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# Prospective Assessment of Elevated Serum Bilirubin in Diagnosis of Acute Appendicitis

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## ABSTRACT

**Background:** Acute appendicitis remains one of the most common surgical emergencies. Elevated serum bilirubin levels have been proposed as potential markers in the diagnosis of acute appendicitis, particularly in distinguishing between uncomplicated and complicated cases.

**The aim of the work:** This study aimed to evaluate the role of elevated serum bilirubin levels in the diagnosis and differentiation of complicated versus uncomplicated acute appendicitis.

**Patients and Methods:** A total of 200 patients diagnosed with acute appendicitis based on clinical and radiological data were prospectively included in this study. All patients underwent appendectomy, and histopathological examinations of the excised appendices were conducted. The patients were classified into three groups: Group I (normal appendix, n=22), Group II (uncomplicated appendicitis, n=136), and Group III (complicated appendicitis, n=42). Serum bilirubin levels were measured preoperatively and analyzed in association with the histopathological findings.

**Results:** In Groups II and III, both WBCs and neutrophil ratios significantly increased, with mean values escalating from 12.58 to 17.26 for WBCs and from 64.37% to 81.58% for neutrophils across Groups I to III. Serum bilirubin and CRP levels also rose, showing significant associations with inflamed appendices. WBCs had the highest diagnostic accuracy (AUC 0.847) for differentiating inflamed from normal appendices, with the best sensitivity (69.1%) and specificity (90.9%). For complications, WBCs remained key, achieving sensitivities of 76.2% and specificities of 79.4%.

**Conclusion:** Serum bilirubin is weaker than leucocytic count and CRP in the diagnosis of acute appendicitis, and in differentiating complicated from non-complicated cases. Nonetheless, it could be combined with these markers to enhance the diagnosis of that emergency surgical condition.

**Keywords:** Acute Appendicitis; Bilirubin; Gangrene.

## INTRODUCTION

Appendicitis is the leading cause of acute abdominal pain that necessitates surgical intervention. It occurs more frequently in males than females, with a ratio of 1.4:1, and can affect individuals of any age group. However, it is most often observed in older children and young adults [1]. The diagnosis of any type of appendicular condition primarily relies on clinical assessment [2]. Nevertheless, even experienced practitioners may overlook or misdiagnose cases. While current blood tests and imaging techniques can assist in the diagnostic process, they lack specificity and may not directly relate to the underlying pathology [3]. These factors could postpone necessary surgical treatment, resulting in appendiceal perforation, which can increase morbidity and length of hospital stay [4]. The rate of perforated appendicitis in adults has been reported to range from 13% to 37% or even higher due to intervention delay [5]. Since delayed diagnosis and treatment of severe appendicitis are linked to higher risks of perforation, postoperative complications, mortality, and prolonged hospital stays, there is an urgent need for a tool to predict the severity of acute appendicitis [6, 7]. Hyperbilirubinemia is commonly seen in patients with septic foci. Among these, acute appendicitis is the most prevalent intra-abdominal septic focus, with *E. coli* and *Bacteroides fragilis* being the primary responsible organisms [8].

Bacteria found in portal blood are typically removed by the liver's reticuloendothelial system, which serves as the first line of defense against toxic substances, bacteria, and their byproducts. However, when the bacterial load exceeds the capacity of Kupffer cells, damage to hepatocytes can result, which is indicated by serum bilirubin levels and may also involve liver enzymes, depending on the type, severity, and location of the injury [9, 10]. It was reported that in the presence of septic foci, both systemic and intrahepatic pro-inflammatory cytokines rise, resulting in increased bile production and flow. Additionally, elevated nitric oxide levels and reduced aquaporins during sepsis can hinder bile flow [11, 12]. Numerous studies have indicated a strong association between hyperbilirubinemia and perforated appendicitis. The mechanism behind this may involve the disruption of hepatic bilirubin conjugation and biliary excretion due to bacterial endotoxins [3, 13-15]. These findings highlight that hyperbilirubinemia can serve as a marker for both acute appendicitis and its perforation [2, 16].

Due to the persistent clinical challenge of accurately diagnosing acute appendicitis and the need to differentiate between uncomplicated and complicated forms of the disease, this study aimed to prospectively evaluate the significance of elevated serum bilirubin levels in diagnosing acute appendicitis.

## PATIENTS AND METHODS

This prospective interventional study was conducted over a one-year period, from January 2022 to January 2023, in the General Surgery Departments of Al-Azhar University Hospitals in New Damietta and Qabbary Hospital. A total of 200 patients diagnosed clinically and radiologically with acute appendicitis were included in this study.

The **inclusion criteria** for this study were patients aged between 15 and 70 years of both genders who presented with right iliac fossa pain and were diagnosed clinically, as well as through laboratory and imaging studies, with acute appendicitis, and subsequently underwent either open or laparoscopic appendectomy.

The **exclusion criteria** for this study included those with deranged liver functions, individuals with hemolytic disease, and patients who were managed conservatively.

**Ethical consideration:** The study gained approval from the local ethical committee and Institutional Review Board of Damietta Faculty of Medicine, Al-Azhar University. An informed written consent was signed by all participants after complete explanation of the indications and possible complications of the surgical intervention.

**Data collection:** The patient's history was comprehensively gathered, including personal details such as sex, age, and residence, as well as presenting symptoms and their duration, which encompassed nausea, anorexia, vomiting, abdominal pain, elevated temperature, and diarrhea or constipation. Additionally, comorbid medical conditions like diabetes, hypertension, and ischemic heart disease were noted, along with any previous surgical history. Clinical examination involved a general assessment of body mass index and vital signs, including pulse, blood pressure, and temperature, as well as a thorough abdominal examination. Routine laboratory investigations conducted included a complete blood count (CBC) with a focus on white blood cell counts and neutrophil ratios, liver function tests measuring serum bilirubin via Cobas C 111 from Roche Diagnostics, renal function tests, C-reactive protein (CRP), and urinalysis to differentiate between appendicitis and urinary tract conditions.

**Ultrasound examination:** Abdominal ultrasonography was performed to look for the radiological features of appendicitis and increase the accuracy of diagnosis (appendicular mass, aperistaltic, non-compressible dilated appendix more than 6 mm outer diameter with preservation of the expected multilayered appearance of bowel, echogenic submucosa not lost, amorphous hyperchoic structure (>10 mm) seen surrounding uncompressible appendix with diameter > 6mm, evidence of an appendicolith or periappendiceal fluid collection or target sign).

**The surgical procedure**: All procedures were performed under general or spinal anesthesia according to the surgical approach and anesthetist preference. The patients were performed via the open or laparoscopic approaches according to the surgeon preference. The grid iron incision was used in open cases, while the classic three-port access was used for the laparoscopic cases (one for the camera and two working ports). Any purulent fluid was aspirated, and good peritoneal toilet was done. The mesoappendix was ligated or coagulated then divided. The base of the appendix was ligated by vicryl 2/0 sutures, followed by transection of the appendix. Either endoloop or an endoclip was used to secure the appendiceal stump in laparoscopic cases. The appendix was exteriorized through the surgical wound in open cases, and through one of the working ports in laparoscopic cases. The wound was closed in layers in the open cases, while the skin at the site of the ports was closed in the laparoscopic cases.

**Histopathological examination:** All the excised specimens were sent to the pathology laboratory to confirm the diagnosis. Based on the surgical findings and the histopathological analysis of the appendices, patients were categorized into three groups: The Group I was consisted of those with a histopathologically normal appendix, Group II included those with an inflamed, non-complicated appendix (simple appendicitis), and Group III comprised patients with complicated appendicitis (either perforated or gangrenous).

**Postoperative care:** After the operation, all patients were transferred to the recovery room and subsequently to the internal ward, where they received 1000 ml of IV fluids over six hours. Once bowel sounds were audible, patients were permitted to start oral fluid intake, with guidance to advance their oral intake on the following day as tolerated. All patients were typically discharged on the first or second postoperative day, barring any encountered complications.

**Outcomes:** The primary outcome measure was the sensitivity, specificity, and accuracy of preoperative serum bilirubin in diagnosing acute appendicitis and differentiating complicated from non-complicated cases, while other outcomes included the diagnostic accuracy of additional markers such as WBCs and CRP in the same context.

**Statistical analysis:** Data were analyzed using SPSS version 22, where quantitative data were assessed for normality with the Kolmogorov-Smirnov test and expressed as mean ± SD, while categorical data were presented as percentages and frequencies. For comparing three or more independent groups with quantitative data, One-way ANOVA was applied for parametric data, and the Kruskal-Wallis test was used for non-parametric data. Post-hoc analysis was performed using Bonferroni and Dunn's tests for parametric and non-parametric data, respectively. The Chi-square test or Fisher's exact test was utilized for comparing two or more groups of categorical data, with Z test and Bonferroni correction for post-hoc analysis. The validity of preoperative serum bilirubin in assessing appendicitis was evaluated through various metrics: sensitivity was calculated as true positive divided by the sum of true positive and false negative, specificity as true negative divided by the sum of true negative and false positive, validity as the sum of true positive and true negative divided by all examined, positive predictive value (PPV) as true positive divided by the sum of true positive and false positive, and negative predictive value (NPV) as true negative divided by the sum of true negative and false negative. A probability (p value) of less than 0.05 was deemed statistically significant for all included tests.

## RESULTS

The mean ages of the included patients were 33.41, 36.93, and 37.55 years in Groups I, II, and III respectively, with no significant difference between the three groups (p = 0.535). Although age distribution was statistically comparable between the three groups, gender distribution was significantly different, as there was a significant increase in male gender prevalence in Group III (81%), compared to the other two groups (54.5% and 59.6% respectively). The BMI of the included cases had mean values of 27.74, 27.86, and 27.48 kg/m2 in our three groups respectively, which was comparable between the three groups (p = 0.869). The prevalence of medical comorbidities showed no significant difference between the three groups (p > 0.05). Hypertension was present in 9.09%, 14.71%, and 11.9%, while diabetes mellitus was present in 9.09%, 11.76%, and 11.9% of cases in the three groups, respectively. In addition, ischemic heart disease was present in only two patients, one in Group I and the other in group III (Table 1). The prevalence of appendicitis-related symptoms did not significantly differ between the three study groups (p > 0.015). Migrating pain was reported by 27.27%, 39.7%, and 30.95%, whereas anorexia was present in 13.64%, 20.59%, and 21.43% of cases in Groups I, II, and III respectively. Nausea was present in 31.82%, 36.76%, and 38.1% of cases, while vomiting occurred in 31.82%, 35.92%, and 38.1% of cases in the same groups, respectively. Moreover, diarrhea was reported by 4.55%, 8.82%, and 4.76% of patients in the same three groups respectively (Table 2). Patients in Group III showed higher prevalence of fever that was present in 66.67% of its cases, compared to 27.27% and 44.85% of patients in Groups I and II, respectively. Right iliac tenderness was encountered in 81.82%, 90.04%, and 92.86% of cases, while rebound tenderness was detected in 50%, 58.82%, and 61.9% of cases in groups I, II, and III respectively. The previous two manifestations showed no significant difference between the study groups (p = 0.359 and 0.650, respectively). Preoperative laboratory parameters are shown in the following table. Hemoglobin, platelet count, AST, ALT, and albumin levels were statistically comparable between the three groups (p > 0.05). Nonetheless, total leucocytic count, neutrophil ration, bilirubin, and CRP expressed a significant difference between the three study groups. Both WBCs and neutrophil ratio showed a significant rise in Groups II and III. The former had mean values of 12.58, 15.03, and 17.26, while the latter had mean values of 64.37%, 78.61%, and 81.58% in groups I, II, and III respectively. Serum bilirubin had mean values of 0.75, 0.86, and 0.96 mg/dl, whereas CRP had mean values of 38.19, 46.87, and 55.9 gm/dl in the same three groups respectively (p = 0.006 and 0.003 respectively). Both parameters showed an increase in associated with inflamed appendix, especially the complicated ones (Table 3). WBCs had the largest area under curve (0.847), compared to bilirubin (0.64) and CRP (0.641), to differentiate between inflamed and normal appendix. With a cut-off value of 13.95, it had the highest sensitivity and specificity (69.1% and 90.9% respectively) to differentiate inflamed from normal appendix. CRP had a 62.4% sensitivity and a 77.3% specificity (cut-off = 41.25), while serum bilirubin had sensitivity and specificity of 55.1% and 72.7% (cut-off = 0.85) respectively to differentiate between cases with inflamed and normal appendix (Table 4 & Figure 1). When differentiating complicated from uncomplicated patients, WBCs was the most important parameter as it had sensitivity and specificity of 76.2% and 79.4% respectively, using a cut-off value of 16.75 (AUC = 0.771). Regarding the other two parameters, serum bilirubin has a 64.3% sensitivity and 77.2% specificity when a cut-off value of 1.05 mg/dl was used. CRP had sensitivity and specificity of 88.1% and 47.8% respectively, when a cut-off value of 42.1 mg/dl was used (Table 5).

Table (1): Demographic data of the three study groups

| | | Group I (normal) (n= 22) | Group II (non-complicated) (n= 136) | Group III (Complicated) (n= 42) | P | P1 | P2 | P3 |
|---|---|---|---|---|---|---|---|---|
| **Age (years)** | | 33.41 ± 14.111 | 36.93 ± 14.754 | 37.55 ± 15.348 | 0.535 | 0.908 | 0.869 | 1 |
| **Gender** | **Male** | 12 (54.5% | 81 (59.6% | 34 (81.0% | **0.027** | > 0.05 | > 0.05 | **< 0.05** |
| | **Female** | 10 (45.5% | 55 (40.4% | 8 (19.0% | | | | |
| **BMI** | | 27.74 ± 3.158 | 27.86 ± 4.200 | 27.48 ± 4.204 | 0.869 | 1 | 1 | 1 |
| **Comorbidities** | **HTN** | 2 (9.09%) | 20 (14.71%) | 5 (11.9%) | 0.731 | > 0.05 | > 0.05 | > 0.05 |
| | **DM** | 2 (9.09%) | 16 (11.76%) | 5 (11.9%) | 0.932 | > 0.05 | > 0.05 | > 0.05 |
| | **IHD** | 1 (4.55%) | 0 (0%) | 1 (2.38%) | 0.083 | > 0.05 | > 0.05 | > 0.05 |

Data is expressed as mean and standard deviation or as percentage and frequency. P is significant when < 0.05. P1: Group I vs Group II. P2: Group I vs Group III. P3: Group II vs Group III. P value adjustment was applied using Bonferroni method.

Table (2): Symptoms and clinical signs in the three study groups.

| | Group I (normal) (n= 22) | Group II (non-complicated) (n= 136) | Group III (Complicated) (n= 42) | P | P1 | P2 | P3 |
|---|---|---|---|---|---|---|---|
| **Migrating pain** | 6 (27.27%) | 54 (39.7%) | 11 (30.95%) | 0.193 | > 0.05 | > 0.05 | > 0.05 |
| **Anorexia** | 3 (13.64%) | 28 (20.59%) | 9 (21.43%) | 0.493 | > 0.05 | > 0.05 | > 0.05 |
| **Nausea** | 7 (31.82%) | 50 (36.76%) | 16 (38.1%) | 0.879 | > 0.05 | > 0.05 | > 0.05 |
| **Vomiting** | 7 (31.82%) | 48 (35.29%) | 16 (38.1%) | 0.880 | > 0.05 | > 0.05 | > 0.05 |
| **Diarrhea** | 1 (4.55%) | 12 (8.82%) | 2 (4.76%) | 0.584 | > 0.05 | > 0.05 | > 0.05 |
| **Fever** | 6 (27.27%) | 61 (44.85%) | 28 (66.67%) | **0.006** | > 0.05 | **< 0.05** | **< 0.05** |
| **Tenderness** | 18 (81.82%) | 123 (90.04%) | 39 (92.86%) | 0.359 | > 0.05 | > 0.05 | > 0.05 |
| **Rebound tenderness** | 11 (50%) | 80 (58.82%) | 26 (61.9%) | 0.650 | > 0.05 | > 0.05 | > 0.05 |

Data is expressed as percentage and frequency. P is significant when < 0.05. P1: Group I vs Group II. P2: Group I vs Group III. P3: Group II vs Group III. P value adjustment was applied using Bonferroni method.

Table (3): Laboratory parameters in the three study groups

| | Group I (normal) (n= 22) | Group II (non-complicated) (n= 136) | Group III (Complicated) (n= 42) | P | P1 | P2 | P3 |
|---|---|---|---|---|---|---|---|
| **Hemoglobin** | 12.78 ± 1.063 | 12.82 ± 1.100 | 12.80 ± 1.013 | 0.990 | 1 | 1 | 1 |
| **WBCs** | 12.58 ± 1.308 | 15.03 ± 2.085 | 17.26 ± 2.547 | **< 0.001** | **< 0.001** | **< 0.001** | **< 0.001** |
| **Neutrophil ratio** | 64.37 ± 5.645 | 78.61 ± 6.944 | 81.58 ± 5.161 | **< 0.001** | **< 0.001** | **< 0.001** | **0.031** |
| **Platelets** | 334.41 ± 78.960 | 317.94 ± 70.281 | 309.62 ± 72.771 | 0.424 | 0.958 | 0.573 | 1 |
| **AST** | 31.26 ± 8.855 | 34.69 ± 8.768 | 35.59 ± 8.668 | 0.158 | 0.269 | 0.185 | 1 |
| **ALT** | 42.07 ± 9.548 | 38.85 ± 8.852 | 41.20 ± 7.592 | 0.126 | 0.325 | 1 | 0.383 |
| **Bilirubin** | 0.75 ± 0.195 | 0.86 ± 0.272 | 0.96 ± 0.253 | **0.006** | 0.190 | **0.006** | 0.072 |
| **Albumin** | 4.03 ± 0.355 | 4.12 ± 0.386 | 4.04 ± 0.368 | 0.349 | 0.972 | 1 | 0.662 |
| **CRP** | 38.19 ± 11.179 | 46.87 ± 20.788 | 55.90 ± 21.181 | **0.003** | 0.184 | **0.003** | **0.035** |

Data is expressed as mean and standard deviation or as. P is significant when < 0.05. P1: Group I vs Group II. P2: Group I vs Group III. P3: Group II vs Group III. P value adjustment was applied using Bonferroni method.

Table (4): Diagnostic ability of WBCs, CRP, bilirubin in differentiating normal and diseased participants

| | WBCs | Bilirubin | CRP |
|---|---|---|---|
| **AUC** | 0.847 | 0.640 | 0.641 |
| **95% CI of AUC** | 0.779, 0.915 | 0.543, 0.737 | 0.548, 0.734 |
| **P** | **< 0.001** | **0.032** | **0.031** |
| **Cut off** | 13.95 | 0.85 | 41.25 |
| **Youden's J index** | 0.6 | 0.278 | 0.397 |
| **Sensitivity** | 69.1% | 55.1% | 62.4% |
| **Specificity** | 90.9% | 72.7% | 77.3% |
| **PPV** | 98.4% | 94.2% | 95.7% |
| **NPV** | 26.7% | 16.7% | 20.2% |
| **Accuracy** | 71.5% | 57.0% | 64.0% |

P is significant when < 0.05.

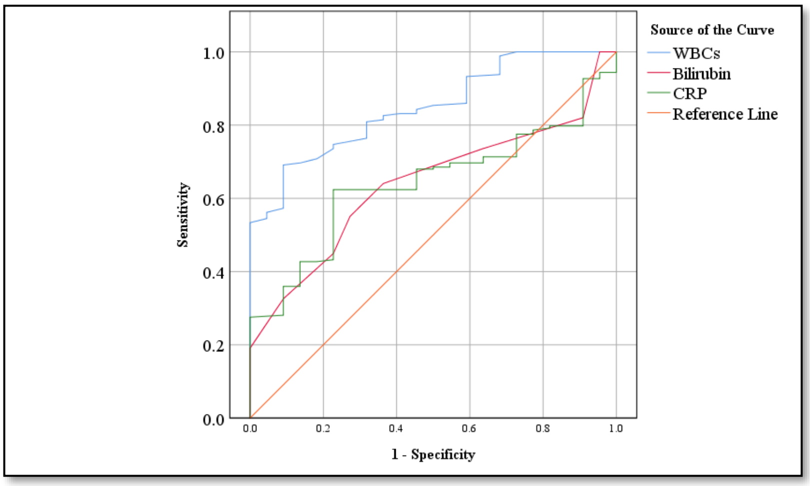


Figure (1): ROC curve for Diagnostic ability of WBCs, CRP, and bilirubin in differentiating normal and diseased participants

Table (5): Diagnostic ability of WBCs, CRP, and bilirubin in differentiating uncomplicated and complicated cases

| | WBCs | Bilirubin | CRP |
|---|---|---|---|
| **AUC** | 0.771 | 0.633 | 0.609 |
| **95% CI of AUC** | 0.667, 0.875 | 0.537, 0.730 | 0.509, 0.708 |
| **P** | **< 0.001** | **0.009** | **0.034** |
| **Cut off** | 16.75 | 1.05 | 42.1 |
| **Youden's J index** | 0.556 | 0.415 | 0.359 |
| **Sensitivity** | 76.2% | 64.3% | 88.1% |
| **Specificity** | 79.4% | 77.2% | 47.8% |
| **PPV** | 53.3% | 46.6% | 34.3% |
| **NPV** | 91.5% | 87.5% | 92.9% |
| **Accuracy** | 78.7% | 74.2% | 57.3% |

**P is significant when < 0.05.**

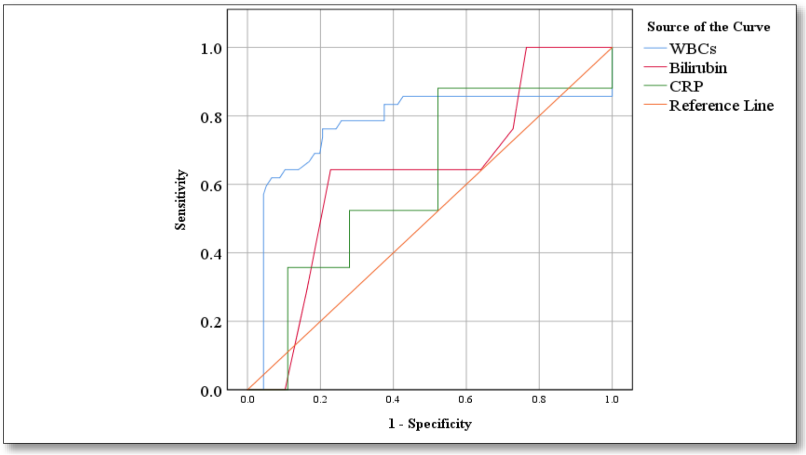


Figure (2): ROC curve for Diagnostic ability of WBCs, CRP, and bilirubin in differentiating uncomplicated and complicated cases

## DISCUSSION

At present, the preoperative diagnosis relies on clinical evaluation, which includes a comprehensive patient history and physical examination. This assessment is supplemented by biochemical and hematological tests, such as WBCs count and C-reactive protein (CRP), along with appropriate radiological examinations like CT scans and abdominal ultrasounds [17, 18]. However, these methods can be limited by factors such as accessibility, clarity, efficiency, and cost, particularly in smaller hospitals. As a result, there has been growing interest among surgeons in the potential of simple laboratory parameters to assist in diagnosing acute appendicitis and predicting perforations [19]. Bilirubin levels are believed to increase in response to intra-abdominal infections, leading to a temporary rise in portal temperature and inflammatory-mediated cholestasis [20, 21].

Previous research has indicated that hyperbilirubinemia in patients with appendicitis serves as a useful indicator of acute appendicitis and may also predict appendiceal perforation [22-24]. One should notice that the incidence of negative appendectomy was 11% in our trial (22/200), and that lies within the previously reported range of negative appendectomy which ranges between 4% and 45% [25-27].

We intended to remove the appendix even if it was appearing normal by gross examination. It was previously reported that grossly healthy appendix does not exclude the presence of histological acute appendicitis, as an appendix that looks normal during a laparoscopic examination may still have "endo-luminal appendicitis," with signs of inflammation that can only be detected through histological analysis [28]. Moreover, the removal of an appendage that appears normal in patients showing clinical and laboratory signs of acute appendicitis leads to an immediate and complete resolution of their symptoms, alongside the findings from various lab and imaging tests [29]. Additionally, normal-appearing appendices taken from these patients exhibit alterations in several markers, including substance P (a key responder to extreme stimuli), neuroendocrine markers, vasoactive intestinal polypeptide, gastric inhibitory polypeptide, calcium-binding protein, cyclooxygenases 1 and 2, tumor necrosis factor, prostaglandin E2, mast cell tryptase, nitric oxide synthase, CD8 lymphocytes, protein gene product 9.5, vascular endothelial growth factor, class 2 histocompatibility complex, synaptophysin, enolase, and S100 protein [30, 31]. The observed changes in these neuroimmune markers suggest the existence of a neuroimmune endocrine condition in the appendix that can mimic the symptoms of acute appendicitis, even when there is no actual inflammation present [32].

In the current study, WBCs showed a significant increase in appendicitis cases compared to subjects with normal appendix ($p < 0.001$). In addition, complicated cases had higher WBCs counts compared to patients with simple appendicitis ($p < 0.001$). Acute appendicitis triggers an inflammatory response. Research indicates that the WBC count rises significantly during this response, typically due to a bacterial infection in the appendix [33].

Moderate leukocytosis is a common laboratory finding in acute appendicitis cases [34]. Studies consistently reveal that 80-85% of adults with appendicitis have a WBC count exceeding 10,500 cells/μL

[35, 36]. Another previous study reported that WBCs had a mean value of 9.28 x109/L in patients with normal appendix, compared to 12.65 and 14.37 in patients with simple and complicated appendicitis, respectively [21].

The current study revealed that neutrophil ratio had a significant rise in patients with appendicitis compared to normal-appendix subjects. Also, the same parameter was higher in complicated cases compared to non-complicated ones ($p = 0.031$).

**Eren *et al*.** [4] agreed with our findings as neutrophil ratio had mean values of 63.7% in cases with normal appendix, compared to 77.48% and 80.66% in patients with simple and complicated appendicitis respectively ($p < 0.001$).

In the current study, WBCs had sensitivity and specificity of 69.1% and 90.9% respectively for the diagnosis of acute appendicitis when a cut-off value of 13.95 was used (highest AUC value among other parameters 0.847). Earlier studies have shown that the sensitivity and specificity of WCC range from 67% to 97.5% and 31.9% to 81%, respectively [37, 38].

**Rafiq *et al*.** [39] found very high sensitivity and specificity at the same cut-off value, reporting figures of 87% and 92%, respectively. Another previous study reported that WBCs had a 71.2% sensitivity and a 67.2% specificity for the diagnosis of acute appendicitis when a cut-off value of 11.9 was used. WBCs had a better diagnostic profile compared to serum bilirubin in the detection of appendicitis cases (AUC = 0.748 vs. 0.621 for serum bilirubin) [19].

In the current study, when a cut-off value of 16.75 was used for WBCs, it had a 76.2% sensitivity and a 79.4% specificity in the detection of complicated cases. **Antić *et al*.** [40] reported that WBC was an independent variable for the diagnosis of complicated appendicitis. The cut-off value was 15.05 for WBC with a sensitivity of 60.5% and a specificity of 70.7%. The previous study confirms our findings. **Feng *et al.*** [41] reported that the same parameter had sensitivity and specificity of 44% and 71% respectively for detecting appendiceal perforation, when a cut-off value of 15.38 was applied.

On the other hand, **Kar *et al*.** [42] reported low diagnostic value of WBCs in the prediction of complicated appendicitis, as WBCs > 11 had 21.43% sensitivity and 2.33% specificity in the detection of perforated appendicitis. **Käser *et al.*** [22] also reported similar findings.

In this study, CRP had mean values of 38.19, 46.87, and 55.9 gm/dl in groups I, II, and III, respectively, with a significant difference between the three groups.

**Chambers *et al.*** [21] and his colleagues reported that CRP had mean values of 26.97, 52.77, and 117.05 mg/dl in patients with normal, simple inflamed, and complicated appendicitis. The previous findings suggest the significant rise of that acute phase reactant in appendicitis patients, especially the complicated ones. The same findings were also reported in another study that reported that the same marker had median values of 0.72, 1.15, and 5.1 mg/dl in patients with normal, simple inflamed, and complicated appendicitis, with a significant difference between the three groups ($p < 0.001$) [4].

In the current study, serum CRP had sensitivity and specificity of 62.4% and 77.3% respectively, with an AUC of 0.641 when using a cut-off value of 41.25 mg/dl. The predictive values of C-reactive protein (CRP) in appendicitis show considerable variation: sensitivities reported range from 40% to 99%, while specificities vary from 27% to 90% [43, 44]. Consistent with our results, **Ortega-Deballon *et al.*** [45] found that CRP levels are the most valuable laboratory indicator for diagnosing acute appendicitis and are closely related to the severity of inflammation.

In contrast, **Amalesh *et al.*** [46] noted that the accuracy of CRP for diagnosing acute appendicitis is low and that CRP levels are not helpful in making surgical decisions.

In the current study, when a cut-off value of 0.85 mg/dl was used, it yielded sensitivity and specificity of 55.1% and 72.7% respectively with an AUC of 0.64, which was the lowest among the other tested three parameters. In two earlier studies, the reported sensitivities and specificities of serum bilirubin levels at 1.0 mg/dl for diagnosing appendicitis were 30% to 88% [24] and 69% to 56% [34], respectively.

In the present study, CRP had sensitivity and specificity of 88.1% and 47.8% respectively, for detecting complicated cases, with an AUC of 0.609, when a cut-off value of 42.1 mg/dl was used. **Feng *et al.*** [41] reported that CRP had 89% sensitivity and 75% specificity for detecting appendiceal perforation, with a cut-off value of 55 mg/dl.

In the current study, serum bilirubin had mean values of 0.75, 0.86, and 0.96 mg/dl in Groups I, II, and III respectively, with a significant difference between the three groups ($p = 0.006$). **Sevinç *et al.*** [19] reported that serum bilirubin > 1 mg/dl had sensitivity and specificity of 19.1% and 92.4% respectively for the diagnosis with acute appendicitis (AUC 0.621).

Additionally, **Khan** [47] reported that total serum bilirubin had 82.07% sensitivity and 100% specificity to differentiate between patients with normal and inflamed appendix, when a cut-off value of 1.1 mg/dl was applied.

In the current study, serum bilirubin had sensitivity and specificity of 64.3% and 77.2% respectively, with an AUC of 0.633, and a cut-off value of 1.05 mg/dl. The relationship between hyperbilirubinemia and severe appendicitis has been recognized for a long time. However, this measure is not commonly utilized in everyday clinical practice, likely because of its low sensitivity. **Sevinç *et al.*** [19] reported that using a cut-off value of 1 mg/dl for serum bilirubin, it had sensitivity and specificity of 34.4% and 81.4% for the detection of perforation in patients with appendicitis (AUC = 0.594).

**Jastrzębski *et al.*** [48] reported that the ideal cut-off level for total bilirubin to predict complicated appendicitis was found to be 0.94 mg/dl, demonstrating a sensitivity of 59.5%, specificity of 74.3%, PPV of 44.9%, and NPV of 83.9%. The area under the curve measured 0.652.

**Eren *et al*.** [4] showed that high total bilirubin levels increased the risk of appendiceal gangrene or perforation fivefold, while elevated direct bilirubin levels raised the risk 36 fold, with all findings statistically significant. In other previous studies, reported sensitivities for serum bilirubin to detect the perforation were between 38% and 89%, and specificities were between 66% and 87% [22, 23, 42].

**Atahan *et al*.** [23] reported that the AUC for total bilirubin was greater than 0.8, and for WBC counts, it was over 0.70, indicating that total bilirubin is a more effective and valuable indicator than WBC count for distinguishing between perforated appendicitis and acute suppurative appendicitis or lymphoid hyperplasia.

It has been proposed that the pathogenic mechanism behind hyperbilirubinemia not linked to liver dysfunction may involve increased bilirubin production triggered by oxidative stress from various infections. Additionally, bilirubin is believed to have antioxidant properties, helping to neutralize excessive reactive oxygen species generated by oxidative stress through elevated bilirubin levels in the body [49, 50]. Moreover, E. coli infections can lead to the breakdown of red blood cells (hemolysis) [51]. These mechanisms could contribute to hyperbilirubinemia in cases of acute appendicitis.

In line with our results, **Khan** [47] reported that in cases with positive surgical findings, the average total serum bilirubin was 2.26 mg/dL, with a range of 1.2 to 11.5 mg/dL. In contrast, the average for cases with negative findings was 0.7 mg/dL, within a range of 0.5 to 1.1 mg/dL. However, total serum bilirubin had higher values in patients with complicated appendicitis than patients with simple appendicitis. The latter finding was not detected in our study.

**Chambers *et al.*** [21] reported that the same parameter had mean value of 1.26, 1.75, and 2.05 mg/dl in patients with normal, simply inflamed, and complicated appendix, respectively, indicating the increase of serum bilirubin in association with acute appendicitis, and more increase in complicated cases. In addition, **Eren *et al.*** [4] reported that serum bilirubin had a median value of 0.34 mg/dl in cases with normal appendix, which increased up to 0.57 and 1.25 mg/dl in patients with simple and complicated appendicitis ($p < 0.001$). Furthermore, another study reported that patients with simple appendicitis had a mean serum bilirubin of $0.9 \pm 0.5$ mg/dl compared to $1.1 \pm 0.5$ mg/dl in the complicated group, with a significant rise in the latter ($p < 0.001$) [52].

Our study has some limitations, including collecting patients from a single surgical institution. More studies including more cases should be conducted to reveal the best diagnostic marker for that common surgical emergency, and the impact of appendiceal inflammation on serum bilirubin.

**Conclusion:** Serum bilirubin is weaker than leucocytic count and CRP in the diagnosis of acute appendicitis, and in differentiating complicated from non-complicated cases. Nonetheless, it could be combined with these markers to enhance the diagnosis of that emergency surgical condition. More studies including more cases from different surgical emergency centers should be conducted in the future.

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