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RESEARCH

Systemic immune inflammation index may be a new powerful marker for the accurate early prediction of complications in patients with acute appendicitis

Sistemik immün inflamasyon indeksi, akut apandisitli hastalarında komlikasyonun doğru erken tahmini için yeni ve güçlü bir belirteç olabilir

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Abstract

Purpose: To investigate the relationship between the systemic immune-inflammatory index (SII) and acute appendicitis (AA).

Materials and Methods: We retrospectively evaluated patients aged over 18 years who were diagnosed with AA and underwent surgery at our clinic from January 1, 2019, through July 31, 2022. The patients were divided into three groups: complicated acute appendicitis (CAA), uncomplicated acute appendicitis (UAA), and control. The clinical and laboratory characteristics of the patients evaluated at the emergency department were recorded. The neutrophil/lymphocyte ratio (NLR), the platelet/lymphocyte ratio (PLR), and SII (neutrophil count x platelet count/lymphocyte count) were calculated.

Results: The study included a total of 1,456 patients, of whom 628 had UAA, 104 had CAA, and 714 were controls. The NLR, PLR, and SII values were statistically significantly higher in the CAA group than in the control group and the UAA group. The multivariate logistic regression analysis revealed that SII was an independent predictor of CAA development (odds ratio [OR]: 4.65; 95% confidence interval [CI]: 2.31–10.17). The predictive power of SII in the prediction of CAA (area under the curve [AUC]: 0.809) was much higher than that of NLR (AUC: 0.729), neutrophil count (AUC: 0.696), and C-reactive protein (AUC: 0.732) alone. It was determined that an SII value greater than 1,989.2 had a sensitivity of 78.4% and a specificity of 88.5% in predicting CAA development.

Conclusion: SII is a simple, inexpensive, and promising marker that could predict both the diagnosis and severity of appendicitis.

Öz

Amaç: Bu çalışmada, sistemik immün-inflamatuar indeks (SII) ile Akut Apandisit (AA) arasındaki ilişkiyi araştırmayı amaçladık.

Gereç ve Yöntem: 1 Ocak 2019-31 Temmuz 2022 tarihleri arasında kliniğimizde AA tanısı konup ameliyat edilen, 18 yaş üstü hastaları retrospektif olarak analiz ettik. Hastalar; Complicated Akut apandisit (CAA), Uncomplicated Akut Apandisit (UAA) ve kontrol grubu olarak üçe ayrıldı. Hastaların Acil servisteki klinik ve laboratuvar özellikleri değerlendirildi. Hastaların nötrofil/lenfosit oranı (NLR) ve trombosit/lenfosit oranı (PLR) ve SII (nötrofil sayısı x trombosit sayısı /lenfosit sayısı) hesaplandı.

Bulgular: Çalışmaya 628 UAA, 104 CAA hastası ve 714 kontrol grubu olmak üzere toplam 1456 hasta dahil edildi. NLR, PLR ve SII değerleri CAA grubunda, UAA grubundan kontrol grubundan istatistiksel olarak anlamlı derecede yüksek bulundu. Multivariate lojistik regresyon analizi; SII'nın (odds ratio [OR]: 4.65; 95% confidence interval [CI]: 2.31–10.17). CAA gelişimi için bağımsız prediktör olduğunu gösterdi. SII (AUC: 0.809)'in CAA'yı tahmin etme gücünü, tek başına NLR (AUC: 0.729), Neutrophil (AUC: 0.696) ve CRP 'den (AUC: 0.732) çok daha yüksek olarak tespit ettik.1989.2'den daha yüksek SII değerleri CAA gelişimini %78,4 duyarlılık ve %88,5 özgüllük ile öngördü

Sonuç: Bulgularımız, SII'nin apandisit tanısını ve ciddiyetini öngörebilen basit, ucuz, kolay ve umut verici bir belirteç olduğunu gösterdi.

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Anahtar kelimeler: Sistemik immün-inflamatuar indeks, akut apandisit, acil servis

INTRODUCTION

Acute appendicitis (AA) is one of the most common causes of abdominal pain requiring immediate medical attention among adults presenting to the emergency department[1–3]. The lifetime incidence of AA is approximately 7%, and the perforation rate can reach up to 20%.[3] The symptoms and clinical findings of patients may be non-specific, which makes an early diagnosis difficult[4]. The diagnosis of AA is largely based on clinical features, and in selected cases, radiological findings[4–7]. Failure to diagnose AA in the early period may lead to negative consequences, such as perforation and appendicular abscesses, which are associated with significant morbidity and even mortality[4–8].

To facilitate a reliable diagnosis of AA, clinical scoring systems such as the Alvarado and the Raja Isteri Pengiran Anak Saleha Appendicitis (RIPASA) scoring systems have been developed[9]. However, due to their lack of sensitivity and specificity, the role of these scoring systems in determining the severity of AA remains controversial[9–12]. In addition to scoring systems, various blood tests have been used to predict the severity of AA. Although white blood cell (WBC) count, C-reactive protein (CRP), procalcitonin, and serum bilirubin levels are generally elevated in patients with appendicitis, they do not have sufficient sensitivity and specificity in differentiating between uncomplicated AA (UAA) and complicated AA (CAA) cases, as is the case with scoring systems[9–14]. Therefore, studies have been conducted to identify markers that can predict UAA and CAA in patients with AA. Recently, due to their easy availability and affordability, the use of complete blood count parameters as biomarkers of many inflammatory diseases has become widespread. The literature has reported that parameters such as red blood cell distribution width, the neutrophil/lymphocyte ratio (NLR), and the platelet/lymphocyte ratio (PLR) are important indicators of systemic inflammation and can be used to determine its prognosis[8,15–17]. The systemic immune-inflammatory index (SII) is a new inflammatory index developed to simultaneously reveal the inflammatory and immune status of patients through the calculation of neutrophil count × platelet count / lymphocyte count[18,19]. SII has been shown to be an accurate marker for inflammation and immune response[20]. Inflammation is prominent in AA, and changes in SII are inevitable. Therefore, SII is likely to be a predictive factor for complications in AA. No previous studies in the literature have examined SII as a predictor of the UAA and CAA distinction. The aim of this study was to evaluate whether NLR, PLR, and SII could be used to predict AA. We also aimed to determine whether SII was a good predictive marker for CAA.

MATERIALS AND METHODS

Participants

This study was conducted between January 1, 2019, and July 31, 2022, at Aksaray Training and Research Hospital, which is a tertiary emergency department that receives an average of 30,000 patients per month. Prior to the study, approval was obtained from the Ethics Committee of Aksaray University Faculty of Medicine (approval number: 2022/02-11). Patient data collected by the researchers were kept private and confidential, and the study was conducted in accordance with the Declaration of Helsinki. The study included retrospectively collected data; therefore, informed consent was waived.

The inclusion criteria were as follows: 1) patients over 18 who experienced ED with abdominal pain, 2) patients who were diagnosed with AA by laboratory tests, USG, and tomography, whose diagnosis was confirmed by general surgery, and who were hospitalized, 3) patients with acute AA that was detected in the histological examination of the appendectomy sample, and 4) patients whose complete records were available for inclusion in the study.

The following patients were excluded from the study: patients with an active infection, a history of inflammatory disease, a fever of unknown origin, active hematological or liver disease, inflammatory bowel disease (Crohn's disease or ulcerative colitis), or a tumor diagnosis according to the pathology result, and patients without complete records.

Procedure

The patients were divided into three groups: the UAA, CAA, and control groups. The UAA group included patients who underwent appendectomy and

had histopathologically confirmed appendiceal inflammation. The CAA group consisted of patients who underwent appendectomy with histopathological findings of perforation, abscesses, and/or any other findings supporting CAA, such as necrosis and gangrene. The control group consisted of patients diagnosed with non-inflammatory abdominal pain (colic pain, inguinal hernia, umbilical hernia, etc.) by physical examination, imaging (CT, USG) and laboratory results in the emergency department.

For all patients in the three groups, the following were obtained from the electronic medical database of the hospital: laboratory results of the blood sample taken at the time of first presentation to the emergency department, abdominal ultrasonography (USG) and abdominal tomography (CT) findings, demographic data, clinical characteristics, and surgical operation notes.

Statistical analysis

SPSS v. 22.0 software package was used for the statistical analysis of the data (version 22.0; SPSS, Inc, Chicago, IL, USA). Descriptive statistics were presented as number, mean ± standard deviation, median (25th-75th percentiles), and percentage (%) values. The conformity of the variables to the normal distribution was analyzed with analytical methods (Kolmogorov-Smirnov test). The chi-square test was conducted to compare categorical variables between two groups. Student's t-test was used for normally distributed data and the Mann-Whitney U test for data without a normal distribution. The one-way analysis of variance test was used to compare the mean values of the CAA, UAA, and control groups. The relationship between clinical variables and CAA and UAA was investigated with a univariate logistic regression analysis. A multivariate logistic regression analysis was undertaken to identify independent predictors after adjusting for possible interactions between parameters, and the odds ratio (OR) and 95% confidence interval (CI) values were determined. The receiver operating characteristic (ROC) analysis was performed to calculate sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) according to the optimal cut-off values of the NLR, PLR, and SII in predicting CAA and UAA. The area under the curve (AUC) values were also obtained. The Delong test was used to compare the AUC values of the parameters (sensitivity +1 − specificity). An AUC value of 0.5-0.6 was interpreted as poor, 0.6-0.7 as moderate, 0.7-0.8 as acceptable, 0.8-0.9 as excellent, and >0.9 as outstanding. A p value of <0.05 was considered statistically significant in all tests. G*Power 3.1 program was used for power analysis of the study. Due to the retrospective nature of the study, in the posthoc type power analysis, the effect size was 0.95 and the type 1 error value was accepted as 0.01, and it was calculated that the sample size of 1415 individuals corresponded to a power of 1.0.

RESULTS

Of the 3229 patients included in the study, 1773(active infection:457, a history of inflammatory disease:39, a fever of unknown origin:17, active hematological or liver disease:108, inflammatory bowel disease :28, a tumor diagnosis according to the pathology result:42, and patients without complete records) were excluded. The study included a total of 1,456 patients, of whom 628 had UAA, 104 had CAA, and 714 were controls. The mean age was 33.2 ± 14.1 years for the UAA group, 34.3 ± 13.4 years for the CAA group, and 34.8 ± 13.6 years for the control group. The male patients constituted 56.1 and 58.5% of the patients in the UAA and CAA groups, respectively. There was no significant difference between the study groups according to gender ($p = 0.163$). The demographic data and hematological parameters of the sample are shown in Table 1.

The NLR, PLR, and SII values were 6.11 ± 1, 20.158 ± 75.6, and 1,797.8 ± 430.2, respectively, in the UAA group; 8.72 ± 5.26, 178 ± 59.1, and 2,514.3 ± 890.9, respectively, in the CAA group; and 2.47 ± 1.21, 143 ± 77.4, 757.1 ± 303.6, respectively, in the control group. All the three parameters were statistically significantly higher in the UAA group than in the control group ($p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively). Similarly, The NLR, PLR, and SII values were statistically significantly higher in the CAA group than in the control group ($p < 0.001$, $p < 0.03$, and $p < 0.001$, respectively) and the UAA group ($p < 0.001$ for all). Statistically significant parameters were included in a logistic regression model. Table 2 presents the diagnostic accuracy of biomarkers that were found to be significant for the differential diagnosis of UAA and CAA in the ROC analysis.

The cut-off values of neutrophil count, CRP, NLR, and SII for the prediction of CAA were determined to be 11.7 (51.46% sensitivity, 70.32% specificity),

39.9 (68.42% sensitivity, 78.61% specificity), 6.9 (56.1% sensitivity, 75.4% specificity), and 1,989.2 (78.44% sensitivity, 88.52% specificity), respectively. We performed the ROC analysis to determine the power of the neutrophil count, CRP, NLR, and SII in predicting CAA. The AUC value of SII was found to be 0.809. The CAA predictive power of SII was much higher than that of NLR (AUC: 0.729), neutrophil count (AUC: 0.696), and CRP (AUC: 0.732) alone (Table 3).

Table 1. Demographic features and hematologic parameters of the groups

Variables	UAA group (n = 628)	CAA group (n = 104)	Control group (n=714)	P-value*	P-value* UAA-CG	P-value* CAA-CG	P-value* UAA-CAA
Age (years)	33.2 ± 14.1	34.3 ± 13.4	34.8 ± 13.6	0.06	<0.001*	0.134	0.026*
Sex, male	343 (56.1%)	24 (58.5%)	109 (55.6%)	0.163			
Laboratory parameters							
WBC (x10^9/L)	14.54 ± 3.59	16.36 ± 4.09	8.16 ± 2.05	< 0.001*	<0.001*	<0.001*	<0.001*
Neutrophil, (x10^9/L)	11.16 ± 4.32	13.91 ± 4.61	5.72 ± 2.06	< 0.001*	<0.001*	<0.001*	<0.001*
Platelet, (x10^9/L)	296 (235-343)	288 (225-337)	300 (237-343)	0.246			
Lymphocyte, (x10^9/L)	1.83 ± 0.65	1.59±0.79	2.09 ± 0.79	< 0.001*	<0.001*	<0.001*	<0.001*
CRP (mg/dL)	52.67 ± 25.65	65.97 ± 31.06	4.06 ± 5.12	< 0.001*	<0.001*	<0.001*	<0.001*
NLR	6.11 ± 1.20	8.72 ± 5.26	2.47 ± 1.21	< 0.001*	<0.001*	<0.001*	<0.001*
PLR	158 ± 75.6	178 ± 59.1	143 ± 77.4	< 0.001*	<0.03*	<0.001*	<0.001*
SII	1,797.8 ± 430.2	2,514.3 ± 890.9	757.1 ± 303.6	< 0.001*	<0.001*	<0.001*	<0.001*

Data are presented as mean ± standard deviation, median and 25th-75th percentiles or number (percentage), *p-value significant at <0.05. UAA, uncomplicated acute appendicitis; CAA, complicated acute appendicitis; CRP, C-reactive protein; WBC, white blood cell; NLR, neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio; SII: systemic immune-inflammation index

Table 2. Predictors of CAA as determined by univariate and multivariate logistic regression analyses

Variables	Univariate logistic regression			Multivariate logistic regression	
	OR (95% CI)	P-value		OR (95% CI)	P-value
White blood cell	1.72 (1.05–3.16)	<0.001		1.32 (0.67–3.84)	0.116
Neutrophil	2.24 (1.14–4.28)	<0.001		1.78 (0.94–3.44)	0.036*
Lymphocyte	2.05 (1.76–2.91)	<0.001		1.38 (1.28–5.96)	0.097
CRP	2.32(1.36–3.91)	<0.001		1.88 (1.18–5.96)	<0.001*
NLR	2.86 (1.58–4.28)	<0.001		2.43 (1.67–4.95)	<0.001*
PLR	2.25 (1.76–4.91)	<0.001		1.71 (1.28–3.96)	0.059
SII	5.38 (3.18–8.45)	<0.001		4.65 (2.31–10.17)	<0.001*

OR: odds ratio; CI: confidence interval; CRP, C-reactive protein; NLR: neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio; SII: systemic immune-inflammation index, *p-value significant at <0.05.

Table 3. ROC curve analysis for the prediction of CAA

Variables	AUC (95% CI)	Cut-off value	Sensitivity (%)	Specificity (%)	+LR	-LR	PPV (%)	NPV (%)	P value
NLR	0.729 (0.684-0.790)	>6.9	56.14	75.47	3.04	0.54	75.0	64.3	0.006
CRP	0.732 (0.675-0.772)	>39.9	68.42	78.61	3.16	0.49	75.3	66.4	<0.001
Neutrophil	0.696 (0.645-0.733)	>11.7	51.46	70.32	2.78	0.60	73.3	59.9	0,754
SII	0.809 (0.768-0.844)	>1,989.2	78.44	88.52	5.16	0.25	78.7	73.4	<0.001

ROC: receiver operating characteristic; AUC: area under the ROC curve; CI: confidence interval, +LR: positive likelihood ratio; −LR: negative likelihood ratio; PPV: positive predictive value; NPV: negative predictive value, CI: confidence interval; CRP, C-reactive protein; NLR: neutrophil/lymphocyte ratio; SII: systemic immune-inflammation index.

DISCUSSION

Radiological methods, especially USG and CT, are widely and successfully used in the diagnosis of AA, which is one of the most common causes of emergency surgery, as well as in the evaluation of AA-related complications[6,20]. However, these methods require special equipment and experienced radiologists and have other disadvantages, such as radiation exposure, high cost, and accessibility problems[20-24]. Therefore, simple laboratory parameters would be useful for physicians working in the emergency department in terms of the prognosis and treatment management of UAA and CAA. In this study, we investigated whether SII could predict AA and differentiate between UAA and CAA. To our knowledge, this is the first study to examine SII as a marker for UAA and CAA differentiation.

In this study, we found statistically significantly higher SII values in the patients with AA (UAA and CAA groups) compared to the controls ($p < 0.001$). In the prediction of CAA, the AUC and OR values of SII were higher than those of neutrophil count, CRP, and NLR alone. We determined that the patients with CAA who had an SII level greater than 1989.2 had a 4.65-fold increased risk of developing CAA than the remaining AA cases with a lower SII. In the ROC analysis, SII had a sensitivity of 78.4% and specificity of 88.5% in the prediction of CAA (AUC: 0.809, 95% CI: 0.768-0.844). These findings suggest that SII is a useful diagnostic and predictive marker for both UAA and CAA.

WBC count and CRP are among the important parameters that are most frequently used in the diagnosis of AA. However, they are not sufficient for the diagnosis of AA due to their low sensitivity and specificity. Previous studies reported that the sensitivity of WBC ranges from 57 to 87%, and its specificity from 43 to 92% [21,22]. In other studies, CRP had a PPV of 95% for AA, a specificity of 52-72%, and a sensitivity of 61-85% [20,24]. In the current study, the WBC count and CRP values had sensitivity values of 51.46% and 68.42%, respectively, and specificity values of 70.32% and 78.61%, respectively, which is in agreement with the literature. The results of our study showed that both parameters were useful diagnostic markers for AA, but CRP was more useful than WBC count in determining the severity of AA.

Many studies have shown that a high NLR can be used to show the severity of the inflammatory response [20,24]. Hajibandeh et al.[8] determined that at a cut-off value of 4.7, NLR predicted the diagnosis of AA with a sensitivity of 88.89% and specificity of 90.91%, while for the diagnosis of CAA, this parameter had 76% sensitivity and 100% specificity at a cut-off value of 8.8. In another study, Ishizuka et al.[25] reported 73% sensitivity and 39% specificity for NLR at a cut-off value of 8.0 in differentiating between CAA and UAA. In our study, when the cut-off value of NLR was taken as 6.9, it was found to have 56.1% sensitivity and 75.4% specificity in predicting CAA, which is similar to the literature. Despite the discrepancies concerning the cut-off values, we believe that NLR is an important parameter in the diagnosis of AA and in differentiating between complicated and uncomplicated cases.

SII, a new-generation comprehensive systemic inflammatory index, has been reported to be a prognostic marker in some malignant diseases, autoimmune diseases, such as Behçet's disease and ankylosing spondylitis, abdominal infections, and many other diseases and conditions, from low-level infection to sepsis [19,20,26-29]. It has been suggested that SII is a more successful marker than PLR and NLR in showing inflammation and immune response [20-27]. Duyan et al. determined that SII could predict AA better than NLR and WBC count [20]. However, despite the presence of many studies in the literature investigating the ability of parameters such as NLR, WBC count, and CRP, to predict CAA, we did not find any study investigating the relationship between CAA and SII. According to the data obtained from our study, SII presents as a more valuable parameter than NLR, WBC count, and CRP alone in predicting the diagnosis of AA and CAA.

There are some limitations to our study. First, it was conducted at a single center. Second, although the number of cases was sufficient, the data were limited due to the retrospective design. Lastly, we were not able to examine the relationship between UAA and CAA, since the parameters were calculated at the time of the patients' first presentation to the emergency department.

The results of this study showed a strong relationship between SII and AA and CAA. SII is a cost-effective, useful, and easily accessible marker that can predict both the diagnosis and severity of appendicitis. It can be a useful indicator for the follow-up of appendicitis cases waiting for emergency appendectomy or for the decision to perform emergency appendectomy in level II emergency departments with a high patient

load. It can also be used effectively in cases where it is difficult to access CT or its use is contraindicated (pregnant women or pediatric patients). There is a need for larger and multicenter prospective studies on this subject to confirm our findings.

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