

A New Marker in the Diagnosis of Acute Complicated Appendicitis in Adult Patients: Neutrophil / Albumin Ratio**Erişkin Hastalarda Akut Komplike Apandisit Tanısında Yeni Bir Belirteç: Nötrofil / Albümin Oranı**Serdar ŞAHİN¹**ABSTRACT**

AIM: Our study aims to search the effectiveness of neutrophil/albumin ratio (NAR) in distinguishing between acute appendicitis (AA) and acute complicated appendicitis (ACA) and to find the best cut-off point of neutrophil/albumin ratio (NAR) for the diagnosis of ACA.

MATERIAL AND METHOD: This study was performed using data from 453 adult patient who underwent appendectomy and divided into two groups as AA and ACA. Demographic data, preoperative white blood cell count (WBC), neutrophil lymphocyte ratio (NLR), neutrophil/albumin ratio (NAR), C-reactive protein value (CRP) surgical outcomes, and pathological outcomes were retrospectively assessed for each groups.

RESULTS: In our study, 362 patients were in the AA group and 91 patients were in the ACA group. WBC, NLR, CRP and NAR were significant parameters in differentiating acute appendicitis from acute complicated appendicitis. Among these parameters, NAR; AUROC sensitivity and specificity values were stronger than others. (AUROC: 0.963, sensitivity: 95.6%, specificity: 85.7%). As a result of the ROC curve analysis, a cut-off value of 2.79 mg/dl was found.

CONCLUSION: NAR is a novel inflammatory marker simply detected through routine preoperative blood results, with no additional time or cost. The neutrophil/albumin ratio (NAR) is a fast, easy to access and reliable parameter to differentiate AA from ACA.

Keywords: Appendicitis, neutrophil/albumin ratio, diagnosis.

ÖZET

AMAÇ: Çalışmamız, akut apandisit (AA) ile akut komplike apandisit (ACA) arasında ayırım yapmada nötrofil/albumin oranının (NAR) etkinliğini araştırmayı ve ACA tanısında nötrofil/albumin oranının (NAR) en iyi kesme noktasını bulmayı amaçlamaktadır.

MATERYAL VE METOD: Araştırmacı, bu çalışmayı apendektomi geçirmiş yetişkin 453 hastanın verilerini kullanarak gerçekleştirdi. Demografik veriler, preoperatif beyaz küre sayısı (WBC), nötrofil lenfosit oranı (NLR), nötrofil/albumin oranı (NAR), C-reaktif protein değeri (CRP) cerrahi sonuçları ve patolojik sonuçlar geriye dönük olarak değerlendirildi. Yazarlar hastaları AA ve ACA şeklinde iki gruba ayırmıştır.

BULGULAR: Çalışmamızda AA grubu 362, ACA grubu 91 hastadan oluştu. WBC, NLR, CRP ve NAR, akut apandisit ile akut komplike apandisit ayırımında önemli parametrelerdi. Bu parametreler arasında NAR; AUROC duyarlılık ve özgüllük değerleri diğerlerinden daha güçlüydü. (AUROC: 0.963, duyarlılık: %95.6, özgüllük: %85.7). ROC eğrisi analizi sonucunda 2,79 mg/dl cut-off değeri bulundu.

SONUÇ: NAR, ek zaman ve maliyet gerektirmeyen, rutin preoperatif kan sonuçlarıyla kolayca saptanan yeni bir inflamatuvar belirteçtir. Nötrofil/albumin oranı (NAR), AA'yı ACA'dan ayırt etmek için hızlı, erişimi kolay ve güvenilir bir parametredir

Anahtar kelimeler: Apandisit, nötrofil/albumin oranı, tanı

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INTRODUCTION

Acute abdominal pain's and abdominal surgical urgency's most common cause is acute appendicitis (AA)¹. While the symptoms and clinical outcomes of AA are well known, early diagnosis can sometimes be difficult². Delay in the diagnosis of early onset AA is a significant problem increasing the risk of complications associated with morbidity and mortality³. As a result, early diagnosis and treatment of ACA are critically important for effective clinical care. The lifetime risk of AA in the United States is about 7%-9%⁴. The risk of perforation was generally given as 20% in the studies⁵. However, this rate can reach up to 50% in elderly patients^{6,7}.

Many studies have researched the early diagnosis of AA. Scoring systems such as Alvarado and RIPASA scores have been criticized for their lack of high specificity⁸. In the literature, blood parameters and biomarkers such as the number of white blood cells (WBC), sedimentation (ESR), C-Reactive protein (CRP), bilirubin levels, neutrophil/lymphocyte ratio (NLR) have been used in the diagnosis of AA and in distinguishing ACA⁹⁻¹³. Additionally, radiological methods were also preferred in this distinction¹⁴. However, it is difficult to separate between uncomplicated and complicated appendicitis. To make this distinction, a new method and/or markers with high sensitivity and specificity are needed.

The neutrophil/albumin ratio (NAR) is a simple, inexpensive and new marker that can be easily calculated from preoperative blood samples. The number of neutrophils increases in active and ongoing inflammation¹⁵. Albumin is a well-known acute phase protein⁶. In this study, our aim was to investigate whether the neutrophil/albumin ratio can distinguish between AA and ACA. The result was to find a cut-off value.

MATERIAL AND METHOD

This study was conducted to retrospectively evaluate 453 adult patients that had undergone appendectomy with the diagnosis of acute appendicitis between 2016-2020, after the Ethics Committee of Kırşehir Ahi Evran University Faculty of Medicine's approval (Decision Number:2021-09/95). Patients who are pregnant, younger than 18 years old, postpartum women and with additional diseases (diabetes mellitus, heart and liver disease, hematological disease, etc.) that may affect inflammatory markers, and cases where AA was excluded because of pathology were not included in the study.

Demographic data, preoperative laboratory values, surgical findings and postoperative histopathology results of 453 cases were analyzed using hospital database records and patient files. Neutrophil count (NEU), lymphocyte count (LYM), White blood cell count (WBC), albumin (Alb), C-reactive protein (CRP) and neutrophil lymphocyte ratio (NLR) values were analyzed using the results of blood samples taken before surgery.

The study divided the patients into 2 groups as AA and ACA. This distinction was based on operative surgical observations, operative notes, and histopathological reports. The AA group consisted of cases with intraoperative gangrene, abscess, perforation, inflamed appendix without purulent fluid, and the ACA group consisted of cases with perforated appendix, abscess formation, purulent fluid in the surgical reports or reported as perforation in the histopathological examination. In this study, we statistically compared and analyzed the demographic data and preoperative laboratory findings.

Statistical analysis:

The data were assessed using the IBM SPSS Statistics for Windows, Version 23.0 software package (IBM Corp.). The unit count and percentage, mean, SD, and median values were provided as descriptive statistics. By using the Shapiro-Wilk test, normality test, and Q-Q graphics, we assessed numerical variables with normal distribution. When 2 groups were compared, we used the Mann-Whitney U analysis for variables, which did not have a normal distribution while we used the independent sample t-test for variables, which demonstrated a normal distribution. Receiving operating characteristic (ROC) curve analysis was performed order to determine the success of laboratory parameters in predicting cases of AA and ACA. Youden index identified the threshold values. We calculated the specificity values based on the obtained threshold values. The value of p 0,05 was set as statistically significant.

RESULTS

A total of 453 patients were studied. The blood values of 138 female and 224 male patients in the AA group, 24 female and 67 male patients in the ACA group were studied. The average age of first group

was 36.20 years (14.36%). In the second group, the average age was 36.55 (16.50%). The youngest patient was 18 years old while the oldest one was 82.

According to the histopathology results, 362 patients (79.9%) have been found to have AA and 91 (20.1%) had ACA. In both groups, the number of men is greater than the women. This was a statistically significant difference (p=0.037). In the ACA group, the mean values of WBC, CRP, Neu/Alb, and Neu/Lym were significantly higher than those in the AA group (p<0.001 for all parameters). A comparison between the AA and ACA groups is presented in

Table 1. The comparison of demographics and preoperative laboratory values between the groups.

	Group 1 (acute appendicitis)	Group 2 (acute complicated appendicitis)	P
<i>Number of patients</i>	362 (%79.9)	91 (%20.1)	
<i>Female</i>	138 (%85.18)	24 (%14.81)	<0.037
<i>Male</i>	224 (%76.97)	67 (%23.02)	<0.037
<i>WBC</i>	11.86 (std:3.50)	18.26 (std:2.86)	<0.001
<i>CRP</i>	2.76 (std:4.33)	6.86 (std:8.58)	<0.001
<i>NLR</i>	4.34 (std:3.25)	11.90 (std:6.18)	<0.001
<i>NAR</i>	1.95 (std:1.09)	3.55 (std:0.58)	<0.001

WBC: White blood cell; CRP: C-reactive protein; NLR: Neutrophil/lymphocyte ratio; NAR: Neutrophil/albumin ratio.

ROC curves were drawn to calculate the efficiency of laboratory parameters (WBC, CRP, Neu/Lym, Neu/Alb) in the diagnosis between AA and ACA is presented in

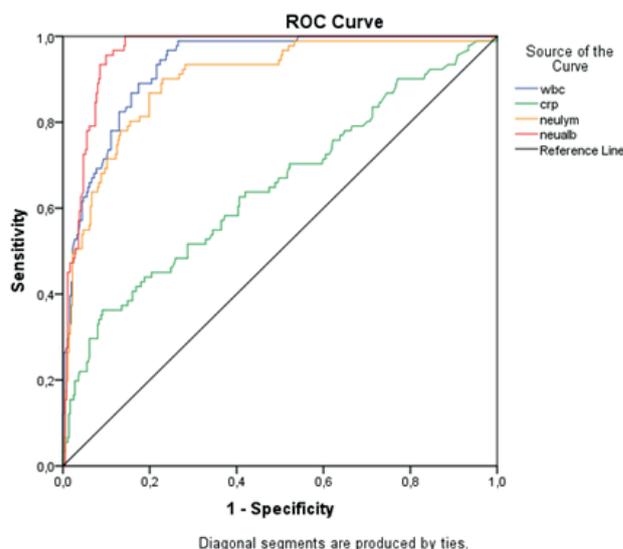


Figure 1. Receiver operating characteristic curve (ROC) analysis of laboratory parameters in distinguishing between the groups.

The prediction of diagnosis between all parameters and AA yielded statistically significant results (p<0.001 for all parameters).

According to the ROC curve results, the AUROC values used to differentiate AA and CA (Neu/Alb, WBC, Neu/Lym, CRP) are 0.650, 0.899,

0.932, 0.963, respectively. According to the same analysis results, the cut-off values were found as 2.79 for CRP, 14.29 for WBC, 5.56 for Neu/Lym, and 7.81 for Neu/Alb. However, the ability of NAR to predict between AA and ACA was greater than the ability of other parameters (NAR area under the ROC [AUROC]: 0.963, sensitivity: 95.6%, specificity: 85.7%). We can see the results of the ROC analysis in

Table 2. ROC analysis of parameters in predicting between the groups.

	AUROC (%)	95% confidence CI		Cut-off	Sensitivity (%)	Specificity (%)	P
		Lower limit	Upper limit				
NAR	0.963	0.947	0.978	2.79	95.6	85.7	0.000
WBC	0.932	0.909	0.956	14.29	96.7	76.0	0.000
NLR	0.899	0.863	0.935	5.56	90.1	77.1	0.000
CRP	0.650	0.582	0.717	7.81	36.3	90.9	0.000

NAR: Neutrophil/albumin ratio; WBC: White blood cell; NLR: Neutrophil/lymphocyte ratio

CRP: C-reactive protein

DISCUSSION

AA is the most common cause of emergency abdominal surgery worldwide, and appendectomy is the most common emergency surgery performed in surgical clinics worldwide^{1, 5}. Although AA is a daily routine in emergency services, its early diagnosis may not always be easy². In cases where the diagnosis or admission to the hospital is delayed for 24 hour, the risk of perforation is high¹⁷. It can be difficult to reach an accurate diagnosis in small hospitals where imaging methods are not available. For these reasons, different biomarkers were used in preoperative blood samples in patients with clinical suspicion of AA. Some of these biomarkers are WBC, Neutrophil%, neutrophil lymphocyte ratio (NLR), sedimentation (ESR), Total Bilirubin (T.Bil.), CRP and immature granulocytes^{9, 18, 19}.

AA is an acute event in which blood parameters change according to the severity of inflammation. The most frequently used markers for this distinction are WBC, CRP and recently NLR. To literature information, mild leukocytosis (WBC) is expected in acute appendicitis cases. However, there are also publications reporting that sensitivity and specificity vary⁵. In the study by Rafiq et al. A very high sensitivity (87%) and specificity (92%) were reported²⁰. The results of our current study also support the literature with a cut-off value of 14.29, sensitivity of 96.7% and specificity of 76% in the distinction between AA and ACA.

It was revealed by Goodman et al. in 1995 that the NLR ratio is a more sensitive parameter than the total leukocyte (WBC) count¹². Since this first study, many studies have been done. In the study of Beecher et al., it is said that NLR is more significant than other parameters in distinguishing between AA and ACA²¹. Because of the study, which included 17 studies by Hajibandeh et al. and was published as the first meta-analysis on this subject in the literature, the authors confirm the same result, although they found different cut-off values⁵. However, the consensus of the authors is that NLR is believed to be an important parameter in the diagnosis of AA and in differentiating complicated cases. In our study, similar results were obtained with a cut-off value of 5.56 (AUROC: 0.899 specificity: 90.1%, sensitivity: 77.1%).

Serum CRP is non-specific and one of the most widely used inflammatory monitoring parameters²². CRP is synthesized from the liver as a positive acute phase reactant in case of inflammation and its level in the blood increases²³. Therefore, it is an expected result that the CRP level increases in both the AA and ACA cases. Kim et al. emphasized that CRP could be used in the diagnosis of ACA²⁴. In another study, it was said that it was a successful parameter in distinguishing between AA and ACA²⁵. In our study, it has lower sensitivity and specificity rates in this distinction compared to other parameters. It is thought that this may be due to the difference between symptom onset and hospital admission. (AUROC: 0.650 sensitivity: 36.3 specificity: 90.9)

Albumin is synthesized in the liver as a negative acute phase reactor,

but since its synthesis is suppressed by cytokines such as TNF alpha and IL-6, the severity of inflammation and its level is inversely proportional²⁶. Considering that the Neutrophil/albumin ratio will increase in case of any inflammation, in our study, it was observed that this ratio was successful with compelling results with a cut-off value of 2.79 in distinguishing AA and ACA (AUROC: 0.963 sensitivity: 95.6%, specificity: 85.7%).

We found a statistically significant difference between the ACA and AA groups in all hematological markers (WBC, NLR, CRP and Neutrophil albumin ratio) in this study. However, the neutrophil/albumin ratio (NAR) was found to be more significant and highly specific in separating the two groups.

This study has some limitations. First, CRP and albumin values could not be reached in some patients, because it was a retrospective study. Therefore, the number of patients is limited. Additionally, we could not evaluate the duration from the onset of symptoms to the duration of admission to the hospital. That the inflammatory markers we used were affected by the abovementioned limitations is highly possible.

CONCLUSION

Early diagnosis and treatment of ACA is critically because it will increase mortality rates, postoperative morbidity and length of hospital stay. NAR is a new inflammatory marker detected simply by routine preoperative blood results, any additional time or cost. Considering the results of this study, the neutrophil/albumin ratio was presented as a usable new marker in predicting the distinction between AA and ACA.

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REFERENCES

1. Debnath J, Kumar R, Mathur A, et al. On the Role of Ultrasonography and CT Scan in the Diagnosis of Acute Appendicitis. *Indian J Surg*. Dec 2015;77(Suppl 2):221-6. doi:10.1007/s12262-012-0772-5
2. Park JJ, Kim KA, Nam Y, Choi MH, Choi SY, Rhie J. Convolutional-neural-network-based diagnosis of appendicitis via CT scans in patients with acute abdominal pain presenting in the emergency department. *Sci Rep*. Jun 12 2020;10(1):9556. doi:10.1038/s41598-020-66674-7
3. Lee JF, Leow CK, Lau WY. Appendicitis in the elderly. *Aust N Z J Surg*. Aug 2000;70(8):593-6. doi:10.1046/j.1440-1622.2000.01905.x
4. Addiss DG, Shaffer N, Fowler BS, Tauxe RV. The epidemiology of appendicitis and appendectomy in the United States. *Am J Epidemiol*. Nov 1990;132(5):910-25. doi:10.1093/oxfordjournals.aje.a115734
5. Hajibandeh S, Hajibandeh S, Hobbs N, Mansour M. Neutrophil-to-lymphocyte ratio predicts acute appendicitis and distinguishes between complicated and uncomplicated appendicitis: A systematic review and meta-analysis. *Am J Surg*. Jan 2020;219(1):154-163. doi:10.1016/j.amjsurg.2019.04.018
6. Freund HR, Rubinstein E. Appendicitis in the aged. Is it really different? *Am Surg*. Oct 1984;50(10):573-6.
7. Franz MG, Norman J, Fabri PJ. Increased morbidity of appendicitis with advancing age. *Am Surg*. Jan 1995;61(1):40-4.
8. Frountzas M, Stergios K, Kopsini D, Schizas D, Kontzoglou K, Toutouzas K. Alvarado or RIPASA score for diagnosis of acute appendicitis? A meta-analysis of randomized trials. *Int J Surg*. Aug 2018;56:307-314. doi:10.1016/j.ijsu.2018.07.003
9. Soldo I, Radisic Biljak V, Bakula B, Bakula M, Simundic AM. The diagnostic accuracy of clinical and laboratory parameters in the diagnosis of acute appendicitis in the adult emergency department population - a case control pilot study. *Biochem Med (Zagreb)*. Oct 15 2018;28(3):030712. doi:10.11613/BM.2018.030712
10. Ramasamy Ramu T, Chinnakkulam Kandhasamy S, Andappan A, Sankar TB. A Prospective Study on the Diagnostic Value of Hyperbilirubinemia as a Predictive Factor for Appendicular Perforation in Acute Appendicitis. *Cureus*. Aug 27 2018;10(8):e3214. doi:10.7759/cureus.3214
11. Keohane D, O'Leary P, Nagle M, Cichelli K, McCormack T. A Correlation of Blood Panel Results and Histologically Confirmed Appendicitis. *Cureus*. Sep 25 2020;12(9):e10641. doi:10.7759/cureus.10641
12. Goodman DA, Goodman CB, Monk JS. Use of the neutrophil:lymphocyte ratio in the diagnosis of appendicitis. *Am Surg*. Mar

1995;61(3):257-9.

13.de Carvalho BR, Diogo-Filho A, Fernandes C, Barra CB. [Leukocyte count, C reactive protein, alpha-1 acid glycoprotein and erythrocyte sedimentation rate in acute appendicitis]. *Arq Gastroenterol*. Jan-Mar 2003;40(1):25-30. Leucograma, proteína C reativa, alfa-1 glicoproteína ácida e velocidade de hemossedimentação na apendicite aguda. doi:10.1590/s0004-28032003000100006

14.Kim HY, Park JH, Lee YJ, Lee SS, Jeon JJ, Lee KH. Systematic Review and Meta-Analysis of CT Features for Differentiating Complicated and Uncomplicated Appendicitis. *Radiology*. Apr 2018;287(1):104-115. doi:10.1148/radiol.2017171260

15.Acarturk G, Acay A, Demir K, Ulu MS, Ahsen A, Yuksel S. Neutrophil-to-lymphocyte ratio in inflammatory bowel disease - as a new predictor of disease severity. *Bratisl Lek Listy*. 2015;116(4):213-7. doi:10.4149/bl_2015_041

16.Ishizuka M, Shimizu T, Kubota K. Neutrophil-to-lymphocyte ratio has a close association with gangrenous appendicitis in patients undergoing appendectomy. *Int Surg*. Oct-Dec 2012;97(4):299-304. doi:10.9738/CC1611

17.Di Saverio S, Podda M, De Simone B, et al. Diagnosis and treatment of acute appendicitis: 2020 update of the WSES Jerusalem guidelines. *World J Emerg Surg*. Apr 15 2020;15(1):27. doi:10.1186/s13017-020-00306-3

18.Unal Y. A new and early marker in the diagnosis of acute complicated appendicitis: immature granulocytes. *Ulus Travma Acil Cerrahi Derg*. Sep 2018;24(5):434-439. doi:10.5505/tjtes.2018.91661

19.Altiner S, Cebeci E, Sucu BB, et al. Role of immature granulocytes and total bilirubin values in the diagnosis of perforated appendicitis in patients over 65 years. *Rev Assoc Med Bras (1992)*. 2022;68(12):1681-1685. doi:10.1590/1806-9282.20220729

20.Rafiq MS, Khan MM, Khan A, Ahmad B. Total leukocyte and neutrophil count as preventive tools in reducing negative appendectomies. *Ulus Travma Acil Cerrahi Derg*. Mar 2015;21(2):102-6. doi:10.5505/tjtes.2015.29626

21.Beecher SM, Hogan J, O'Leary DP, McLaughlin R. An Appraisal of Inflammatory Markers in Distinguishing Acute Uncomplicated and Complicated Appendicitis. *Dig Surg*. 2016;33(3):177-81. doi:10.1159/000444101

22.Walsh AJ, Bryant RV, Travis SP. Current best practice for disease activity assessment in IBD. *Nat Rev Gastroenterol Hepatol*. Oct 2016;13(10):567-79. doi:10.1038/nrgastro.2016.128

23.Hou J, Feng W, Liu W, et al. The use of the ratio of C-reactive protein to albumin for the diagnosis of complicated appendicitis in children. *Am J Emerg Med*. Feb 2022;52:148-154. doi:10.1016/j.ajem.2021.12.007

24.Kim M, Kim SJ, Cho HJ. International normalized ratio and serum C-reactive protein are feasible markers to predict complicated appendicitis. *World J Emerg Surg*. 2016;11:31. doi:10.1186/s13017-016-0081-6

25.Kim TH, Cho BS, Jung JH, Lee MS, Jang JH, Kim CN. Predictive Factors to Distinguish Between Patients With Noncomplicated Appendicitis and Those With Complicated Appendicitis. *Ann Coloproctol*. Oct 2015;31(5):192-7. doi:10.3393/ac.2015.31.5.192

26.Chojkier M. Inhibition of albumin synthesis in chronic diseases: molecular mechanisms. *J Clin Gastroenterol*. Apr 2005;39(4 Suppl 2):S143-6. doi:10.1097/01.mcg.0000155514.17715.39