

## Hyperbilirubinemia in Acute Appendicitis

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**Background:** Early detection of complicated appendicitis in suspected patients is essential because the complication could be fatal. One of the new potential predictors of severity is preoperative hyperbilirubinemia.

**Objective:** To evaluate the bilirubin level in complicated appendicitis.

**Design:** A Single-Center Cross-Sectional, Retrospective Study.

**Setting:** Salmaniya Medical Complex, Bahrain.

**Method:** Three hundred thirty-seven patients with acute appendicitis admitted between January and November 2018 were included in the study. Patients 14 years of age and above who underwent appendectomy were included. Normal appendix or other histopathological diagnoses, elevated bilirubin with hemolytic or liver disease, and age below 14 years (pediatric age group) were excluded. The analysis was performed by the Statistical Package for the Social Sciences (SPSS®) software and Microsoft Excel.

**Result:** The age range was 14 to 77 years. Two hundred sixty (77.2%) were males and 129 (38.3%) were Bahrainis. Thirty-four (10.1%) patients were diagnosed with complicated appendicitis. Eighty-two (24.3%) patients were found to have elevated bilirubin and 12 (3.6%) were associated with complicated appendicitis, P-value of 0.1162. The majority of patients were found to have elevated WBC count, 234 (69.4%), and neutrophil percentage, 208 (61.7%).

**Conclusion:** In our study, we found no significant correlation between high bilirubin levels and complicated appendicitis. Therefore, we do not recommend the routine use of bilirubin in diagnosing acute appendicitis in our center.

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Acute appendicitis is the most common non-traumatic abdominal emergency worldwide, treated primarily with appendectomy<sup>1</sup>. Appendicitis is inflammation of the internal lining of the vermiform appendix that spreads along its layers. This is caused by obstruction of its lumen leading to infection and appendiceal edema. Further progression leads to gangrenous or perforated appendix due to interruption of the blood supply and infarction<sup>2,3</sup>. Delay in the diagnosis of complicated appendicitis can lead to a significantly increased risk of perforation and morbidity and mortality<sup>1,4</sup>. Mortality in complicated appendicitis increases to 6% compared to only 0.3% in uncomplicated cases<sup>2</sup>.

The diagnosis of acute appendicitis is based on clinical symptoms, physical examination, and laboratory results. It commonly affects males more than females, and mostly during the second decade<sup>5</sup>. Several clinical scoring systems have been in use such as the Alvarado score, Appendicitis Inflammatory Response Score (AIR score), Pediatric Appendicitis Score (PAS), and Adult Appendicitis Score<sup>1,2</sup>. However, these do not address specifically the detection of complicated forms of appendicitis<sup>2</sup>. Despite the increase in available diagnostic modalities such as ultrasonography and CT, up to 15% of

appendicitis cases are misdiagnosed and the rate of appendiceal perforation has remained the same<sup>1</sup>.

One of the new potential predictors of severity is preoperative hyperbilirubinemia. Hyperbilirubinemia is a non-invasive and cost-effective diagnostic tool. It was found to be associated with complicated appendicitis with a sensitivity and specificity reaching up to 100% and 99.27% respectively, as well as a positive predictive value of 97.83% and a negative predictive value of 82.93%<sup>2</sup>. Despite this, its role and clinical use remain controversial.

The aim of this study is to evaluate the diagnostic level of preoperative bilirubin in complicated versus uncomplicated appendicitis.

### METHOD

Three hundred thirty-seven patients with acute appendicitis admitted between January and November 2018 were included in the study. The patients were admitted with acute appendicitis and underwent surgery and had a histopathological diagnosis of appendicitis.

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Patients who had no bilirubin test were excluded. Patients 14 years of age and above who underwent appendectomy (open or laparoscopic) were included. Normal appendix or other diagnoses on histopathology, elevated bilirubin in the presence of hemolytic or liver disease, and age below 14 years were excluded. Personal characteristics of the patients were documented: age, nationality and sex. Patients were evaluated by history taking, physical examination, imaging (as indicated), and laboratory investigations. Laboratory parameters included were WBC count, neutrophil percentage and total bilirubin. Final histopathological examination was classified as follows: early acute appendicitis, acute appendicitis, reactive lymphoid hyperplasia, cicatrized appendix, perforated appendix, gangrenous appendix, and purulent appendix with abscess formation. The former four were regarded as uncomplicated and latter three are complicated appendicitis. Data was collected from the National Health Information System (I-SEHA).

Statistical analysis was performed by the Statistical Package for the Social Sciences (SPSS®) software for Mac, version 26.0 and Microsoft Excel. Categorical variables were analyzed using the Chi-square test. Sensitivity and specificity were calculated to analyze the diagnostic value of the markers. A P-value <0.05 is considered statistically significant with a corresponding confidence level of 95%.

**RESULT**

The age of the patients ranged from 14 to 77 years; 260 (77.2%) were males, 129 (38.3%) were Bahrainis, see table 1.

**Table 1: Personal Data of the Patients**

Age	
Minimum age	14 years
Maximum age	77 years
Nationality	
Bahraini	129 (38.3%)
Non-Bahraini	208 (61.7%)
<b>Total</b>	<b>337 (100%)</b>
Sex	
Male	260 (77.2%)
Female	77 (22.8%)
<b>Total</b>	<b>337 (100%)</b>

Non-complicated acute appendicitis formed the majority and includes early acute appendicitis 36 (10.7%), acute appendicitis 241 (71.5%), reactive lymphoid hyperplasia 20 (5.9%), and cicatrized 6 (1.8%). Only 34 (10.1%) patients were complicated appendicitis, which includes perforated appendix in 3 (0.9%) patients, gangrenous in 30 (8.9%) patients, and 1 (0.3%) patient with purulent appendix and abscess formation. Only 82 patients were found to have elevated bilirubin preoperatively. Of them, only 12 (3.6%) patients were associated with complicated acute appendicitis, a P-value of 0.1162, see table 2.

The majority of patients had elevated WBC count, 234 (69.4%), and neutrophil percentage, 208 (61.7%). However, only 82 (24.3%) were found to have elevated total bilirubin levels, see table 3.

**Table 2: Histopathologic Classification and Association between Complicated and Non-complicated Appendicitis with Elevated Bilirubin Levels**

Classification	Histopathology	Elevated Bilirubin		Total	Percentage
		Yes	No		
Complicated	Gangrenous appendix	11	19	30	8.9%
	Perforated appendix	1	2	3	0.9%
	Purulent with abscess	0	1	1	0.3%
Non-complicated	Early appendicitis	6	30	36	10.7%
	Acute appendicitis	62	179	241	71.5%
	Reactive lymphoid hyperplasia	2	18	20	5.9%
	Cicatrized/fibrosed/chronic inflammation	0	6	6	1.8%
<b>Total</b>		<b>82</b>	<b>255</b>	<b>337</b>	<b>100%</b>
<b>P-value</b>				0.1162	

**Table 3: Comparison of Elevation of Laboratory Parameters in Acute Appendicitis**

Laboratory Parameter	WBC Count	Neutrophil Percentage	Total Bilirubin
<b>Number of patients with elevated parameters</b>	234	208	82
<b>Percentage</b>	69.4%	61.7%	24.3%

**DISCUSSION**

Up to 34% of patients presenting with appendicitis develop complicated appendicitis such as gangrenous and perforated appendicitis<sup>2</sup>. This may lead to bacterial peritonitis, urinary disorders, small bowel obstruction, and intra-abdominal abscess formation. Subsequently, these complications lead to high morbidity and mortality rates<sup>2,3,6</sup>.

Complicated appendicitis generates a systemic inflammatory response, such as elevated WBC count, C-reactive protein (CRP), and deranged liver function tests<sup>2</sup>. Hyperbilirubinemia occurs secondary to endotoxins released in the peripheral blood circulation that impede the liver’s mechanism for bilirubin uptake and excretion<sup>2,3</sup>. In addition, the local release of cytokines such as tumor necrosis factor (TNF) and interleukin 6 (IL-6) in response to the bacterial load from the liver parenchyma causes derangement of the liver function<sup>5</sup>. Elevated bilirubin is observed in both catarrhal and phlegmonous forms as well as in perforated appendicitis<sup>6</sup>.

No specific blood marker for diagnosing acute appendicitis has been identified<sup>7</sup>. Several studies have investigated the potential predictor role of preoperative hyperbilirubinemia in diagnosing complicated appendicitis. This not only helps in prioritizing patients on the operating theater waiting list, but also reduces the cost of further investigations<sup>2,8</sup>. Vaziri M et al and D’Souza et al found higher levels of bilirubin in patients with perforated acute appendicitis compared to those with non-perforated simple appendicitis<sup>4,9</sup>. Iftikhar et al concluded that preoperative hyperbilirubinemia is an accurate and specific indicator of complicated appendicitis, and recommended its use as a screening marker for complicated appendicitis<sup>2</sup>.

Sand et al found that hyperbilirubinemia was superior to WBC count and CRP in identifying perforated appendicitis; the

specificity of hyperbilirubinemia for appendiceal perforation and gangrene was 86% and CRP was 35%<sup>2</sup>. Kumar et al presented comparable roles of hyperbilirubinemia and CRP in predicting appendiceal perforation preoperatively, with no superiority of one investigation over the other<sup>6</sup>.

In our study, we found no significant correlation between high bilirubin levels and complicated appendicitis. This is consistent with a cohort study by Chambers et al, in which it was concluded that bilirubin could not be used independently to predict perforated or complicated appendicitis<sup>8</sup>. This is similar to a study by Kanlioz et al who found a low diagnostic value of bilirubin in diagnosing complicated appendicitis; however, it still can be used as a supporting factor to other parameters<sup>3</sup>.

## CONCLUSION

**Hyperbilirubinemia has shown some potential in predicting the severity of acute appendicitis. However, in our study, we found no significant correlation between high bilirubin levels preoperatively and complicated appendicitis. Therefore, we do not recommend the routine use of bilirubin in diagnosing acute appendicitis in our center.**

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**Competing Interest:** None.

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