

Original research article

## Evaluate the value of pre-operative hyperbilirubinemia as a predictor of complicated appendicitis: prospective observational study

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### Abstract

**Aim:** The aim of this study to determine the value of pre operative hyperbilirubinemia as a predictor of complicated appendicitis.

**Material and methods:** The study was a prospective observational study conducted in the Department of General Surgery, Vardhman Mahavir Medical College and safdarjung Hospital, New Delhi, India for 15 months. Total 120 patients who were diagnosed to have appendicitis and admitted in surgery department and who underwent appendicectomy were included in the study. Clinical examination, blood routine examination, Alvarado score, ultrasound abdomen, histopathology examination, pre and post- operative values of total bilirubin, direct bilirubin and indirect bilirubin were studied.

**Results:** In our study 70 (58.33%) were males and 50 (41.67%) were females. Out of the 120 cases 52 were complicated. 74 cases had elevated bilirubin preoperatively in which 41 cases were having complications like gangrene, suppuration and perforation. Out of the 74 cases that had elevated bilirubin pre operatively 38 (51.35%), the bilirubin level came down to normal limits after 72 hours of appendicectomy. On histopathology, 68 were acute appendicitis, 17 were perforated appendicitis, 12 were gangrenous appendicitis, 23 were suppurative appendicitis. From the study of sensitivity and specificity of pre-operative total bilirubin values in predicting perforated appendicitis, it was found that preoperative total bilirubin value of 1.59 mg/dl had the best sensitivity and specificity. Taking preoperative total bilirubin value 1.59 mg/dl as cut off in predicting perforated appendicitis the sensitivity was 68.8, specificity was 95.1 with an accuracy of 90.2.

**Conclusion:** Patients with appendicitis with elevated bilirubin levels have more chance for complications like perforation, gangrene and suppuration.

**Keywords:** Acute appendicitis, Gangrenous appendix, Hyperbilirubinemia, Perforated appendix

### Introduction

Acute appendicitis is the most common cause of “acute surgical abdomen”.<sup>1,2</sup> Appendicectomy is the emergency abdominal operation most frequently performed and is often the first major procedure performed by a surgeon in training. Despite advances in the radiological and laboratory investigations, the diagnosis of appendicitis remains a dilemma. Based on a combination of history, physical examination and laboratory studies experienced clinicians accurately diagnose appendicitis about 80% of the time.<sup>3</sup> Delay in diagnosis and

surgery for this condition may lead to various complications like perforation, abdominal abscess, urinary retention, small bowel obstruction and peritonitis causing an increase in morbidity and even mortality of the patients. Acute appendicitis is the most common intra-abdominal infectious focus in a surgical patient and *Escherichia coli* and *Bacteroides fragilis* are the most frequent bacterial isolates in this condition.<sup>4</sup> In appendicitis, compromised appendix wall integrity leads to translocation of bacteria and endotoxins from the appendix lumen into the portal system.<sup>5</sup> The percentage of appendicectomies performed, where normal appendix found, varies from 15-50% and postoperative complications can occur in up to 50% of these patients.<sup>4,5</sup> Delay in diagnosis of acute appendicitis leads to perforation and peritonitis with increased mortality. Appendicular perforation ranges 50-90% in various series.<sup>6,7</sup> The importance of laboratory investigations like White Blood Cell (WBC) counts and C-reactive protein (CRP) etc. values has been stressed to supplement the clinical diagnosis and to reduce the frequency of unnecessary appendicectomy.<sup>8</sup> The importance of Ultrasonography (USG) as a diagnostic tool for appendicitis has been widely known and studied.<sup>8,9</sup> Various scores combining clinical features and laboratory investigations, have also been developed to reach the diagnosis, such as the Alvarado score and the Modified Alvarado score.<sup>10,11</sup> However, till now there is no confirmatory laboratory marker for the preoperative diagnosis of acute appendicitis and appendicular perforation. Elevation in serum bilirubin was reported recently, but the importance of the raised total bilirubin has not been stressed in acute appendicitis and appendicular perforation.<sup>12</sup> It is well established that when microorganisms invade the body, leukocytes defend it and leads to increase in the leukocyte count. Microbial invasion in the appendix leads to transmigration of microbe and the release of proinflammatory cytokines such as TNF-alpha, IL6 and cytokines. They reach the liver through Superior mesenteric vein (SMV), either directly or indirectly by altering the hepatic blood flow, produce inflammation, abscess or dysfunction of liver.<sup>13,14</sup> Total bilirubin levels upon admission can be used in conjunction with other diagnostic tests such as ultrasonography and routine investigations to help determine the presence of complicated appendicitis and aid in proper clinical management. Present study was conducted to assess relationship between hyperbilirubinemia and acute appendicitis and to find out whether elevated bilirubin levels have a predictive potential for diagnosis of gangrene/suppurative/perforation in acute appendicitis.

### **Material and methods**

The study was a prospective observational study conducted in the Department of General Surgery, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India for 15 months. After taking the approval of the protocol review committee and institutional ethics committee.

### **Methodology**

Total 120 patients who were diagnosed to have appendicitis and admitted in surgery department and who underwent appendicectomy were included in the study. Appendicectomy performed incidentally, patients with appendicular lump, history of alcoholic liver disease, hemolytic or liver diseases associated with hyperbilirubinemia, history of viral hepatitis, Gilbert's disease, Dubin Johnson syndrome were excluded. Data was collected by interview with the participant with help of structured proforma, clinical examination, blood routine examination, Alvarado score, ultrasound abdomen, histopathology examination, pre and post-operative values of total bilirubin, direct bilirubin and indirect bilirubin.<sup>15</sup> The upper limit of normal value in our laboratory for total bilirubin was 1.4 mg/dl (direct- 0.3 mg/dl, indirect- 1.1 mg/dl).

## Results

In our study 70 (58.33%) were males and 50 (41.67%) were females. Out of the 120 cases 52 were complicated (Table 1). In our study acute appendicitis were classified as complicated as uncomplicated. Complications included perforated appendix, gangrenous appendix and appendicitis with suppuration. 74 cases had elevated bilirubin preoperatively in which 41 cases were having complications like gangrene, suppuration and perforation. Out of the 74 cases that had elevated bilirubin pre operatively 38 (51.35%), the bilirubin level came down to normal limits after 72 hours of appendectomy (Table 2).

**Table 1: Distribution of acute appendicitis in complicated and uncomplicated cases.**

Type of appendicitis	Number	Percentage
Acute appendicitis (uncomplicated)	68	56.67
Perforated appendicitis	17	14.17
Gangrenous appendicitis	12	10
Suppurative appendicitis	23	19.17
<b>Total</b>	<b>120</b>	<b>100</b>

**Table 2: Distribution of cases based on preoperative elevated bilirubin**

Type of appendicitis	Bilirubin elevated	Normal bilirubin	Total
Acute appendicitis (uncomplicated)	33	35	68
Gangrenous appendicitis	9	3	12
Suppurative appendicitis	18	5	23
Perforated appendicitis	14	3	17
<b>Total</b>	<b>74</b>	<b>46</b>	<b>120</b>

41 of the 52 cases of complicated appendicitis had elevated total bilirubin levels preoperatively. Of the 41 cases of preoperative hyperbilirubinemia, in 25 (48.07%) cases the bilirubin level came back to normal levels within 72 hours of appendectomy. Out of the 120 patients 10 (8.33%) had alkaline phosphatase less than 46, 109 (90.83%) were between 46-116 and only 1 (0.83%) patients had alkaline phosphatase more than 116. Out of 120 cases 52 patients had a total leucocyte count more than 11000 (Table 3).

**Table 3: Total leucocyte count**

TLC (cells/mm <sup>3</sup> )	Number	Percentage
<4000	3	2.5
4000-11,000	65	54.17
>11,000	52	43.33

In our study CRP was positive in 98 cases (>0.6 mg/l). In hundred cases Alvarado score had a mean of 6.7, maximum being 11 and minimum being 3. On histopathology, 68 were acute appendicitis, 17 were perforated appendicitis, 12 were gangrenous appendicitis, 23 were suppurative appendicitis. From the study of sensitivity and specificity of pre-operative total bilirubin values in predicting perforated appendicitis, it was found that preoperative total bilirubin value of 1.59 mg/dl had the best sensitivity and specificity (Table 4).

It was done using a ROC curve. Area under the curve was 0.844, (0.74-0.96) with 95% CI and a p value of <0.001. Kappa test was done with preoperative bilirubin value of 1.55 mg/dl to find agreement between histopathology finding and total bilirubin. Kappa was 0.68 and p value was <0.001. It showed substantial agreement. Taking preoperative total bilirubin value 1.59 mg/dl as cut off in predicting perforated appendicitis the sensitivity was 68.8, specificity was 95.1 with an accuracy of 90.2.

**Table 4: Predictive power of pre-operative total bilirubin in predicting perforated appendicitis over acute appendicitis**

Total bilirubin (mg/dl)	Perforated appendicitis	Acute appendicitis	Total
±1.55	10	5	15
<1.55	7	63	70
<b>Total</b>	17	68	85

**Table 5: Predictive power of pre-operative total bilirubin in predicting gangrenous appendicitis over acute appendicitis**

Total bilirubin	Suppurative appendicitis	Acute appendicitis	Total
Elevated	18	33	51
Normal	5	35	40
<b>Total</b>	23	68	91

From the study of sensitivity and specificity of pre-operative total bilirubin values in predicting gangrenous appendicitis, it was found that preoperative total bilirubin value of 1.77 mg/dl had the best sensitivity and specificity (Table 5). It was done using a ROC curve. Area under the curve was 0.811, (0.63-0.99) with 95% CI and a  $p < 0.001$ . Kappa test was done with preoperative bilirubin value of 1.80 mg/dl to find agreement between histopathology finding and total bilirubin. Kappa was 0.69 and a  $p$  value of  $< 0.001$  which showed, substantial agreement. Taking preoperative total bilirubin value 1.80 mg/dl cut-off in predicting gangrenous appendicitis the sensitivity was 63.6, specificity was 98.2 with an accuracy of 92.5.

**Table 6: Predictive power of pre-operative total bilirubin in predicting suppurative appendicitis over acute appendicitis**

Total bilirubin (mg/dl)	Suppurative appendicitis	Acute appendicitis	Total
±1.45	13	7	20
<1.45	10	61	71
<b>Total</b>	23	68	91

From the study of sensitivity and specificity of pre-operative total bilirubin values in predicting suppurative appendicitis, it was found that preoperative total bilirubin value of 1.45 mg/dl had the best sensitivity and specificity (Table 6). It was done using a ROC curve. Area under the curve was 0.752, (0.58-0.92) with 95% CI and a  $p = 0.001$ . Kappa test was done with preoperative bilirubin value of 1.47 mg/dl to find agreement between histopathology finding and total bilirubin. Kappa was 0.47 and a  $p < 0.001$  which showed, moderate agreement. Taking preoperative total bilirubin value as 1.47 mg/dl as cut off in predicting gangrenous appendicitis the sensitivity was 57, specificity was 90.7 with an accuracy of 82.4.

### Discussion

In acute appendicitis or appendicular perforation, inflammatory response causes appendix to become more edematous and ischemic. This causes transmigration or translocation of bacteria, toxins, and cytokines leading to endotoxemia/bacteraemia. Invasion of bacteria into the hepatic parenchyma interferes with the physiology of excretion of bile and leads to

hyperbilirubinemia. Hyperbilirubinemia in sepsis is a well-recognised entity and gram negative bacteria are the usual culprits. Hyperbilirubinemia occurs in appendicitis as a result of bacteraemia and endotoxins in the blood. This could happen in complicated appendicitis which is similar to findings in our study.<sup>16</sup>

In our study majority of patients with appendicitis were male 70 (58.33%) which was similar to studies by Chaudary et al and Atahan et al.<sup>17,18</sup> In a study by D'Souza et al elevated total bilirubin preoperatively showed significant diagnostic value of complicated appendicitis.<sup>19</sup>

In a study by Sand et al, the mean bilirubin was  $1.5 \pm 0.9$  mg/dl in patients with appendicular perforation. The sensitivity was 0.70 and specificity was 0.86 compared to a sensitivity of 0.68 and specificity of 0.95 in our study in case of perforation.<sup>20</sup>

In a study of 157 patients by Estrada et al patients with suppuration were significantly more likely to have hyperbilirubinemia. Appendicular perforation was 3 times higher for patients with hyperbilirubinemia when compared to normal bilirubin levels.<sup>21</sup> From our study preoperative hyperbilirubinemia was a predictor of complicated appendicitis similar to a study by Fabio Silva et al.<sup>22</sup>

In the study of 471 patients by Emmanuel et al, hyperbilirubinemia was found in 34% patients with appendicitis. In our study 74 (61.67%) patients had hyperbilirubinemia. 52 patients in our study had complicated appendicitis out of which 41 (78.85%) patients had hyperbilirubinemia. For patients with appendicitis in Emmanuel et al study with hyperbilirubinemia, specificity for perforation was 70% compared to our study in which the specificity was 94.6%.<sup>23</sup>

### Conclusion

Patients with appendicitis with elevated bilirubin levels have more chance for complications like perforation, gangrene and suppuration.

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