboratory values, there was no significant difference in other values as given in Table 2. The CRP value was 8.6 (9.4) mg/L in the nonperforated appendicitis group and 63.7 (134.5) mg/L in the perforated appendicitis group, and there was a statistically significant difference in terms of CRP value between the two groups (p<0.001) (Table 2). SII values of control group, nonperforated appendicitis and acute appendicitis groups are shown graphically in Figure 1. SII values were high enough to be a significant difference between the control group and the acute appendicitis group, but there was no significant difference between the nonperforated and perforated appendicitis groups in terms of SII values.

Table 2. The demographic characteristics and laboratory findings of nonperforated and perforated appendicitis groups

	Nonperforated appendicitis (n=55)	Perforated appendicitis (n=26)	P value
Gender, n (%)			
Female	21 (38.2)	10 (38.5)	0.981
Male	34 (61.8)	16 (61.5)	
Age (year)	12.0 (5.0)	10.5 (5.5)	0.080
WBC (10 ³ /μL)	15.7 (6.1)	17.2 (8.2)	0.197
Neutrophil (10 ³ /μL)	13.2±4.4	14.0±4.7	0.455
Lymphocyte(10 ³ /μL)	1.5 (1.1)	1.5 (1.2)	0.642
Platelet (10 ³ /μL)	290.0 (95.0)	296.5 (77.8)	0.540
NLR	9.1 (5.1)	8.3 (10.0)	0.883
PLR	190.2 (136.5)	186.8 (133.1)	0.808
SII	2597.3 (2026.5)	2656.1 (2796.3)	0.879
CRP (mg/L)	8.6 (9.4)	63.7 (134.5)	<0.001

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

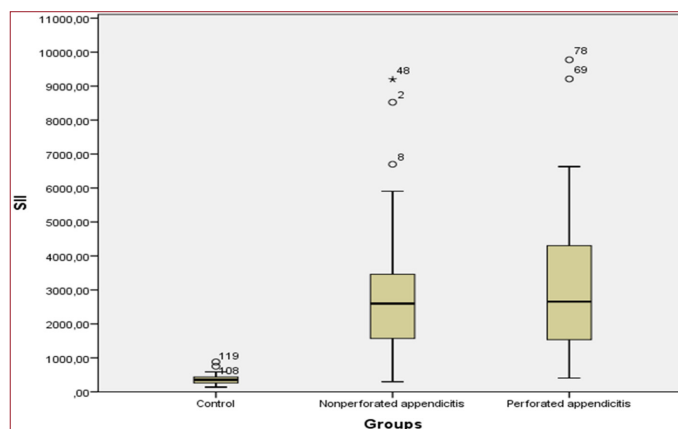


Figure 1: Distribution of the SII values of groups. SII: systemic immune-inflammation index

Figure 2 shows the ROC curve analysis to determine the diagnostic sensitivity and specificity values of NLR, PLR and SII for acute appendicitis. Optimum cut-off value between the sensitivity and specificity were found as 2.235 (sensitivity 96% and specificity 98%) for NLR, 137.055 (sensitivity 73% and specificity 93%) for PLR, and 651.475 (sensitivity 95% and specificity 98%) for SII (p<0.001 for all) (Table 3).

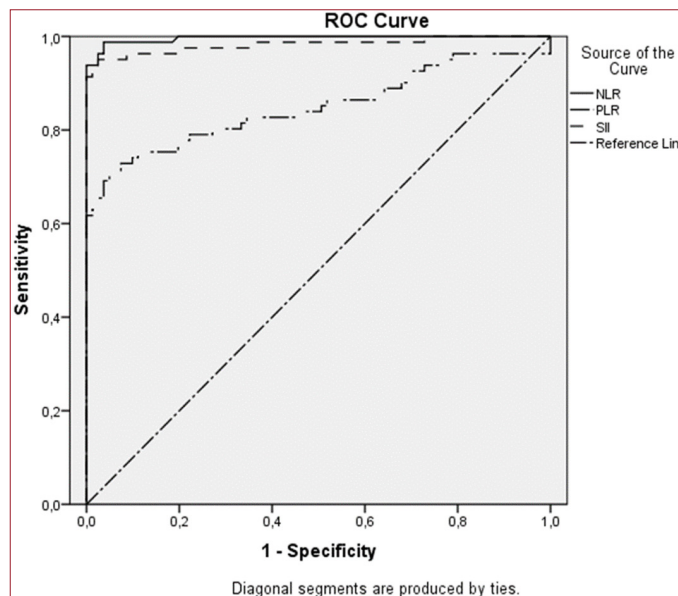


Figure 2. ROC curve of the diagnostic value of NLR, PLR and SII for acute appendicitis. ROC, receiver operating characteristic, NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio, SII, systemic immune-inflammation index

Table 3. Predictive power of the NLR, PLR and SII in the diagnosis of acute appendicitis

	AUC (95% CI)	Optimum cut-off value	P value	Sensitivity (%)	Specificity (%)
NLR	0.996 (0.991-1.000)	2.235	<0.001	96	98
PLR	0.848 (0.784-0.912)	137.055	<0.001	73	93
SII	0.982 (0.962-1.000)	651.475	<0.001	95	98

Abbreviations: AUC, area under receiver operating characteristic (ROC) curve; CI, confidence interval, NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio, SII, systemic immune-inflammation index. Note: AUC > 0.600 and p <0.05 were accepted as significant.

DISCUSSION

AA is the first line of surgery related to acute abdomen in children. However, it can be difficult to diagnose appendicitis in childhood, because there is no specific test that can be used to distinguish appendicitis from other causes of abdominal pain. The development of specific diagnostic tests for appendicitis will both aid in early diagnosis and help prevent complications and unnecessary surgery. Delayed diagnosis in AA can lead to perforation and peritonitis while fear of these complications might lead to negative laparotomies.^[1-3,5] Especially in rural hospitals where CT and/or US is not available, laboratory tests with high sensitivity and specificity become essential in reaching a reliable differential diagnosis.

Laboratory tests and imaging methods have an important place in the diagnosis of AA due to the incompatibility and inadequacy of pediatric patients in examination and in telling their stories. The most preferred laboratory tests are WBC value, NP, CRP, NLR, PLR, MPV, and serum sodium level.^[2-6,14-17] In a meta-analysis study conducted by Acharya et al. for the diagnosis of AA, the place of values such as WBC, CRP, bilirubin, procalcitonin, Ddimer and interleukin-6 in the diagnosis was investigated. Sensitivity, specificity, and AUC for WBC were 79%, 55%, and 0.75%, and 76%, 50%, and 0.80% for CRP, respectively.^[18]

Similar to the studies previously reported in the literature, neutrophil, lymphocyte, WBC values, NLR and PLR rates are compared to the control group, the AA group was found to be significantly higher in the AA group.^[6,14-18] Pehlivanlı et al. reported in their study that PLR value could be a new biomarker for the diagnosis of appendicitis, and it could be of and predictive value in differentiation of acute appendicitis from perforated appendicitis also.^[16] In our study, the PLR value was significantly higher in the AA group than in the control group. However, when the nonperforated and perforated groups were compared, no significant difference was found between the PLR values. In addition, the sensitivity of PLR using ROC curve analysis in diagnosing AA was 73%, its specificity was 93% in our study.

According to Duman et al. It showed that WBC count and NLR were useful markers in supporting the clinical diagnosis of appendicitis, but had no predictive value in differentiating perforated appendicitis from AA.^[3] Elmas et al. reported that WBC count and NLR were significantly higher in the group with AA compared to the control group.^[15] Similarly, in our study, it was found that WBC count and NLR increased significantly in AA cases but were not useful in the differentiation of perforated and nonperforated cases. In addition, the specificity of the NLR using ROC curve analysis in diagnosing AA was found as 98% and the sensitivity as 96%, which is consistent with the literature data.^[2,3]

CRP is one of the most commonly used diagnostic markers to identify acute inflammatory conditions. Patients with appendicitis are likely to have an elevated CRP

measurement, and many studies have found that CRP is useful in diagnosing appendicitis.^[1-3,6] Narci et al. reported in their study that the CRP value was higher in the AA group.^[2] Duman et al. stated that CRP values increased significantly in perforated appendicitis.^[3] In our study, the CRP value was found to be significantly higher in the perforated appendicitis group compared to the nonperforated group.

Recently identified SII; It has proven to be a strong prognostic indicator for poor outcomes for patients with hepatocellular carcinoma and small cell lung cancer.^[11-13] Trifan et al. showed increased SII is a predictor of poor outcome after supratentorial intracerebral hemorrhage.^[7] It has been reported in studies conducted in recent years that SII increases in inflammatory diseases such as Behçet's disease and asthma.^[8,10] Appendicitis develops with the inflammation caused by the obstruction of the appendix lumen and the infection added to it.^[2] In our study, SII was determined to be significantly higher in the acute appendicitis group compared to the control group. In addition, the optimum cut-off value of SII was determined as 651.475 by using ROC curve analysis in the diagnosis of AA, and its sensitivity was 95% and its specificity was 98%. In our study, although the SII value in the perforated appendicitis group was higher than the nonperforated group, there was no statistically significant difference.

The limitations of our study were the relatively small number of patients, retrospective and single-center design. Multicenter and prospective studies with larger numbers of patients can provide more valuable results.

CONCLUSION

To the best of our knowledge, present study is the first report to demonstrate the diagnostic value of SII in children with AA. We think that SII may be useful as novel marker supporting AA diagnosis in children. However, further studies are needed to optimize the use of this new marker in the diagnosis of AA.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Süleyman Demirel University Ethics Committee (Date: 06.01.2022, Decision No: 11).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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