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## Diagnostic value of hyperbilirubinemia and basic laboratory tests in simple and complicated appendicitis

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### Abstract

This study aimed to investigate the effectiveness of total serum bilirubin and basic laboratory tests [White Blood Cell (WBC), Neutrophil and Lymphocyte Count, Neutrophil-Lymphocyte Ratio (NLR), Platelet Count, Mean Platelet Volume (MPV), Platelet Distribution Width (PDW), Platelet-Lymphocyte Ratio (PLR), C-reactive protein (CRP), Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT)] levels in determining the severity of acute appendicitis (AA) preoperatively in patients operated for AA and reported as AA (Simple-Complicated) as a result of pathology. The medical records of 552 adult patients aged > 18 years who underwent appendectomy for a diagnosis of AA between January 2015 and December 2019 at the General Surgery Clinic of Harran University Faculty of Medicine were retrospectively evaluated. After applying the predefined exclusion criteria, 386 patients were included in the final analysis. Patients were divided into two groups based on the pathology results: Simple or Complicated AA. Demographic characteristics, preoperative total bilirubin levels, and basic laboratory tests were examined. The effectiveness of these tests in differentiating between Simple and Complicated AA was investigated. The mean age of the 386 patients included in this study was  $35.33 \pm 15.28$  years (range, 18–88 years). Based on the pathology results, 296 (76.7%) patients were diagnosed with Simple AA, and 90 (23.3%) patients were diagnosed with Complicated AA. According to the pathology results, the Complicated AA group had a significantly higher mean age ( $p = 0.001$ ), mean length of hospital stay ( $p < 0.001$ ), mean NLR ( $p = 0.008$ ), mean PLR ( $p = 0.036$ ), mean total bilirubin ( $p = 0.002$ ), and mean preoperative CRP ( $p < 0.001$ ) than the Simple AA group. Although total bilirubin and CRP levels showed statistically significant differences between the Simple and Complicated AA groups, no single parameter with sufficient sensitivity and specificity was identified in the preoperative period.

**Keywords:** Appendicitis; appendectomy; clinical laboratory techniques; bilirubin

### Introduction

Acute appendicitis (AA) is an inflammatory process caused by luminal obstruction due to any cause, in which increased luminal pressure, circulatory disorder, and bacterial proliferation are observed [1]. AA is the most common cause of acute abdominal surgery across all age groups. AA develops in 7-10% of the general population during their lifetime, with the highest incidence observed in the second and third decades of life [2,3].

The diagnosis of AA is primarily based on clinical symptoms and physical examinations. Radiological imaging methods, such as ultrasonography (US), computed tomography (CT), and magnetic

resonance imaging (MRI), are examinations with high sensitivity and specificity for diagnosing AA and detecting complications. However, these methods are expensive and time-consuming. Radiation exposure can cause side effects, particularly in pediatric and young adult patients, and imaging equipment is not always available in emergency settings. Numerous scoring systems have been designed to aid in the diagnosis. In the Alvarado scoring system, which is the most popular, scoring is based on the patient's history, clinical findings, and leukocyte and neutrophil counts [4-6]. Hence, clinical suspicion of AA should precede radiological evaluation, and clinical and laboratory findings should form the basis for the diagnostic workup.

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Although it is the most common surgical emergency, an accurate diagnosis of AA remains challenging, even after diagnostic tests. Although the classic symptoms and signs of AA may not always be present, different clinical signs and symptoms may mimic AA. Therefore, AA is the most frequently misdiagnosed and sometimes undiagnosed surgical emergency. Appendicitis perforation caused by a delay in diagnosis, abscess formation, or appendectomy with misdiagnosis increases mortality and morbidity in patients [7-11]. Notably, 17-20% of patients with AA exhibit appendiceal perforation, which is particularly prevalent in the elderly [10].

The diagnostic value of blood tests, such as C-reactive protein (CRP) and white blood cell (WBC) counts, has been extensively addressed in previous studies. However, no single clinical or laboratory test has been defined to reliably predict AA or appendicitis perforation [12]. Therefore, a simple and inexpensive test is needed to predict the degree and severity of AA and to decide on the appropriate treatment.

In recent years, studies have shown increased serum bilirubin levels in patients with AA. In addition, some studies have demonstrated that perforated and gangrenous appendicitis may be correlated with hyperbilirubinemia [7,13-15]. Elevated serum bilirubin levels can be explained by the interaction of increased endotoxin in the liver with bilirubin excretion in the bile ducts due to the invasion of gram-negative bacteria into the appendix and subsequent translocation directly into the portal system. Therefore, preoperative bilirubin levels can be used to predict complicated appendicitis or rupture, along with the clinical picture of the patient [7,14,16].

The goal of this study is to investigate the effectiveness of total serum bilirubin and basic laboratory tests [WBC, Neutrophil and Lymphocyte Count, Neutrophil-Lymphocyte Ratio (NLR), Platelet Count, Mean Platelet Volume (MPV), Platelet Distribution Width (PDW), Platelet-Lymphocyte Ratio (PLR), CRP, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT)] preoperatively in determining the severity of AA in patients operated for AA and reported as AA (Simple-Complicated) as a result of pathology.

## Material and Methods

This study was approved by the Clinical Research Ethics Committee of Harran University (approval number: 46766; date: October 25, 2019). This study was conducted retrospectively using the medical records of 552 adult patients aged > 18 years who were diagnosed with AA and underwent laparoscopic or open appendectomy between January 2015 and December 2019 at the Harran University Faculty of Medicine General Surgery Clinic.

Adult patients over 18 years of age who were operated on with the diagnosis of AA based on clinical and laboratory findings with or without imaging methods and whose pathology was called Simple or Complicated AA were included in the study.

Patients without histopathological AA (normal appendix, reactive lymphoid hyperplasia, acute mucosal/submucosal inflammation, periappendicitis), patients under 18 years of age, patients with suspected chronic liver disease, patients with disease associated with hepatobiliary hyperbilirubinemia, patients with hemolytic disease, patients with a history of alcoholism, patients with previously known liver disease (viral hepatitis, cirrhosis, Gilbert's disease, Dubin-Johnson syndrome, benign recurrent intrahepatic cholestasis, and other documented biliary, hemolytic, or liver diseases associated with hyperbilirubinemia), patients with a lack of data in the patient file, and patients who incidentally underwent AA surgery during surgical operation for any other reason were excluded from the study. After applying the exclusion criteria, 386 patients were included in the study.

The demographic characteristics and preoperative WBC, neutrophil, lymphocyte, and platelet counts, MPV, and PDW values of all patients were recorded. The NLR was calculated by dividing the neutrophil count by the lymphocyte count, and the PLR was calculated by dividing the platelet count by the lymphocyte count. The CRP, AST, ALT, and total bilirubin levels were also recorded. The postoperative hospital stay and discharge status (discharged or exitus) of the patients were evaluated.

All patients included in the study were divided into two groups: Simple and Complicated appendicitis, according to the pathology results. Suppurative/phlegmonous histopathological findings caused by pathological infiltration of the muscularis propria with polymorphonuclear cells were accepted as Simple AA; gangrenous/necrotizing, perforated, and abscess histopathological findings were accepted as Complicated AA.

## Statistical Analysis

The data were entered into a Microsoft Excel file and transferred to IBM SPSS version 23.0 (IBM Corp., Armonk, NY, USA) for statistical analysis. Before statistical analysis, checks were performed to ensure that no data entry errors were present and that the parameters were within the expected range. The normality of continuous variables was evaluated using the Shapiro–Wilk test, along with visual inspection of histograms and examination of skewness and kurtosis coefficients.

Continuous variables are expressed as mean  $\pm$  standard deviation, and categorical variables are presented as frequency (n) and percentage (%). The Mann–Whitney U test was used to compare non-normally distributed continuous variables and binary variables. The chi-square test was used to examine the relationships between categorical variables, and Spearman's correlation analysis was used to examine the relationships between continuous variables. Logistic regression analysis (Backward: Wald) was performed to determine the variables predicting the pathology results, and receiver operating characteristic (ROC) analysis was performed to calculate the sensitivity, specificity, and positive and negative predictive values. In all analyses,  $p < 0.05$  was considered statistically significant.

Results

The mean age of the 386 patients included in the study was 35.33 ± 15.28 years (median: 31.0, range: 18–88). Of the patients, 194 (50.3%) were female and 192 (49.7%) were male. Based on the pathology results, 296 (76.7%) patients were diagnosed with Simple AA, and 90 (23.3%) patients were diagnosed with Complicated AA. The sex distribution was compared between groups using chi-square analysis: in the Simple AA group, 150 (50.7%) were female and 146 (49.3%) were male; in the Complicated AA group, 44 (48.9%) were female and 46 (51.1%) were male. No statistically

significant difference was found between the groups in terms of sex distribution ( $\chi^2 = 0.031$ ,  $df = 1$ ,  $p = 0.860$ ). The Mann-Whitney test was performed to determine whether sociodemographic characteristics and laboratory parameter means differed significantly between the pathology groups, and the findings are shown in Table 1. According to the pathology results, the mean age of the patients with complicated AA ( $40.41 \pm 16.69$ , median = 36) was significantly higher than that of the patients with Simple AA ( $33.79 \pm 14.51$ , median = 29) ( $U = 10152.50$ ,  $z = -3.419$ ,  $p = 0.001$ ).

Table 1. Distribution of sociodemographic and laboratory parameters by pathology result (simple and complicated)

| Parameter                 | Mean ± SD            |                      | p       |
|---------------------------|----------------------|----------------------|---------|
|                           | Simple               | Complicated          |         |
| Age                       | 33.79 ± 14.51        | 40.41 ± 16.69        | 0.001   |
| Duration of hospital stay | 3.44 ± 1.51          | 5.06 ± 2.94          | < 0.001 |
| Pre-op WBC                | 15040.10 ± 6531.81   | 16436.30 ± 15355.51  | 0.580   |
| Pre-op neutrophil         | 11647.81 ± 4804.12   | 11961.10 ± 4023.29   | 0.336   |
| Pre-op lymphocyte         | 2054.39 ± 966.01     | 1758.36 ± 858.04     | 0.006   |
| NLR                       | 7.50 ± 5.97          | 9.10 ± 6.91          | 0.008   |
| Pre-op PLT                | 266440.84 ± 74236.37 | 265754.44 ± 80487.57 | 0.731   |
| PLR                       | 158.06 ± 90.85       | 193.88 ± 135.99      | 0.036   |
| Pre-op MPV                | 7.93 ± 1.46          | 7.77 ± 1.30          | 0.462   |
| Pre-op PDW                | 19.71 ± 1.52         | 19.36 ± 1.68         | 0.361   |
| Total bilirubin           | 0.84 ± 0.47          | 1.07 ± 0.64          | 0.002   |
| AST                       | 22.88 ± 10.02        | 24.56 ± 15.14        | 0.702   |
| ALT                       | 21.58 ± 15.14        | 26.04 ± 27.52        | 0.548   |
| Pre-op CRP                | 4.99 ± 7.29          | 12.72 ± 11.64        | < 0.001 |

Mann–Whitney U test was used. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; MPV, mean platelet volume; NLR, neutrophil-to-lymphocyte ratio; PDW, platelet distribution width; PLR, platelet-to-lymphocyte ratio; PLT, platelet count; Pre-op, preoperative; SD, standard deviation; WBC, white blood cell.

Despite these findings, no statistically significant difference was found between the mean preoperative WBC, preoperative neutrophil, preoperative platelet count, preoperative MPV, preoperative PDW, AST, and ALT values of patients who had Complicated and Simple appendicitis according to the pathology results ( $p > 0.05$ ). Spearman’s correlation analysis was performed to examine the

relationships between AST, ALT, and total bilirubin levels. A significant, statistically positive correlation ( $r = 0.518$ ,  $p < 0.01$ ) was found between AST and ALT levels (Table 2). However, no statistically significant relationship was found between AST and total bilirubin ( $r = -0.005$ ,  $p = 0.702$ ) or between ALT and total bilirubin ( $r = 0.007$ ,  $p = 0.548$ ).

Table 2. Correlation coefficients between AST, ALT and total bilirubin

| Variable           | Mean ± SD     | 1       | 2     | 3 |
|--------------------|---------------|---------|-------|---|
| 1. AST             | 23.27 ± 11.42 | –       |       |   |
| 2. ALT             | 22.62 ± 18.82 | 0.518** | –     |   |
| 3. Total Bilirubin | 0.89 ± 0.53   | -0.005  | 0.007 | – |

\*  $p < 0.05$ ; \*\*  $p < 0.01$

Values are Spearman's correlation coefficients (r). \* $p < 0.05$ ; \*\* $p < 0.01$ . Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; SD, standard deviation.

Logistic regression analysis (Backward: Wald) was performed to determine the parameters predicting pathology results. Preoperative lymphocyte count, NLR, PLR, total bilirubin, and CRP, which were statistically significantly correlated with the pathology results, were added to the model. The analysis result was completed in a four-step process, and the most important parameters predicting the pathology results in the fourth stage were total bilirubin and CRP  $\chi^2$  (2, n = 386) = 49.693, p < 0.001 (Wald = 97.823, df = 1, p < 0.001). Nagelkerke pseudo R<sup>2</sup> value was found to be 0.182. This value indicates that the model

explains approximately 18% of the variance in the pathology results, suggesting that while total bilirubin and CRP levels were statistically significant, they accounted for only a modest proportion of the variability between Simple and Complicated appendicitis. The results of the logistic regression analysis are presented in Table 3. As shown in Table 3, a one-unit increase in total bilirubin level increased the odds of complicated appendicitis by 1.716-fold, and a one-unit increase in CRP level increased the odds of complicated appendicitis by 1.082-fold.

**Table 3.** Results of the logistic regression analysis conducted to determine the parameters predicting the pathology result

| Parameter       | Regression coefficient (B) | Standard error | p       | OR (95% CI)           |
|-----------------|----------------------------|----------------|---------|-----------------------|
| Total bilirubin | 0.540                      | 0.234          | 0.021   | 1.716 (1.086 – 2.713) |
| CRP             | 0.079                      | 0.014          | < 0.001 | 1.082 (1.053 – 1.112) |
| Constant        | -2.338                     | 0.277          | < 0.001 | 0.096                 |

Abbreviations: B, regression coefficient; CI, confidence interval; CRP, C-reactive protein; OR, odds ratio.

ROC analysis was performed to calculate the cutoff, sensitivity, and specificity values of total bilirubin. As a result of the analysis, it was found that area under the curve (AUC) = 0.61 (95% confidence interval [CI]: 0.54 – 0.68). At the optimal cut-off of  $\geq 0.86$ , sensitivity was 57.8% (95% CI: 46.9 – 68.1), specificity was 65.5% (95% CI: 59.8 – 70.9), positive likelihood ratio (LR+) was 1.68 (95% CI: 1.3 – 2.1), negative likelihood ratio (LR-) was 0.64 (95% CI: 0.5 – 0.8), positive predictive value (PPV) was 33.8% (95% CI: 26.4 – 41.8), and negative predictive value (NPV) was 83.6% (95% CI: 78.2 – 88.1) (Table 4).

Similarly, ROC analysis was performed to calculate the cutoff, sensitivity, and specificity values of the CRP parameter. As a result of the analysis, it was found that AUC = 0.719 (95% CI: 0.655 – 0.784). At the optimal cut-off of  $\geq 8.66$ , sensitivity was 61.11% (95% CI: 50.3 – 71.2), specificity was 82.09% (95%

CI: 77.2 – 86.3), LR+ 3.41 (95% CI: 2.5 – 4.6), LR- 0.47 (95% CI: 0.4 – 0.6), PPV 50.9% (95% CI: 41.1 – 60.7), NPV 87.4% (95% CI: 82.9 – 91.1) (Table 4).

When total bilirubin and CRP parameters were used together, AUC = 0.64 (95% CI: 0.57 – 0.71) was found as a result of ROC analysis. Sensitivity was 36.67% (95% CI: 26.8 – 47.5), specificity was 91.22% (95% CI: 87.4 – 94.2), LR+ 4.17 (95% CI: 2.6 – 6.6), LR- 0.69 (95% CI: 0.6 – 0.8), PPV 55.9% (95% CI: 42.4 – 68.8), NPV 82.6% (95% CI: 78.0 – 86.5) (Table 4).

When total bilirubin or CRP parameters were used together, the AUC was 0.69 (95% CI: 0.63 – 0.75) as a result of ROC analysis. Sensitivity was 82.22% (95% CI: 72.7 – 89.5), specificity was 56.08% (95% CI: 50.2 – 61.8), LR+ 1.87 (95% CI: 1.6 – 2.2), LR- 0.32 (95% CI: 0.2 – 0.5), PPV 36.3% (95% CI: 29.7 – 43.3), NPV 91.2% (95% CI: 86.1 – 94.9) (Table 4).

**Table 4.** Sensitivity and specificity values of total bilirubin and CRP in predicting pathology result

| Parameter                                               | OR (95% CI)           | Sensitivity (95% CI) | Specificity (95% CI) | LR + (95% CI)    | LR – (95% CI)    | PPV (95% CI)       | NPV (95% CI)       |
|---------------------------------------------------------|-----------------------|----------------------|----------------------|------------------|------------------|--------------------|--------------------|
| Total bilirubin ( $\geq 0.86$ )                         | 1.716 (1.086 – 2.713) | 57.78 (46.9 – 68.1)  | 65.54 (59.8 – 70.9)  | 1.68 (1.3 – 2.1) | 0.64 (0.5 – 0.8) | 33.8 (26.4 – 41.8) | 83.6 (78.2 – 88.1) |
| CRP ( $\geq 8.66$ )                                     | 1.082 (1.053 – 1.112) | 61.11 (50.3 – 71.2)  | 82.09 (77.2 – 86.3)  | 3.41 (2.5 – 4.6) | 0.47 (0.4 – 0.6) | 50.9 (41.1 – 60.7) | 87.4 (82.9 – 91.1) |
| Total bilirubin ( $\geq 0.86$ ) and CRP ( $\geq 8.66$ ) |                       | 36.67 (26.8 – 47.5)  | 91.22 (87.4 – 94.2)  | 4.17 (2.6 – 6.6) | 0.69 (0.6 – 0.8) | 55.9 (42.4 – 68.8) | 82.6 (78.0 – 86.5) |
| Total bilirubin ( $\geq 0.86$ ) or CRP ( $\geq 8.66$ )  |                       | 82.22 (72.7 – 89.5)  | 56.08 (50.2 – 61.8)  | 1.87 (1.6 – 2.2) | 0.32 (0.2 – 0.5) | 36.3 (29.7 – 43.3) | 91.2 (86.1 – 94.9) |

Abbreviations: CI, confidence interval; CRP, C-reactive protein; LR+, positive likelihood ratio; LR-, negative likelihood ratio; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value.

## Discussion

AA is one of the most common surgical emergencies worldwide, affecting approximately 7% of the general population during their lifetime, with approximately 300,000 hospital visits reported annually in the United States [17]. Complicated appendicitis, encompassing gangrenous, perforated, and abscess-associated forms, carries substantially higher morbidity and mortality than simple appendicitis, with overall mortality rising from below 1% to approximately 5% in cases of perforation [18,19]. No single clinical or laboratory test can reliably predict disease severity, and none of the existing scoring systems can assess the risk of perforation [12]. In the present study, 386 patients were analyzed: 296 (76.7%) with simple and 90 (23.3%) with complicated appendicitis. The most important finding was that, among all parameters evaluated, CRP demonstrated moderate discriminatory ability (AUC = 0.719), and total serum bilirubin showed limited performance (AUC = 0.61), and neither marker alone was sufficient to distinguish complicated from simple appendicitis preoperatively.

Patients with complicated appendicitis had a significantly longer mean hospital stay than those with simple appendicitis ( $p < 0.001$ ), consistent with the literature [16], and this was attributable to the infectious complications that arose when the pathogenic organisms spread beyond the appendix. Complicated appendicitis is more frequent in older patients, partly because atypical presentations delay diagnosis [20]. In our study, the mean age of patients with complicated appendicitis was significantly higher than that of patients with simple appendicitis ( $40.41 \pm 16.69$  vs.  $33.79 \pm 14.51$  years;  $p = 0.001$ ). The sex distribution did not differ significantly between the groups ( $\chi^2 = 0.031$ ,  $p = 0.860$ ), indicating that sex is unlikely to confound the laboratory findings in this cohort.

Although commonly elevated in AA, WBC count is not a specific marker and is also increased in many other inflammatory conditions [21]. Large inter-study variations in WBC values make definitive diagnostic conclusions difficult [22-25], and the count is insufficient as a standalone test [26]. In uncomplicated cases, leukocyte values typically range from 10,000 to 18,000 cells/mm<sup>3</sup> [27], and approximately 80–90% of patients show a left shift with leukocytosis [28]. Yang et al. [29] reported that the proportion of leukocytes and neutrophils correlates with the degree of appendiceal inflammation, whereas Panagiotopoulou et al. [11] noted that leukocyte count is useful in diagnosing AA but not in differentiating perforated from non-perforated cases. Consistent with these reports, the WBC and neutrophil counts did not differ significantly between the simple and complicated groups in our study ( $p > 0.05$ ), confirming that classical inflammatory cell counts cannot distinguish disease severity.

Physiological stress responses during acute infection lead to an increase in neutrophil count and a decrease in lymphocyte count. The NLR reflects this response and has been proposed as a useful inflammatory parameter [30,31]. Kahraman et al. [32]

reported that NLR can be used to diagnose AA and differentiate between complicated and uncomplicated forms. Eren et al. [33] found that the likelihood of AA was 16.9 times higher when NLR was  $\geq 4.0$ , and the risk of gangrene or perforation was 3.2 times higher when NLR was  $\geq 4.5$ . In our study, the NLR was significantly higher in the complicated group ( $p = 0.008$ ), driven primarily by a significantly lower lymphocyte count ( $p = 0.006$ ) rather than by an increase in neutrophil or WBC counts. The PLR has also been reported to help predict complicated appendicitis [32] and was significantly higher in the complicated group ( $p = 0.036$ ). Notably, platelet count alone, despite being an acute-phase reactant, did not differ significantly between the groups, suggesting that PLR is more effective than platelet count alone owing to the concurrent decrease in lymphocyte count in complicated diseases. These findings collectively indicate that ratio-based inflammatory indices are more informative than absolute cell counts in differentiating complicated appendicitis from simple appendicitis.

CRP levels were significantly elevated in the complicated appendicitis group ( $p < 0.001$ ), consistent with the existing literature [16]. At the optimal cut-off of 8.66 mg/L, CRP yielded a sensitivity of 61.11%, specificity of 82.09%, PPV of 50.9%, and NPV of 87.4%. According to the established diagnostic criteria, an LR+ above 5 or an LR– below 0.2 indicates a strong diagnostic test, and an AUC of 0.75 or above reflects good diagnostic performance [34]. With an AUC of 0.719, LR+ of 3.41, and LR– of 0.47, CRP demonstrated moderate but not strong discriminatory ability. The higher NPV (87.4%) relative to PPV (50.9%) suggests that CRP is more useful for ruling out complicated diseases than for confirming them.

The total serum bilirubin level was significantly higher in the complicated group ( $p = 0.002$ ). Prior meta-analytic data using a predefined cutoff of 1 mg/dL reported an AUC of 0.73, sensitivity of 0.49, and specificity of 0.82 for hyperbilirubinemia as a predictor of appendiceal perforation [35], findings corroborated by systematic reviews and further studies [36,37]. In our study, at the lower optimal cut-off of 0.86 mg/dL selected by the Youden index rather than a predefined threshold, total bilirubin yielded an AUC of 0.61, sensitivity of 57.8%, specificity of 65.5%, PPV of 33.8%, NPV of 83.6%, LR+ of 1.68, and LR– of 0.64, indicating poor-to-fair diagnostic performance that falls below the generally accepted threshold for clinically meaningful discriminatory ability. The higher NPV (83.6%) relative to PPV (33.8%) suggests that bilirubin has greater utility in identifying uncomplicated cases than in confirming complicated diseases. Although CRP has generally been reported to have higher sensitivity but lower specificity than bilirubin [11,38,39], in our study, CRP outperformed total bilirubin in both sensitivity (61.11% vs. 57.8%) and specificity (82.09% vs. 65.5%). This divergence may be explained by differences in cutoff methodology (Youden index vs. predefined thresholds), case-mix variation, differences in blood sampling timing, and the retrospective single-center design. No significant correlation

was found between total bilirubin and AST ( $r = -0.005$ ,  $p = 0.702$ ) or ALT ( $r = 0.007$ ,  $p = 0.548$ ) levels. Furthermore, AST and ALT values did not differ significantly between the simple and complicated groups ( $p > 0.05$ , respectively) and remained within the normal reference ranges in both groups. These findings collectively support the view that bilirubin elevation in complicated appendicitis results from alternative mechanisms, such as portal bacteremia, endotoxin-mediated impairment of hepatocyte bile excretion, and cytokine-mediated cholestasis, rather than direct hepatocellular injury.

Several studies have indicated that combined laboratory evaluations are necessary for the diagnosis of AA. One study reported that when multiple markers are combined, there is an exponential increase in the predictive and distinctive power of AA [26]. Another study reported that the combined inflammatory parameters (including WBC, polymorphonuclear leukocyte (PMNL) count, PMNL ratio, body temperature, and CRP) of 502 patients over 10 years of age had an accuracy similar to the total accuracy of their clinical findings (0.85) [40]. In another study, 99% sensitivity and 6% specificity were detected when any of the following were present:  $\text{CRP} \geq 8 \text{ mg/L}$ ,  $\text{WBC} \geq 10.4 \times 10^3 \text{ cells/mm}^3$ , or  $\text{PMNL ratio} > 74 \%$ . Sensitivity was 98%, and specificity was 12% when WBC or CRP levels were increased [29]. The absence of these laboratory findings may help exclude the diagnosis of AA; however, their low specificity severely limits their clinical applicability. Because different cutoff points were used in most of these studies, it is difficult to compare the results. However, based on these results, when the WBC, CRP, and PMNL ratios are within normal limits, the probability of AA is low. Therefore, if clinical findings of AA occur in a patient, according to very small studies, a diagnosis of AA is unlikely when none of the laboratory markers are elevated [26].

In our study, the combined use of total bilirubin and CRP as a diagnostic tool yielded a high specificity of 91.22% and an LR+ of 4.17. These values indicate that the simultaneous elevation of both markers is a moderate-to-strong indicator of complicated disease, providing high confidence when the test result is positive.

However, the clinical utility of this “dual-positive” approach is severely limited by its low sensitivity (36.67%). It must be explicitly emphasized that although the combined use of total bilirubin and CRP yields a high specificity of 91.22%, the sensitivity of only 36.67% is critically low, implying that approximately two-thirds of complicated appendicitis cases would be missed. A false-negative rate of this magnitude renders this combination clinically unacceptable as a screening or triage tool for complicated appendicitis. The gain in specificity does not offset the unacceptably high miss rate for conditions in which a delayed diagnosis carries a significant risk of morbidity and mortality. Therefore, this combination cannot be recommended for clinical use in its current formulation.

The AUC of 0.64 further reflects this limited discriminatory power. Although high specificity is valuable for “ruling in” a

diagnosis, a diagnostic strategy in an emergency setting must first and foremost be safe. In acute surgical conditions, relying on a marker with such a high false-negative rate could lead to catastrophic delays in treatment. Consequently, although these biochemical parameters provide supplementary information, they cannot replace clinical judgment or advanced cross-sectional imaging in the definitive management of AA.

Although the ‘AND’ combination achieved high specificity (91.22%), its overall discriminatory power ( $\text{AUC} = 0.64$ ) remained lower than that of CRP alone ( $\text{AUC} = 0.719$ ), reflecting the inherent sensitivity-specificity trade-off of conjunctive models; marker combination strategies should therefore be selected according to the clinical objective — rule-in versus rule-out.

In the second model, we assessed the diagnostic performance based on the positivity of total bilirubin or CRP levels. This disjunctive approach led to a notable improvement in diagnostic power ( $\text{AUC}, 0.69$ ; 95% CI, 0.63 – 0.75). In contrast to the high specificity/low sensitivity profile of the simultaneous elevation model, this strategy prioritizes clinical sensitivity, shifting the focus toward a safer screening tool.

The most striking finding in this model was the significant increase in sensitivity to 82.22%, with an NPV of 91.2%. In the context of AA, these metrics are clinically superior as triage tools. A high NPV implies that when both total bilirubin and CRP levels fall below their respective study-defined cut-off values (total bilirubin  $< 0.86 \text{ mg/dL}$  and  $\text{CRP} < 8.66 \text{ mg/L}$ ), the likelihood of the patient having complicated appendicitis is remarkably low. This finding should be interpreted in the context of study-specific thresholds, which are below the conventional laboratory reference ranges. This provides clinicians with a safer “rule-out” mechanism, potentially identifying patients who may be suitable for closer observation rather than immediate aggressive intervention.

However, this gain in sensitivity came at the cost of specificity, which decreased to 56.08%. With a PPV of only 36.3%, nearly two-thirds of the patients flagged by this “either/or” combination would actually have simple rather than complicated appendicitis. While this leads to a higher rate of false positives, it is often argued in emergency surgery that the risks associated with a false positive (over-triage) are far less catastrophic than the complications arising from a false negative (under-triage) in a perforated case.

An LR– of 0.32 further supports this approach as a moderate rule-out tool. Although an AUC of 0.69 still falls short of the definitive accuracy provided by CT imaging, the “OR” combination of these biochemical markers offers a much more balanced and clinically applicable profile for initial screening.

Although the disjunctive (“OR”) combination of total bilirubin and CRP achieved a higher sensitivity (82.22%) and a higher NPV (91.2%) than CRP alone (sensitivity 61.11%, NPV 87.4%),

its overall discriminatory power, as reflected by the AUC (0.69), was paradoxically lower than that of CRP used as a single marker (AUC: 0.719). This apparent contradiction is explained by the fundamental difference between global discrimination and rule-out performance: AUC summarizes diagnostic ability across all possible thresholds and reflects balanced sensitivity–specificity performance, whereas NPV and the LR– (0.32) specifically quantify the ability to safely exclude the target condition at a fixed operating point. In the emergency surgical context, where the primary safety imperative is to avoid missing complicated appendicitis rather than minimizing false positives, a tool with a high NPV and low LR– is clinically preferable, even when its AUC is marginally inferior to that of a single marker. Consequently, the recommendation to favor the “OR” combination over CRP alone is not based on overall discriminatory superiority, but on its more favorable rule-out profile — a distinction that must be explicitly acknowledged to avoid misinterpretation of the AUC data.

In summary, our data suggest that while neither marker combination is perfect, the “OR” strategy is the more pragmatic choice for the emergency department. It prioritizes the detection of complicated cases, ensuring that the majority of high-risk patients are identified early, even if further radiological confirmation is required owing to lower specificity.

Our study had some limitations. First, our study was a single-center study, which limits the generalizability of the findings to the broader population. Evaluations were performed according to the results obtained from a single laboratory. Additionally, the possible presence of hematological malignancies was not assessed in this cohort. Problems such as blood drawn waiting in the tube reduce the optimization of complete blood measurements (especially for platelet parameters). Furthermore, the low Nagelkerke  $R^2$  value of 0.182 indicates that the logistic regression model explains only approximately 18% of the variance in the outcome, highlighting that additional unmeasured clinical and laboratory variables likely contribute to the differentiation between Simple and Complicated appendicitis.

## Conclusion

Among the laboratory parameters investigated, CRP level demonstrated moderate diagnostic value (AUC = 0.719), whereas total bilirubin level showed only limited discriminatory ability (AUC = 0.61) in distinguishing complicated from simple appendicitis preoperatively. Neither marker exhibited sufficient sensitivity or specificity when used in isolation as a standalone diagnostic test. Furthermore, the relatively low Nagelkerke  $R^2$  value of 0.182 indicates that these biochemical parameters explain only a modest proportion of the variance between the two groups, reaffirming that no single laboratory parameter (serological or otherwise) can reliably guide the management of suspected appendicitis alone. It is important to emphasize that a single predictive factor (serological or radiological) cannot be used alone to determine the treatment for patients with suspected

appendicitis. Therefore, other important complementary diagnostic tools for AA and appendicitis perforation should be considered in the future.

Clinical examination remains the primary diagnostic tool for diagnosing simple and perforated appendicitis. However, CRP and total bilirubin levels may guide surgeons in intermediate cases. In cases with high CRP and bilirubin levels, these findings may support early surgical decision-making or prompt referral to a surgical center, thereby reducing the morbidity and mortality associated with complicated AA. Therefore, future studies with larger populations should evaluate whether total bilirubin and CRP levels are strong diagnostic tools.

## Ethical Approval

*The study was initiated following the approval of the Clinical Research Ethics Committee of Harran University dated 25.10.2019 and numbered 46766.*

## Patient Consent

*Owing to the retrospective design of the study, in which anonymized data were obtained from patient medical records, the requirement for written informed consent was waived by the Clinical Research Ethics Committee of Harran University. The study was conducted in accordance with the principles of the Declaration of Helsinki.*

## Conflict of Interest

*The authors confirm the absence of any conflicts associated with this work.*

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