

# External validation of the Appendistat™ score and comparison with CRP levels for the prediction of complicated appendicitis

✉ Birkan Birben, M.D.,<sup>1</sup> ✉ Bedriye Müge Sönmez, M.D.,<sup>2</sup> ✉ Sadettin Er, M.D.,<sup>1</sup>  
✉ Sabri Özden, M.D.,<sup>1</sup> ✉ Murat Tuğra Kösa, M.D.,<sup>2</sup> ✉ Mesut Tez, M.D.<sup>3</sup>

<sup>1</sup>Department of Genaral Surgery, Ankara City Hospital, Ankara-Turkey

<sup>2</sup>Department of Emergency Medicine, Ankara City Hospital, Ankara-Turkey

<sup>3</sup>Department of Genaral Surgery, Ankara Trainig and Research Hospital, Ankara-Turkey

## ABSTRACT

**BACKGROUND:** In acute appendicitis, the treatment approach may vary depending on the age and comorbidities of the patient and whether the appendix is complicated. In this study, we validated the appendistat™ score, including the logistic regression model of complicated appendicitis, and compared the efficacy of this scoring with C-reactive protein in predicting complicated appendicitis.

**METHODS:** Demographic characteristics, pathology, and laboratory results of patients who underwent appendectomy for acute appendicitis were retrospectively screened, those over 18 years of age were included in the study. The appendistat™ scores, including the logistic regression model of complicated appendicitis, were obtained.

**RESULTS:** Complicated appendicitis was present in 13 (10.1%) patients and non-complicated appendicitis in 116 (89.9%). Two (15.4%) of the complicated appendicitis cases were female and 11 (84.6%) were male. The mean age of complicated appendicitis cases was 44 (20–77) years, and their median value of C-reactive protein was 41.00 mg/L. In the ROC curve analysis, the cut-off value for C-reactive protein was 23.5 mg/L and that of the appendistat™ as 9.6. The area under the curve values of the appendistat™ score and C-reactive protein were 0.787 and 0.750, respectively.

**CONCLUSION:** Appendistat™ is a successful scoring system that contains appropriate parameters. However, C-reactive protein detecting or excluding complicated appendicitis at a similar rate to Appendistat™ suggests that the latter does not have a significant advantage in clinical practice.

**Keywords:** Acute appendicitis; appendistat™ score; complicated appendicitis; C-reactive protein.

## INTRODUCTION

Increasing time periods between symptom onset and surgical treatment is a risk factor for complicated appendicitis.

[1] Pus formation, presence of necrosis, or development of perforation in the appendix due to the progression of inflammation and infection indicate complicated appendicitis. [2] The treatment approach varies depending on the patient's age and comorbidities and whether the appendix is complicated. [3] There are scoring systems that assist clinicians in the diag-

nosis of appendicitis, such as the Alvarado system. [4] However, due to the deficiency of the available scoring systems in diagnosis, new scoring systems are still being developed. Several parameters have also been used to evaluate appendicitis inflammation. Among biochemical markers, C-reactive protein (CRP), leukocyte and bilirubin values are useful in assessing the severity of inflammation. [5] In the appendistat™ scoring system, two different logistic regression models were constructed using parameters that significantly differentiate uncomplicated appendicitis (AUA) (gender, bilirubin, CRP,

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Address for correspondence: Birkan Birben, M.D.

Ankara Şehir Hastanesi, Genel Cerrahi Kliniği, 06800 Ankara, Turkey

Tel: +90 312 - 552 60 00 E-mail: birkanbirben53@gmail.com

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and leukocytes) and complicated appendicitis (gender, age, CRP, and leukocytes) according to the multivariate analysis. In this study, we validated the appendistat™ score, including the complicated appendicitis model and compared its efficacy to CRP in predicting complicated appendicitis.

## MATERIALS AND METHODS

### Patient Data

After approval of the ethics committee of Ankara Numune Training and Research Hospital of Health Sciences University (approval number: E-18-1994), patients who underwent appendectomy for acute appendicitis between February 2018 and December 2018 were retrospectively evaluated. The demographic characteristics, pathology results, total bilirubin, direct bilirubin, CRP and leukocyte values were retrospectively obtained from the medical records. According to the pathology results (pus, necrosis, and perforation), the appendicitis cases were classified as complicated, AUA, and normal findings. All patients over the age of 18 years who underwent appendectomy for acute appendicitis were included in this study. Patients that underwent interval appendectomy and presented with other pathologies and those with incomplete data were excluded from this study. The appendistat™ score was calculated based on age, gender, and CRP and leukocyte values of the patients using the following formula:

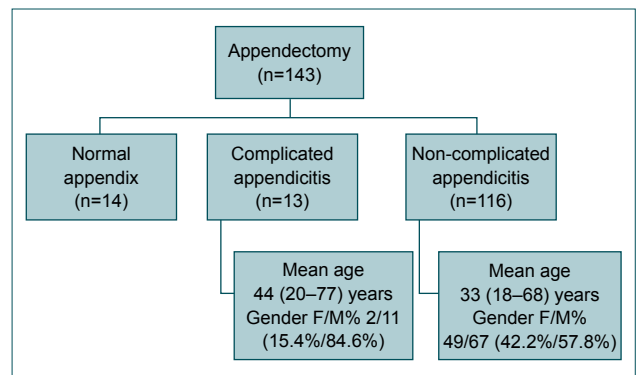
$$p = \frac{1}{1 + e^{-(8.814 + 0.364 \times \log_2 CRP + 1.768 \times \log_2 WCC + 0.025 \times \text{age} + 0.647 \times [\text{if female} | \text{if male}])}} \quad [2].$$

### Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics ver. 21.0 (IBM Co., Armonk, NY, USA). Power analysis ( $\alpha=0.05$ ; power=80%) was performed using G\*Power, version 3 (Erdfelder, Faul, & Buchner, Germany) to determine the sample size. The mean and the standard deviation (SD) were measured for calculating numerical parameters, while the frequency and the percentage were determined for categorical variables. We measured the performance of the score using receiver operating characteristic (ROC) curves, and the overall performance of the ROC analysis was quantified by computing the area under the curve (AUC) and 95% confidence intervals. An area of 1 indicated perfect performance, whereas 0.5 indicated a performance that was not different from chance. Sensitivity, specificity, as well as positive and negative predictive values are presented for the results of ROC analyses concerning optimal cutoffs.

## RESULTS

Of 143 patients that underwent appendectomy, 59 (41.3%) were female, and 84 (58.7%) were male. The mean age of the patients was 34 (18–77) years. The pathology results were normal in 14 (9.8%) patients. Of the remaining 129 patients, 13 (10.1%) had complicated appendicitis (seven periapendicular abscesses, five necrotized appendicitis, one perforated appendicitis) and 116 (89.9%) had AUA. Two (15.4%) of the complicated appendicitis were female, and 11 (84.6%) were male, with a mean age of 44 (20–77) years. In the complicated appendicitis group, the mean value of leukocytes was  $15,877 \times 10^6/L$  (3,000–25,800), and the median CRP value was 41.00 mg/L. The mean appendistat™ score of the complicated appendicitis cases was calculated as 10.11 (8.05–11.35). In the AUA group, there were 49 (42.2%) women and 67 (57.8%) men, with a mean age of 33 (18–68) years. The mean leukocyte and median CRP values of the AUA group were  $13,815 \times 10^6/L$  (3,300–31,000) and 14.00 mg/L, respectively. The patients with AUA were found to have a mean appendistat™ score of 9.07 (7.19–11.17) (Fig. 1).



**Figure 1.** Pathology results and demographic characteristics of patients that underwent appendectomy (F: Female; M: Male).

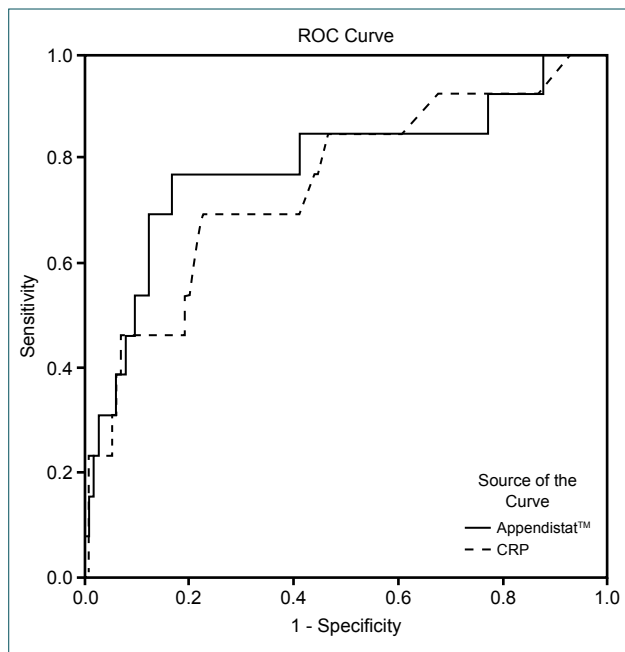
In the ROC curve analysis, the area under the curve (AUC) values of the appendistat™ score, CRP, leukocyte, total bilirubin, and direct bilirubin were 0.787, 0.750, 0.637, 0.574, and 0.471, respectively (Table 1). According to the same analysis, the cut-off value for differentiating complicated appendicitis and AUA was 23.5 mg/L for CRP,  $13,650 \times 10^6/L$  for leukocytosis, 9.6 for the appendistat™ score, 0.16 mg/dl for direct bilirubin, and 0.69 mg/dl for total bilirubin.

The results of the ROC curve analysis of the sensitivity and specificity of the appendistat™ score and CRP in detecting complicated appendicitis are presented in Figure 2. The sensitivity values of the appendistat™ score, CRP, leukocyte, total bilirubin and direct bilirubin were 73.68%, 40%, 56.14%,

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**Table 1.** Results of the receiver operating characteristic analysis

	Area under the curve	Confidence interval 95%
Appendistat™	0.787	(0.631–0.944)
C-reactive protein	0.750	(0.598–0.902)
Leukocytosis	0.637	(0.459–0.815)
Total bilirubin	0.574	(0.336–0.812)
Direct bilirubin	0.471	(0.167–0.775)



**Figure 2.** Comparison of appendistat™ scores and CRP concerning sensitivity and specificity according to the receiver operating characteristic (ROC) curve analysis.

73.08%, and 98.17%, respectively, and their specificity values were 76.92%, 96.43%, 76.92%, 50%, and 0%, respectively. The positive predictive values (PPVs) of the appendistat™ score, CRP, leukocyte, total bilirubin and direct bilirubin were calculated as 96.55%, 60%, 95.52%, 92.68%, and 89.17%, respectively, and their negative predictive values (NPVs) were determined as 25%, 92.31%, 16.67%, 17.65%, and 0%, respectively (Table 2).

## DISCUSSION

While medical antibiotic treatment may be an option for patients with AUA, surgery is the effective treatment option for complicated appendicitis.<sup>[6,7]</sup> Our study is valuable because it

provides the validation of the appendistat™ score in the detection of complicated appendicitis and presents the comparison of this score with CRP, which is a parameter included in this scoring system and a commonly used biological marker.

Kim et al.<sup>[8]</sup> emphasized that increased levels of CRP were associated with complicated appendicitis. In a similar study, the authors suggested that increased CRP levels in multivariate analysis were more successful than other biochemical markers in differentiating complicated appendicitis from AUA.<sup>[9]</sup> Eddama et al.<sup>[2]</sup> reported the cut-off value of CRP to be 40 mg/L for the identification of complicated appendicitis. In our study, the CRP cut-off value for complicated appendicitis was 23.5 mg/L. Our lower CRP cut-off value may be related to the time between the onset of symptoms and presentation to the hospital, which was not examined in our study and that of Eddama et al.<sup>[2]</sup> Another possible reason may be the higher mean age of our patients (44 years) compared to the mean age reported by Eddama et al.<sup>[2]</sup> (33 years).

In many studies, since it is stated that bilirubin levels increase, especially in patients with peritonitis, we have used bilirubin as a routine biochemical parameter in patients with acute abdomen in our clinical practice. Lin et al.<sup>[10]</sup> stated that bilirubin reduced peritonitis in mice with its anti-inflammatory effect. Eren et al.<sup>[11]</sup> specifically noted that increased direct bilirubin levels might be a marker for complicated appendicitis. In the current study, the sensitivity of direct bilirubin in detecting complicated appendicitis was 98.17%. Sandstrom et al.<sup>[12]</sup> reported that similar to the literature, the bilirubin values provided more significant results in complicated appendicitis than CRP and leukocytes, but the PPV values were higher in AUA cases. Eddama et al.<sup>[2]</sup> found that bilirubin, leukocyte, and CRP were correlated with each other in AUA, but the same correlation was not observed in individuals with normal pathology findings and those with complicated appendicitis. The authors also stated that bilirubin, CRP and leukocyte val-

**Table 2.** Sensitivity, specificity, PPV, NPV and accuracy of the investigated scoring systems and biochemical parameters

	Sensitivity (CI 95%)	Specificity (CI 95%)	PPV (CI 95%)	NPV (CI 95%)	Accuracy (CI 95%)
Appendistat™	73.68% (64.61–81.49)	76.92% (46.19–94.96)	96.55% (91.16–98.70)	25.00% (17.85–33.83)	74.02% (65.49–81.39)
C-reactive protein	40.00% (16.34–67.71)	96.43% (91.11–99.02)	60.00% (32.32–82.49)	92.31% (88.80–94.78)	89.76% (83.13–94.44)
Leukocytosis	56.14% (46.54–65.42)	76.92% (46.19–94.96)	95.52% (88.64–98.31)	16.67% (12.21–22.33)	58.27% (49.19–66.95)
Total bilirubin	73.08% (58.98–84.43)	50.00% (11.81–88.19)	92.68% (84.84–96.63)	17.65% (7.89–34.90)	70.69% (57.27–81.91)
Direct bilirubin	98.17% (93.53–99.78)	0.00% (0.00–24.71)	89.17% (88.92–89.41)	0 –	87.70% (80.53–92.95)

PPV: Positive predictive value; NPV: Negative predictive value.

ues alone or in combination provided significant results in the differentiation of complicated appendicitis and AUA. However, bilirubin was not a predictive marker of complicated appendicitis according to the multivariate analysis, including age, gender, leukocyte and CRP parameters. In addition, they observed a higher rate of appendicitis among men and a higher incidence of complicated appendicitis with increasing age. In another study, Dhillon et al.<sup>[3]</sup> reported that of the patients over 65 years of age that were suspected of having AUA according to the results of clinical examination and radiological findings, half had a pathology result in favor of complicated appendicitis and conservative treatment might not be appropriate for the elderly population.

Chambers et al.<sup>[13]</sup> constructed a logistic regression model comprising the CRP, bilirubin, and leukocyte parameters for the differentiation of AUA and complicated appendicitis, and calculated the AUC of this model as 0.641. In the development of appendistat™ scoring, important, independent and determinant data for the diagnosis of complicated appendicitis and AUA were analyzed. In the appendistat™ scoring model for complicated appendicitis, the AUC was reported to be 0.718.<sup>[2]</sup> In our validation study, the AUC of the appendistat™ score was 0.787 for complicated appendicitis. In our study, age and gender parameters that are included in appendistat™ scoring were also important given that complicated appendicitis was more common among men, and the mean age of these cases was higher. Thus, it was concluded that the better performance of the appendistat™ score than the model presented by Chambers et al. might be related to the inclusion of age and gender in the former, and these parameters should be considered in the evaluation of complicated appendicitis. In our study, the appendistat™ score was more successful than CRP in detecting complicated appendicitis, but CRP was more specific and had a higher NPV.

The limitations of this study can be considered as the small number of patients evaluated in validation compared to the appendistat™ study,<sup>[2]</sup> the retrospective nature of the study, and the construction of the model-based solely on pathology results.

In conclusion, the appendistat™ score is a successful scoring system with appropriate parameters in identifying complicated appendicitis cases. However, given the difficulty of scoring calculation and the ability of the CRP parameter to detect or exclude complicated appendicitis at a similar rate, we suggest that this scoring system does not have a significant advantage in clinical practice.

**Ethics Committee Approval:** Approved by the local ethics committee.

**Peer-review:** Internally peer-reviewed.

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**Conflict of Interest:** None declared.

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ORJİNAL ÇALIŞMA - ÖZET

## Appendistat™ skoru doğrulaması ve komplike apandisitleri ön görmede CRP düzeyleriyle karşılaştırılması

**Dr. Birkan Birben,<sup>1</sup> Dr. Bedriye Müge Sönmez,<sup>2</sup> Dr. Sadettin Er,<sup>1</sup>  
Dr. Sabri Özden,<sup>1</sup> Dr. Murat Tuğra Kösa,<sup>2</sup> Dr. Mesut Tez<sup>3</sup>**

<sup>1</sup>Ankara Şehir Hastanesi, Genel Cerrahi Kliniği, Ankara

<sup>2</sup>Ankara Şehir Hastanesi, Acil Tıp Kliniği, Ankara

<sup>3</sup>Ankara Eğitim ve Araştırma Hastanesi, Genel Cerrahi Kliniği, Ankara

**AMAÇ:** Akut apandisitlerde hastanın yaşı, komorbiditesi ve apendiksın komplike olup olmamasına göre hastaya uygulanacak tedavi yaklaşımı değişebilir. Bu çalışmada, komplike apandisit lojistik regresyon modelini içeren Appendistat™ skorunun doğrulamasını yapıp aynı zamanda appendistat™ skoru ile C-reaktif protein'in komplike apandisitleri ön görmedeki etkinliğini karşılaştırdık.

**GEREÇ VE YÖNTEM:** Akut apandisit nedeniyle hastanemizde apendektomi yapılan hastaların demografik özellikleri, patoloji ve laboratuvar sonuçları geriye dönük olarak tarandı. On sekiz yaş üzeri apendektomi yapılan hastalar çalışmaya dahil edildi. Komplike apandisit lojistik regresyon modelini içeren Appendistat™ skoru kullanıldı.

**BULGULAR:** On üç (%10.1) hastada komplike ve 116 (%89.9) hastada non-komplike apandisit izlendi. Komplike apandisitlerin 2'si (%15.4) kadın 11'i (%84.6) erkekti. Komplike apandisitlerin yaş ortalaması 44 (20–77) yıl ve C-reaktif protein'in median değeri 41.00 mg/L idi. ROC eğri analizinde c-reaktif protein için kestirim değeri 23.5mg/L olarak bulundu. Appendistat™ skoru için kestirim değeri 9.6 olarak bulundu. Appendistat™ skoru ve C-reaktif protein'in Area Under the Curve'ü sırasıyla 0.787/0.750 idi.

**TARTIŞMA:** Appendistat™ skoru doğru parametreleri içeren başarılı bir skorlama sistemidir. C-reaktif protein parametresinin de komplike apandisitleri benzer oranda belirleyebilmesi ya da dışlayabilmesi göz önüne alındığında; klinik uygulamada bu skorlama sisteminin belirgin üstünlüğü olmadığını düşündürmektedir.

**Anahtar sözcükler:** Akut apandisit; Appendistat™ skoru; C-reaktif protein; komplike apandisit.

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