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Predictive Role of Hematological Markers on Pediatric Appendicitis: Still a Mystery

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ABSTRACT

Aim: The diagnosis of appendicitis may be challenging in the pediatric population. It can be very difficult to examine a child or to take a medical history. The role of laboratory findings is still unclear. Therefore, we aimed to evaluate the diagnostic value of hematological parameters such as white blood cell, neutrophil to eosinophil ratio, and neutrophil to lymphocyte ratio.

Material and Methods: We retrospectively analyzed patients who underwent surgery with suspected appendicitis between February 2018 and February 2020. Preoperative data were gathered from patient records. Histopathological assessment was accepted as the gold standard in the diagnosis of appendicitis.

Results: The study population consists of 368 patients with a mean age of 11.95±3.68 years, 56.25% (n=207) of whom were male. The pathological examination revealed that 63.6% (n=234) of the patients were acute appendicitis, 18.5% (n=68) phlegmonous, and 8.7% (n=32) perforated. White blood cells, neutrophil-eosinophil ratio, and neutrophil-lymphocyte ratio were not diagnostic in acute appendicitis. On the other hand, the same parameters are useful markers in differentiating phlegmonous and perforated appendicitis.

Conclusion: There is no established biomarker for acute appendicitis. Although the white blood cell count is a well-known parameter in scoring systems, it is not capable of guiding the surgeon. The neutrophil to eosinophil ratio may be a novel diagnostic index for phlegmonous and perforated appendicitis. Understanding whether a child is experiencing appendicitis is still a diagnostic challenge for the clinician. Although clinical symptoms, scoring systems, and imaging methods and laboratory tests are important in the diagnosis of appendicitis, there are not any specific markers helping the surgeon.

Keywords: Appendicitis; neutrophil to eosinophil ratio; white blood cell; neutrophil to lymphocyte ratio; pediatric surgery.

Hematolojik Belirteçlerin Pediatrik Apandisitte Tanısal Rolü: Gizemini Koruyor

ÖZ

Amaç: Apandisit tanısı pediyatrik popülasyonda zor olabilir. Çocukları muayene etmek veya hikaye almak oldukça zor olabilmektedir. Laboratuvar bulgularının rolü hala belirsizdir. Bu nedenle beyaz kan hücresi, nötrofil / eozinofil oranı ve nötrofil / lenfosit oranı gibi hematolojik parametrelerin tanısal değerinin değerlendirilmesi amaçlandı.

Gereç ve Yöntemler: Şubat 2018 ile Şubat 2020 arasında apandisit şüphesiyle ameliyat edilen hastalar retrospektif olarak incelendi. Ameliyat öncesi veriler hasta kayıtlarından toplandı. Apandisit tanısında histopatolojik değerlendirme altın standart olarak kabul edildi.

Bulgular: Çalışma popülasyonu, yaş ortalaması 11,95±3,68 yıl idi, % 56,25'i (n=207) erkek olmak üzere 368 hastadan oluşmaktadır. Patolojik inceleme hastaların % 63,6'sının (n=234) akut apandisit,% 18,5'inin (n=68) flegmonöz ve % 8,7'sinin (n=32) perfore olduğunu ortaya koydu. Akut apandisitte beyaz kan hücreleri, nötrofil-eozinofil oranı ve nötrofil-lenfosit oranı tanısal değildi. Öte yandan, aynı parametreler flegmonöz ve perfore apandisiti ayırt etmede yararlı belirteçlerdir.

Sonuç: Akut apandisit için spesifik bir biyobelirteç yoktur. Beyaz kan hücresi sayısı skorlama sistemlerinde iyi bilinen bir parametre olmasına rağmen, cerraha yol gösterme kabiliyetine sahip değildir. Nötrofil / eozinofil oranı, flegmonöz ve perfore apandisit için yeni bir tanı indeksi olabilir. Bir çocuğun apandisit olup olmadığını anlamak bazen cerrahları zorlamaktadır. Klinik semptomlar, skorlama sistemleri, görüntüleme yöntemleri ve laboratuvar yardımcı olsa da cerraha tanı koyduracak spesifik bir yöntem veya marker bulunmamaktadır.

Anahtar Kelimeler: Apandisit, nötrofil-eozinofil oranı, beyaz küre, nötrofil-lenfosit oranı, çocuk cerrahi.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is The most frequent abdominal emergency in the pediatric population is appendicitis (1). Diagnosis of appendicitis may be challenging in the pediatric population due to nonspecific symptoms and patient incompatibility.. The risk of complications such as perforation (20%-50%) (2) is higher than in adults, while negative laparotomy rates range from 9% to 40%. (2,3).

Accurate diagnosis rates have improved with the assistance of sonography and computed tomography (4). However, radiation exposure is the main limitation of the computed tomography, and the accuracy of the sonography is operator dependent. White blood cell (WBC) count supports clinical data and contributes to scoring systems, but its specificity is relatively low (5). Several studies have suggested that normal WBC and C-Reactive Protein (CRP) levels can be used to determine the need for surgery in adult patients (6). Also, these parameters can be used in the exclusion of appendicitis in the pediatric population (7).

Increasing evidence has reported a correlation between bacterial infections and hematological markers such as eosinopenia and lymphopenia (8,9). Deep eosinopenia is defined as a good marker for the early diagnosis of bacterial infections (10).

Decreased eosinophil count and increased neutrophil count have been associated with bacterial infections, so we hypothesized that the neutrophil/eosinophil ratio (NER) would be a useful predictor of appendicitis in children.

MATERIAL AND METHODS

Study Design and Settings

This study was conducted in retrospective design in a single tertiary healthcare center. Data were gathered from pediatric patients who underwent appendectomy between February 2018 and February 2020. Ethics committee approval was obtained from the Aksaray University Human Research Ethics Committee with protocol number 2020/09-43 and dated 21.10.2020.

Study Population

All patients between the ages of 1 and 18 years who underwent an operation for appendicitis were analyzed. A total of 34 patients (9.2%) were excluded from the study because of negative laparotomy. The remaining 334 patients were assigned into 3 groups according to the histopathological findings as acute (63,6%), perforated (8,7%) and phlegmonous (18,5%) appendicitis.

Data Collection

WBC, neutrophil, lymphocyte, and eosinophil levels of the patients were collected from patient files. The neutrophil to eosinophil ratio (NER) was calculated as the ratio of the neutrophil count to the eosinophil count. The neutrophil to lymphocyte ratio (NLR) was calculated as the ratio of the neutrophil count to the lymphocyte count.

Histopathological diagnoses (acute, perforated, phlegmonous appendicitis or non-appendicitis) of the specimens were documented.

Statistical Analysis

All statistical analyses were performed using SPSS 20.0 (IBM Corp., Armonk, NY, USA). Q-Q plots, histograms and Shapiro Wilk normality tests were used to test the assumption of normal distribution for the variables under consideration. ROC curves were constructed to illustrate the sensitivity and specificity performance characteristics of WBC, NLR, NER and cutoff values were estimated by using the index of Youden. General descriptive statistics were summarized as counts and percentages for categorical variables, and median (min-max)-mean±st.dev. for continuous variables. A "p" value of less than 0.05 was considered statistically significant.

RESULTS

Demographic and clinical characteristics of patients

Appendectomy was performed on 368 patients in 2 years in our hospital. Among them, 34 (9.2%) of the patients were excluded from the study due to negative laparotomy. Finally, the study consisted of 334 patients, the mean age was 11.95 and 56.2% were male (Table 1). 207 (56,2%) of the patients were males. According to histopathological diagnosis, 68 patients (18.5%) had phlegmonous appendicitis, 32 patients (8.7%) perforated appendicitis, and 234 patients (63.6%) had acute appendicitis (Table 2).

Table 1. Descriptive statistics for the study population

	Mean±S.Dev	Median (Min.-Max.)
Age	11.95±3.68	12.00 (1.00-18.00)
Hospitalization	1.52±1.23	1.00 (1.00-5.00)
WBC	12.51±5.04	11.80 (3.40-28.16)
Neu %	72.51±14.67	76.40(4.36-96.00)
Lym%	19.89±12.64	16.70 (2.23-60.20)
Eos%	1.08±1.72	0.50 (0.01-16.90)
NLR	6.26±5.86	4.59 (0.49-40.29)
NER	445.22±567.14	145.00(1.30-2463.00)

Table2. Frequencies of nominal variables

		Frequency	Percent (%)
Cinsiyet	Female	161	43.8
	Male	207	56.2
Acute Ap.	No	134	36.4
	Yes	234	63.6
Phlegmonous Ap.	No	300	81.5
	Yes	68	18.5
Perforated Ap.	No	336	91.3
	Yes	32	8.7

In terms of diagnostic value of WBC, NLR, and NER for acute (Figure 1), phlegmanous (Figure 2) and perforated (Figure 3) appendicitis AUC was used.

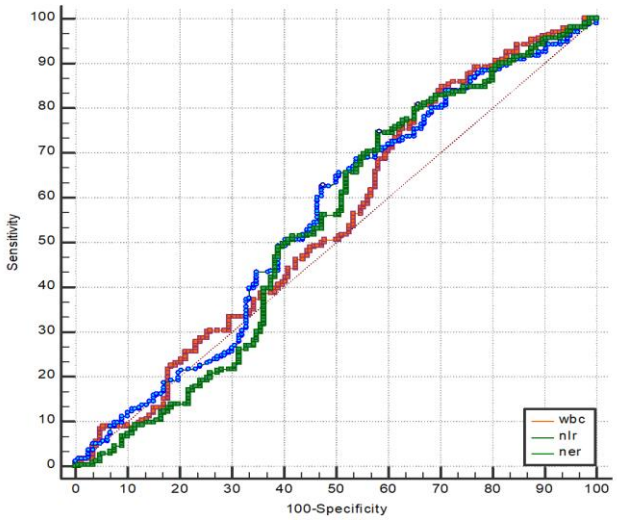

Figure 1. WBC-NLR-NER for acute appendicitis

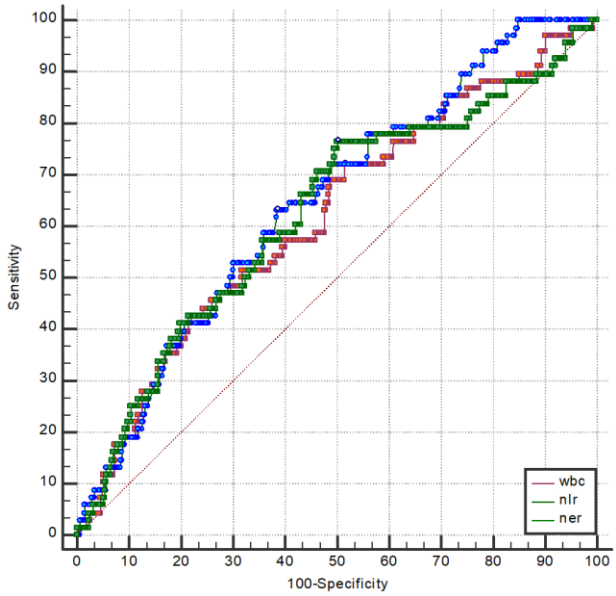

Figure 2. WBC-NLR-NER for phlegmonous appendicitis

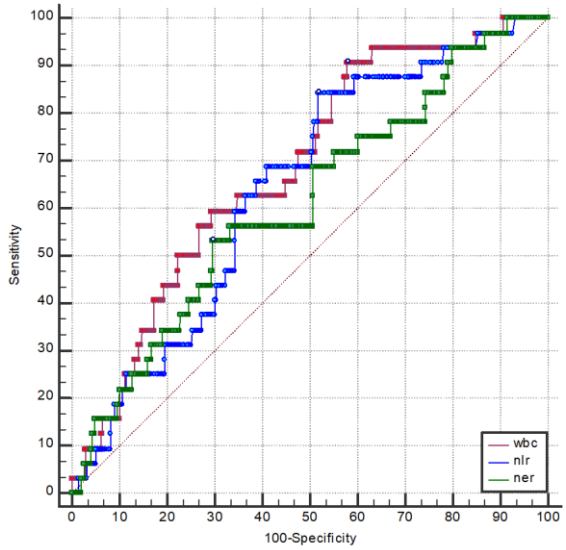

Figure 3. WBC-NLR-NER for perforated appendicitis

Diagnostic value of WBC, NER and NLR

WBC, NER and NLR are not capable of diagnosing acute appendicitis, as it is understood from Table 3 and Figure 1.

Table 3. Diagnostic performance of WBC, NLR and NER variables for acute pancreatitis

	Area	Std. Error	p	95% Confidence Interval	
				Lower Bound	Upper Bound
WBC	0.547	0.031	0.135	0.495	0.598
NLR	0.555	0.031	0.078	0.503	0.606
NER	0.538	0.032	0.242	0.486	0.589

For phlegmonous appendicitis, the areas under the diagnostic curve and thus diagnostic performance of WBC, NLR and NER variables for pancreatitis were found to be significant (p=0.002, p<0.001 and 0.001, respectively). The cut-off values calculated according to the Youden index and the corresponding sensitivity and selectivity points were calculated as follows; 72.86 sensitivity and 48.55 specificity points 11.28 as the cutpoint for WBC, 63.24 sensitivity and 61.41 specificity points 5.43 as the cutpoint for NLR and 76.47 sensitivity and 49,84 specificity points 126 as the cutpoint for NER. AUC levels were compared and no statistically significant difference was detected between WBC-NLR (p=0.334), WBC-NER (p=0.835) and NLR-NER (p=0.345). In terms of diagnostic value, there was no statistically significant difference between these three parameters (Table 4 and Figure 2).

Table 4. Diagnostic performance of WBC, NLR and NER variables for phlegmonous appendicitis

	Area	Std. Error	p	95% Confidence Interval	
				Lower Bound	Upper Bound
WBC	0.616	0.038	**0.002**	0.565	0.666
NLR	0.645	0.035	**<0.001**	0.595	0.693
NER	0.623	0.039	**0.001**	0.572	0.672

Similar to phlegmonous appendicitis, the diagnostic performance of WBC, NLR and NER variables were found to be significant for perforated appendicitis (p<0.001, p<0.001 and 0.036, respectively) (Table 5). Since WBC, NLR and NER variables were found to have significant discriminating power for perforated appendicitis, the cut-off points for these variables were calculated according to the Yuden index and expressed as follows; 10.45 as the cut-off for WBC (sensitivity:90.62 - specificity: 42.07), 4.10 as the cut-off for NLR (sensitivity:84.37 - specificity: 48.13) and 445 for NER (sensitivity:53.13 - specificity: 70.32). AUC levels were compared and no statistically significant difference was detected between WBC-NLR (p=0.380), WBC-NER (p=0.130) and NLR-NER (p=0.346). In terms of diagnostic value, there was no statistically significant difference between these three parameters.

Table 5. Diagnostic performance of WBC, NLR and NER variables for perforated appendicitis

	Area	Std. Error	p	95% Confidence Interval	
				Lower Bound	Upper Bound
WBC	0.683	0.045	<0.001	0.634	0.730
NLR	0.644	0.045	<0.001	0.593	0.692
NER	0.610	0.052	0.036	0.559	0.660

DISCUSSION

Appendicitis is one of the diseases that require emergent surgical intervention in childhood. Phlegmonous appendicitis can easily lead to perforation (1,2). Therefore accurate examination and surgery are necessary. Early diagnosis of cases 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 (1-4).

Understanding whether a child is experiencing appendicitis is still a diagnostic challenge for the clinician. Although clinical symptoms, scoring systems, and imaging methods and laboratory tests are important in the diagnosis of appendicitis, there are not any specific markers helping the surgeon.

Appendicitis usually begins as local inflammation and becomes a generalized inflammatory response. Laboratory tests are used to detect the systemic inflammation (10). Although, various markers have been used to improve the correct diagnosis of appendicitis (11-15) none of them were reliable in diagnosing appendicitis in children.

There are so many studies concerning appendicitis in children, and they are aiming to decrease negative laparotomy rates, and related complications. Negative laparotomy rate ranges between 9% and 40% in the literature (2,3,). We encountered a ratio of 9.2% for negative laparotomy in this study.

Some studies have shown that normal WBC and CRP levels can exclude appendicitis in adults (18). It is important to remember the fact that serum inflammatory markers are age-dependent (17), the adult results have not been proven in children. Gronroos (16) has shown that 7 children with normal levels of WBC and CRP. Shellekens et al. have shown that leukocytes had better diagnostic accuracy for appendicitis (20).

The NLR is a recently developed inflammatory marker, which is promising for diagnosing appendicitis in children. Indeed, the potential role of NLR in the diagnosis of appendicitis has been observed in several studies (22,23). Furthermore, Markar et al. have reported that NLR has a better diagnostic accuracy than WBC (24).

In our study we observed the diagnostic value of WBC, and NLR for appendicitis in children and there was no statistically significant difference between these two parameters.

On the other hand, eosinopenia is a good marker for bacterial infections with a specificity of 91% (9). The pathophysiology of eosinopenia in bacterial infections is still unclear. Eosinophils seem to be active in immune response and also they have bactericidal effects (21). The systemic inflammatory response causes neutrophilia and eosinopenia, resulting in an increase in NER, which is a novel parameter defined in our study.

This study should be evaluated in light of some limitations. First, our study as retrospective manner. More patients who underwent appendectomy may reflect the actual potential of NER in children. Secondly, we did not record the onset of symptom initiation, so we could not accurately predict the effect on the parameters.

CONCLUSION

In our study, diagnostic values of WBC, NLR, and NER were evaluated for appendicitis in children. WBC, NER, and NLR, which are understood to have no diagnostic power for acute appendicitis, have the ability to diagnose with indistinguishable accuracy in the diagnosis of phlegmonous and perforated appendicitis. These parameters are easily measured in emergency departments.

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