

# Efficacy of bilirubin values in diagnosing acute appendicitis in patients with normal white blood cell count and predicting complicated appendicitis

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## ABSTRACT

**BACKGROUND:** Laboratory parameters have important diagnostic value in the evaluation of acute appendicitis. This study aimed to evaluate the efficacy of bilirubin values in predicting acute and complicated appendicitis in patients with leukocyte values in the normal reference range.

**METHODS:** This study included 200 patients aged 18 and over who underwent appendectomy with leukocyte values within the normal reference range. The demographic characteristics, total and direct bilirubin and C-reactive protein values of the patients were examined. According to the pathology results, the patients were divided into two groups as a normal appendix and acute appendicitis. Acute appendicitis was further classified as simple and complicated.

**RESULTS:** Of the 200 patients included in this study, 110 (55%) were female and 90 (45%) were male, and the mean age was  $37 \pm 16$  years. The pathology results were reported as normal in 45 (22.5%) and acute appendicitis in the remainder of the sample. Of those diagnosed with acute appendicitis, 141 (91%) had simple appendicitis and 14 (9%) had complicated appendicitis. When the normal appendix and acute appendicitis groups were compared, the total and direct bilirubin levels were higher in the patients diagnosed with acute appendicitis. According to the receiver operator characteristic curve analysis, the area under the curve values of total bilirubin and direct bilirubin for the prediction of acute appendicitis were 0.597 and 0.625, respectively.

**CONCLUSION:** In patients with normal leukocyte values, high bilirubin levels may be useful in predicting the diagnosis of acute appendicitis.

**Keywords:** Acute appendicitis; complicated appendicitis; direct bilirubin; total bilirubin.

## INTRODUCTION

The most important tools in diagnosing acute appendicitis are physical examination, laboratory evaluation, and radiological imaging. In patients with appendicitis, leukocyte, C-reactive protein (CRP) and bilirubin parameters are most frequently used in laboratory evaluation.<sup>[1]</sup> The presence of leukocytosis is one of the most frequently used and the most important parameters in the diagnosis of acute appendicitis.<sup>[2]</sup> In patients with suspected appendicitis, it is often difficult to make a diagnosis by analyzing a single laboratory value. In addition, any

delay in diagnosis may lead to complicated appendicitis, which may cause severe morbidity and mortality.<sup>[3,4]</sup> In this study, we aimed to investigate the efficacy of bilirubin values in diagnosing acute appendicitis and predicting complicated appendicitis in patients that had normal-range leukocyte values.

## MATERIALS AND METHODS

### Patient Data

After obtaining ethical approval (number: E1-20-847) from the local ethics committee of Ankara City Hospital, 1,129

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patients aged 18 years or older who were evaluated with the suspicion of acute appendicitis in the emergency department between January 2019 and March 2020 and who underwent appendectomy were retrospectively reviewed. Patients receiving immunosuppressive therapy, pregnant women with appendicitis, malignant cases, patients with known liver disease and bile metabolism problems, and those with leukocytosis and leukopenia were excluded from this study. In our hospital, the normal reference range for the white blood cell count is accepted as  $4,000-10,200 \times 10^6/L$ . This study included 200 patients with a white blood cell value within the normal range who underwent appendectomy. The demographic characteristics of the patients and their total and direct bilirubin and CRP values were examined. The pathological diagnosis of the patients was used as the gold standard. According to the pathology results, the patients were divided into two groups as those with a normal appendix and those with acute appendicitis. The acute appendicitis cases were further grouped as simple and complicated (abscess, necrosis, perforation, and generalized peritonitis).

### Statistical Analysis

The data were analyzed statistically using SPSS v. 23.0 (SPSS Inc, Chicago, IL, USA). The Shapiro-Wilk test and skewness and kurtosis values were used to analyze the data distribution. All data were expressed as mean  $\pm$  standard deviation (SD) or median (interquartile range) values according to data distribution. The statistical analysis of the results was performed using unpaired Student's t-tests with normally distributed data. For the other type of data, the Mann-Whitney U test was used. The association between categorical variables was tested using the chi-square or Fisher's exact test. Significance was considered when  $p < 0.05$ .

We measured the prognostic performance of the laboratory parameters using receiver operating characteristic (ROC) curves and calculated sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (+LR), and negative likelihood ratio (-LR) for different cut-off values.

## RESULTS

Of the 200 patients who underwent an appendectomy, 110 (55%) were female and 90 (45%) were male, and their mean age was  $37 \pm 16$  (range, 18–87) years. According to the pathology results of the patients, 45 (22.5%) patients had a normal appendix, 141 (91%) patients had simple appendicitis, and 14 (9%) patients had complicated appendicitis (Fig. 1). Of the patients in the normal appendix group, 27 (60%) patients were female and 18 (40%) patients were male, and the mean age was  $39 \pm 15$  years. In this group, the median CRP value was 3 (3–21) mg/dl, the median total bilirubin value was 0.60 (0.50–0.90) mg/dl, and the median direct bilirubin value was 0.20 (0.10–0.30) mg/dl. In the simple appendicitis

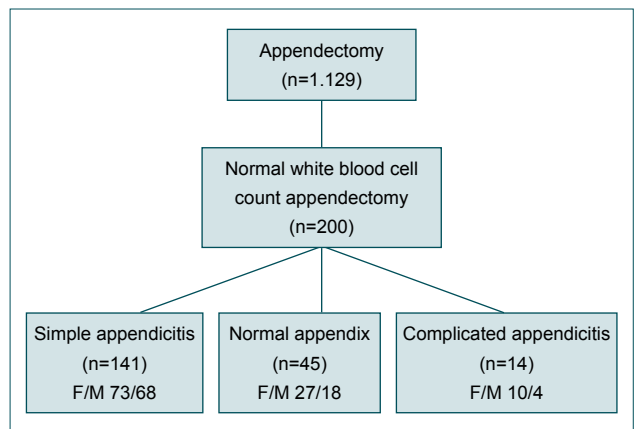


Figure 1. Distribution of patients (F: Female, M: Male).

group, there were 73 (51.8%) females and 68 (48.2%) males. The mean age was calculated as  $35 \pm 15$  years. The median values of CRP, total bilirubin and direct bilirubin were obtained as 30 (12–63) mg/dl, 0.70 (0.50–1.00) mg/dl, and 0.20 (0.10–0.30) mg/dl, respectively. Lastly, 10 (71.4%) of the patients in the complicated appendicitis group were female and four (28.6%) were male. The mean age of this group was  $46 \pm 19$  years. The median CRP, total bilirubin and direct bilirubin values were calculated as 61 (15–135) mg/dl, 1.00 (0.80–1.30) mg/dl, and 0.30 (0.20–0.40) mg/dl, respectively (Table 1).

When the normal appendix and acute appendicitis groups were compared, no statistically significant difference was ob-

Table 1. Comparison of the data between the normal appendix, simple appendicitis and complicated appendicitis groups

	Normal appendix	Simple appendicitis	Complicated appendicitis
Age (years)			
Mean	39	35	46
SD	15	15	19
Total bilirubin mg/dl			
Median	.60	.70	1.00
Percentile 25	.50	.50	.80
Percentile 75	.90	1.00	1.30
CRP mg/dl			
Median	3	30	61
Percentile 25	3	12	15
Percentile 75	21	63	135
Direct bilirubin mg/dl			
Median	.20	.20	.30
Percentile 25	.10	.10	.20
Percentile 75	.30	.30	.40

SD: Standard deviation; CRP: C-reactive protein.

served according to age ( $p=0.258$ ). It was determined that the total and direct bilirubin levels were significantly higher in the acute appendicitis group ( $p=0.000$ ), but there was no statistically significant difference between the two groups in terms of the CRP values ( $p=0.064$ ). The comparison of the simple and complicated appendicitis groups revealed no significant difference in total bilirubin ( $p=0.690$ ), direct bilirubin ( $p=0.597$ ), and CRP ( $p=0.179$ ). However, age was observed to be significantly higher in the complicated appendicitis group ( $p=0.012$ ) (Table 2).

In the ROC analysis, for predicting acute appendicitis, the area under the curve was calculated as 0.597 and 0.625 for total bilirubin and direct bilirubin, respectively (Fig. 2). The cut-off value of total bilirubin was 0.75 in predicting acute appendicitis. At this value, the sensitivity, specificity, PPV and NPV of total bilirubin were 50.65%, 62.79%, 82.98% and 26.21%, respectively. At the cut-off value of 0.25, direct bilirubin had a sensitivity of 44.37%, the specificity of 74.42%, PPV of 85.90%, and NPV of 27.59% in the prediction of acute appendicitis (Table 3).

## DISCUSSION

Currently, the most frequently used laboratory value in the diagnosis of acute appendicitis is elevated white blood cell count. In a study undertaken by Ünal, the negative appendectomy rate was 5.9%, and the complicated appendicitis rate was 17.5%.<sup>[5]</sup> In a similar study conducted by Shin et al.,<sup>[6]</sup> the negative appendectomy rate was 5.4% while the complicated appendicitis rate was 28.7%. In our sample, in-

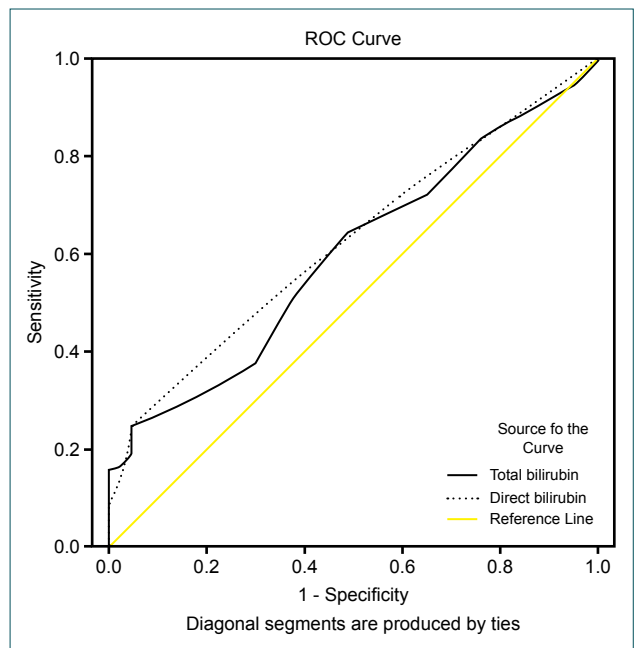


Figure 2. ROC curve of acute appendicitis.

cluding acute appendicitis cases with a normal white blood cell count, the negative appendectomy rate was much higher and the complicated appendicitis rate was lower at 22.5 and 9%, respectively. Given the higher negative appendectomy and lower complicated appendicitis rates in individuals with a normal white blood cell count, it may be an option to follow-up these patients conservatively if their bilirubin values are also within the normal range. Er et al.<sup>[7]</sup> stated that among the cases that underwent surgery with the suspicion of acute appendicitis, the white blood cell count values were within the normal range in 16.2% of patients, and the authors also reported that the negative appendectomy rate was 19%. Dayawansa et al.<sup>[8]</sup> reported that normal CRP and white blood cell values were insufficient to exclude acute appendicitis. To our knowledge, there is no study in the literature in which the predictive ability of bilirubin values in diagnosing appendicitis was investigated in patients with a normal-range normal white blood cell count. Nevler et al.<sup>[9]</sup> reported that high total and direct bilirubin values were significant in the diagnosis of acute appendicitis, and their cut-off values were 0.73 and 0.13, respectively. In a similar study, Adams et al.<sup>[10]</sup> determined that bilirubin values were statistically significantly higher in the acute appendicitis group

**Table 2.** Comparison of the data between the normal appendix-acute appendicitis and simple-complicated appendicitis groups

	Normal appendix/ acute appendicitis p-value	Simple/complicated appendicitis p-value
Age (years)	.258	.012
Total bilirubin mg/dl	.000	.690
CRP mg/dl	.064	.179
Direct bilirubin mg/dl	.000	.597

CRP: C-reactive protein.

**Table 3.** ROC analysis of acute appendicitis

	AUC	95% CI		Cut-off value	Sensitivity	Specificity	PPV	NPV
		Lower	Upper					
Total bilirubin	.597	.508	.687	.75	50.65%	62.79%	82.98%	26.21%
Direct bilirubin	.625	.538	.712	.25	44.37%	74.42%	85.90%	27.59%

CI: Confidence interval; AUC: Area under the curve; PPV: Positive predictive value; NPV: Negative predictive value.

than in the normal appendix group, although they were both within the normal reference range. Al-Abed et al.<sup>[11]</sup> also suggested that a high bilirubin value was a laboratory parameter that could be effectively used in the diagnosis of acute appendicitis. Similarly, Sushruth et al.<sup>[12]</sup> reported that high total and direct bilirubin values were significant in the diagnosis of acute appendicitis. In these studies, in patients with acute appendicitis, increased bilirubin levels and elevated white blood cell counts were also presented. In case of a suspicion of acute appendicitis, a combined evaluation of these laboratory parameters is even more useful in diagnosis. In our study, a high bilirubin value alone was an effective parameter in diagnosing appendicitis in patients with normal white blood cell count values.

The differentiation between simple and complicated appendicitis is very important in the treatment of the condition. Especially in recent years, medical treatment has become popular in simple appendicitis. In terms of not only treatment but also morbidity, mortality, length of hospital stay, and complications, it is also important to effectively distinguish between simple and complicated appendicitis. In their experimental study, Lin et al.<sup>[13]</sup> showed that bilirubin had an anti-inflammatory effect and relieved peritonitis. Ramu et al.<sup>[14]</sup> reported that high bilirubin values provided significant results for perforated appendicitis, and the cut-off value of bilirubin was calculated as 1.3 mg/dl. In a similar study, Saxena et al.<sup>[15]</sup> found that high bilirubin values were significant for the prediction of perforated appendicitis and had a cut-off value of 4 mg/dl. Elevated bilirubin has a predictive value in the diagnosis of both acute and complicated appendicitis. However, in our study, we were not able to show the contribution of bilirubin values to the diagnosis of patients with complicated appendicitis who had normal white blood cell count values.

Eren et al.<sup>[16]</sup> stated that high CRP values constituted an increased risk for acute and complicated appendicitis. In a similar study, Sushruth et al.<sup>[12]</sup> reported that a high CRP value was a significant parameter in diagnosing acute appendicitis. Recent studies show that when evaluated together, leukocyte, CRP and bilirubin parameters greatly contribute to the diagnosis of acute and complicated appendicitis.<sup>[3,17]</sup> However, in our study, elevated CRP measured preoperatively did not significantly differ between the groups; therefore, it did not provide a significant result for the differentiation of acute and complicated appendicitis cases.

In conclusion, the diagnosis of appendicitis is made clinically and radiologically. The leukocyte value is the most frequently used and the most important parameter in clinical diagnosis. High bilirubin values may help diagnose acute appendicitis in patients with a normal leukocyte value. A limitation of our study can be considered as its single-center design. We consider that it is necessary to conduct further studies in multiple centers with a higher volume of patients.

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**Conflict of Interest:** None declared.

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## ORJİNAL ÇALIŞMA - ÖZET

### Beyaz küresi normal hastalarda akut apandisit tanısı koymada ve komplike apandisiti ön görmede bilirubin değerlerinin etkinliği

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**AMAÇ:** Akut apandisit değerlendirilmesinde laboratuvar parametreleri önemli tanısal değere sahiptir. Bu çalışmanın amacı, lökosit değerleri normal referans aralığında olan hastalarda bilirubin değerlerinin akut ve komplike apandisiti ön görmedeki etkinliğini değerlendirmektir.

**GEREÇ VE YÖNTEM:** Lökosit değeri normal referans aralığında olan ve apendektomi yapılan 18 yaş ve üzeri 200 hasta çalışmaya dahil edildi. Hastaların demografik özellikleri total ve direkt bilirubin ve C-reaktif protein değerleri incelendi. Hastalar patoloji sonucuna göre normal apandiks ve akut apandisit olarak ikiye ayrıldı. Akut apandisitlerde, basit apandisit ve komplike apandisit olarak sınıflandırıldı.

**BULGULAR:** Çalışmaya dahil edilen 200 hastanın 110'u (%55) kadın, 90'ı (%45) erkekti ve yaş ortanca değeri 37±16 yıl idi. Patoloji sonuçları 45'inde (%22.5) normal apandiks, geri kalanında ise akut apandisit olarak raporlandı. Akut apandisit tanısı alanların 141'inde (%91) basit apandisit ve 14'ünde (%9) komplike apandisit saptandı. Normal apandiks ve akut apandisit karşılaştırıldığında total ve direkt bilirubin seviyeleri akut apandisit tanısı alanlarda daha yüksek bulundu. Akut apandisiti ön görmede işlem karakteristik eğrisi analizinde total bilirubin ve direkt bilirubin'in eğri altında kalan alanı sırasıyla 0.597 ve 0.625 idi.

**TARTIŞMA:** Lökosit değerinin normal olduğu hastalarda yüksek bilirubin değerleri akut apandisit tanısını ön görmede faydalı olabileceği sonucuna varıldı.

**Anahtar sözcükler:** Akut apandisit; direkt bilirubin; komplike apandisit; total bilirubin.

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