

# Estimation of serum bilirubin level as a diagnostic laboratory marker of acute appendicitis and its role in prediction of appendicular perforation



Manoranjan Ghosh<sup>1</sup>, Monali Patole Mukherjee<sup>2</sup>, Vikram Chaturvedi<sup>3</sup>, Dipankar Mukherjee<sup>4</sup>

<sup>1</sup>Assistant Professor, Department of Paediatric Surgery, Bankura Sammilani Medical College, Bankura, <sup>2</sup>RMO Cum Clinical Tutor, Department of Paediatric Surgery, <sup>3</sup>Associate Professor, Department of Surgical Oncology, <sup>4</sup>Assistant Professor, Department of Plastic Surgery, Medical College Hospital, Kolkata, West Bengal, India

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## ABSTRACT

**Background:** Acute appendicitis is the most common cause of surgical abdomen. A delay in diagnosis and subsequent delay in intervention may lead to appendicular perforation which leads to peritonitis and further complications including death. In this study, we tried to evaluate – “Estimation of serum bilirubin level as a diagnostic laboratory marker of acute appendicitis and its role in prediction of appendicular perforation.” **Aims and Objectives:** The objectives of the study are as follows: To study the relationship between hyperbilirubinemia and acute appendicitis and to evaluate its credibility as a diagnostic marker for acute appendicitis. To evaluate whether elevated Bilirubin levels have a predictive potential for diagnosis of appendicular perforation. **Materials and Methods:** Patients clinically diagnosed with acute appendicitis, supported by imaging studies, who gave consent for the study were included in the study. All those patients underwent estimation of serum bilirubin levels along with other investigations. Data collected were compiled and analyzed. **Results:** In this study, among 408 patients, sensitivity of serum bilirubin in predicting acute appendicitis was 74.59%. Specificity of serum bilirubin in predicting acute appendicitis was 12.38%. Positive predictive value of serum bilirubin in predicting acute appendicitis was 71.06%. Negative predictive value of serum bilirubin in predicting acute appendicitis was 14.44%. Odds ratio was 0.4147. **Conclusion:** Serum Bilirubin level appears to be a promising marker for diagnosing acute appendicitis and perforation.

**Key words:** Acute appendicitis; Appendicular perforation; Hyperbilirubinemia

## INTRODUCTION

Acute appendicitis is the most common cause of acute surgical abdomen.<sup>1,2</sup> Appendectomy is the most frequently performed urgent abdominal surgery. Despite advancements in various imaging modalities and laboratory investigations, diagnosis of acute appendicitis most of the time depends on history and clinical examination.

Although an experienced surgeon can clinically diagnose acute appendicitis 80%<sup>3</sup> of the time, there are conditions where diagnosis becomes challenging especially in cases

of retrocecal and retroileal appendicitis. A delay in diagnosis and subsequent delay in intervention may lead to appendicular perforation (50–90% in various series<sup>4,5</sup>) which leads to peritonitis and further complications including death. It has been observed that appendectomy performed in cases of diagnostic dilemma results in the removal of a normal appendix in 15–40% of patients. Post-operative complications have also been reported in up to 50% of patients in few studies.<sup>6,7</sup>

Hence, to aid in clinical diagnosis and reduce the number of unnecessary appendectomies, the role of various

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### Address for Correspondence:

Dr. Dipankar Mukherjee, Assistant Professor, Department of Plastic Surgery, Medical College Hospital, Kolkata - 700 073, West Bengal, India. **Mobile:** +91-7278169968. **E-mail:** dr.dipankarmukherjee@gmail.com

laboratory investigations, total leukocyte count (TLC), and C-reactive protein (CRP) have been stressed.<sup>8</sup> There are various scoring systems too in place like ALVARADO,<sup>9</sup> MODIFIED ALVARADO<sup>10</sup> to help the surgeon arrive at a diagnosis of acute appendicitis. Apart from the laboratory investigations, various imaging studies such as USG and CT scans are also widely used in diagnosing acute appendicitis.<sup>11</sup> Despite these investigations, there are no confirmatory laboratory markers for diagnosing acute appendicitis and appendicular perforation. An association of hyperbilirubinemia with appendicitis has been observed, but its diagnostic role as a lab marker is still being investigated.

In acute microbial invasion, leukocytes take part in the defense mechanism, and TLC is elevated. In bacterial invasion of appendix, transmigration of bacteria takes place and various pro-inflammatory cytokines (TNF- $\alpha$ , IL-6) are released which reach the liver through superior mesenteric vein to cause hepatic dysfunction thereby leading to hyperbilirubinemia.<sup>12</sup>

In view of the above facts, the study was conducted to evaluate the association of elevated serum bilirubin levels with acute appendicitis and its credibility as a diagnostic marker for acute appendicitis and appendicular perforation.

### Aims and objectives

The objectives of the study are as follows:

1. To study the relationship between hyperbilirubinemia and acute appendicitis and to evaluate its credibility as a diagnostic marker for acute appendicitis
2. To evaluate whether elevated Bilirubin levels have a predictive potential for diagnosis of appendicular perforation.

## MATERIALS AND METHODS

This study was conducted in a Medical College and Hospital of Eastern India, in the Department of Surgery from August 2020 to July 2022. It is a cross-sectional and observational study. Patients admitted either through outpatient department (OPD) or EMERGENCY during the said time period at above mentioned Medical College were included in the study. Four hundred and eight patients with clinical diagnosis of acute appendicitis or appendicular perforation were studied.

### Selection criteria

Inclusion criteria for this study were:

1. Patients clinically diagnosed with acute appendicitis
2. Patient diagnosed with acute appendicitis on imaging
3. Patient willing to give consent for the study.

The exclusion criteria were:

1. Patients with pre-existing liver disease
2. H/O of chronic alcoholism
3. HbsAG positive patients
4. Cholelithiasis
5. Hemolytic disorders
6. Immunocompromised patients
7. Patients on AKT/ART.

### Procedure

After a thorough history and physical examination, certain laboratory investigations and imaging studies were performed on all the patients suspected of acute appendicitis or appendicular perforation, admitted during the given time period. Patient data were collected and age, sex, address, history of similar episodes in the past, any comorbidities were noted. CBC, LFT (Total bilirubin, direct and Indirect, SGPT, SGOT, and ALP), serology, and USG abdomen were performed for all the patients, apart from other routine pre-operative investigations.

## RESULTS

This study was conducted in a Medical College and Hospital of Eastern India, in the Department of Surgery, from August 2020 to July 2022. Clearance from the Institutional ethics committee was obtained before the commencement of the study. Four hundred and eight consecutive patients of clinically suspected acute appendicitis and appendicular perforation, who had given consent to participate in the study, were included and all the above mentioned laboratory investigations and imaging studies were done for all the participated patients. Subsequently clinical diagnosis was confirmed per operatively and the data were compiled and analyzed. The following observations were thus obtained from our study.

Among 408 patients, 228 were males (56%) and 180 were females (44%) (Figure 1).

From Table 1, it is seen that among these 408 patients, normal total bilirubin level was found in 114 (28%) patients and 294 (72%) patients had hyperbilirubinemia.

From Table 2, it is seen that 318 patients had uncomplicated acute appendicitis and remaining 90 patients had appendicular perforation.

Among these 318 patients with uncomplicated acute appendicitis, 226 patients (71%) had serum bilirubin level more than 1 mg/dL, whereas hyperbilirubinemia was found in 77 patients (85%) among the 90 patients with perforated appendicitis.

Number of patients of uncomplicated and perforated appendicitis in relation to total bilirubin levels (Figure 2).

From Table 3, it is seen that the mean total bilirubin of all 408 patients was  $1.5 \pm 0.8$  mg/dL (range 0.7–2.3 mg/dL) and direct bilirubin was  $1.0 \pm 0.7$  mg/dL (range 0.3–1.7 mg/dL).

From Table 4, it is seen that the mean total bilirubin level among the uncomplicated acute appendicitis patient was  $1.4 \pm 0.65$  mg/dL (range 0.75–2.05 mg/dL), whereas in the appendicular perforation patients, the mean total bilirubin level was  $1.9 \pm 1.16$  mg/dL (range 0.74–3.06 mg/dL) which is shown in Fig 3.

Similarly among the uncomplicated acute appendicitis patients, the direct bilirubin and indirect bilirubin range were  $(0.9 \pm 0.57)$  mg/dL and  $(0.5 \pm 0.21)$ , mg/dL respectively, and among the perforated appendicitis patients, the direct bilirubin and indirect bilirubin range were  $(1.2 \pm 1.06)$  mg/dL and  $(0.7 \pm 0.33)$  mg/dL, respectively.

The following values were obtained from our study with respect to total bilirubin levels in acute appendicitis:

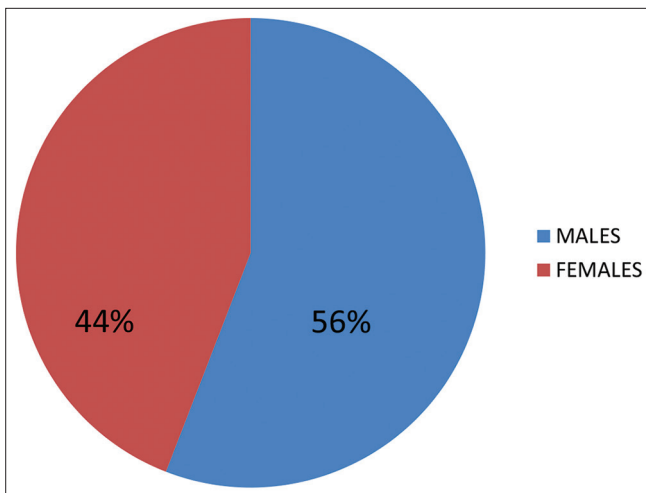


Figure 1: Sample size distribution according to gender

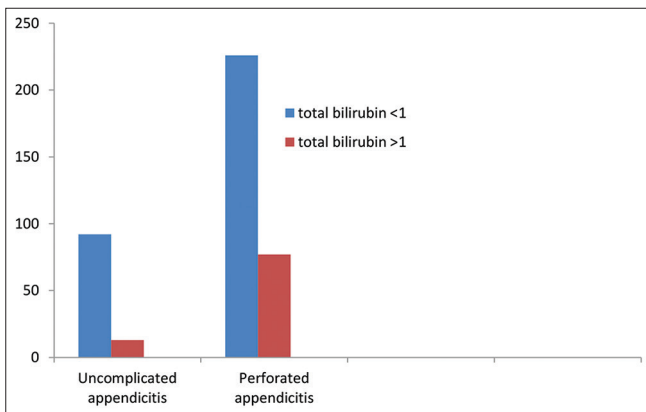


Figure 2: Relation of complications of appendicitis with bilirubin level

## DISCUSSION

Acute appendicitis is the most common cause of the right iliac fossa pain presenting to surgeons in the OPD or Emergency. A thorough history and clinical examination can help a clinician to rule out other potentially treatable gynecological/urological causes other than appendicitis, for example, ruptured ectopic pregnancy, ovarian cyst torsion, ureteric colic, or testicular torsion. Having arrived at a provisional diagnosis of acute appendicitis, certain tests

Table 1: Distribution of patients as per bilirubin levels

Total bilirubin (mg/dL)	Number of patients	Percentage
≤1	114	28
>1	294	72
Total	408	100

Table 2: Relation of complications of appendicitis with bilirubin level

Total bilirubin (mg/dL)	Patients with uncomplicated acute appendicitis		Patients with perforated appendicitis	
	Number	Percentage	Number	Percentage
≤1	92	29	13	15
>1	226	71	77	85
Total	318	100	90	100

Table 3: Mean distribution of bilirubin levels

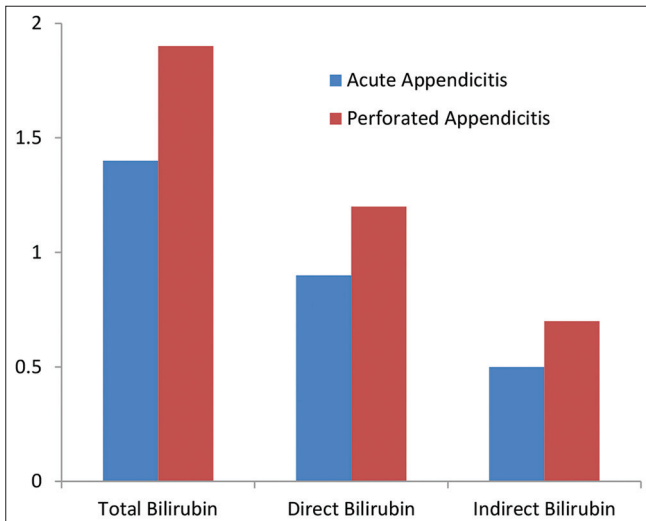
Parameters	Mean	SD
Total bilirubin (mg/dL)	1.5	0.8
Direct bilirubin (mg/dL)	1.0	0.7
Indirect bilirubin (mg/dL)	0.5	0.2

Table 4: Relation of complications of appendicitis with mean distribution of bilirubin level

Bilirubin levels (mg/dL)	Diagnosis			
	Acute appendicitis		Perforated appendicitis	
	Mean	SD	Mean	SD
Total bilirubin	1.4	0.65	1.9	1.16
Direct bilirubin	0.9	0.57	1.2	1.06
Indirect bilirubin	0.5	0.21	0.70	0.33

Table 5: Different statistical parameters related to the study

Statistical parameters	Values
Sensitivity	74.59%
Specificity	12.38%
Positive predictive value	71.06%
Negative predictive value	14.44%
Odds ratio	0.4147



**Figure 3:** Correlation of acute appendicitis and perforated appendicitis with total, direct and indirect bilirubin levels

(both laboratory and radiological) are then performed to arrive at a definitive diagnosis. Among other blood tests, serum bilirubin levels appear to be a promising marker for diagnosing acute appendicitis.

The relation between hyperbilirubinemia and acute appendicitis is multifactorial and is hypothesized that elevated bilirubin is a result of portal sepsis leading to hepatocyte dysfunction or damage. The low percentage of getting a positive blood culture compared to a higher number of cases of hepatic dysfunction means that there are other substances involved in the mechanism. The role of bacterial infection especially Gram-negative bacteria in causing this through the release of endotoxins or cytokines (TNF alpha and IL-6) cannot be overemphasized. The end result of up regulation of these cytokines during the early part of sepsis is direct hepatocyte damage, cholestasis, or a combination leading to hyperbilirubinemia.

The lipopolysachharides released from the bacterial membranes lead to hemolysis thereby further increasing the total bilirubin levels. Few authors believe that direct bacterial invasion into the portal system or hepatic parenchyma interferes with bilirubin excretion into the biliary canaliculi, a process thought to be more of biochemical than obstructive in nature, thus producing liver dysfunction and pyogenic liver abscess.

In our study, from table 5 it is seen that the sensitivity, positive predictive value, and negative predictive value of total serum bilirubin in suspected acute appendicitis was 74.59%, 71.06%, and 14.44%, respectively, which matches the findings of a similar study conducted by Kar *et al.*,<sup>13</sup> in February 2022, in which their figures were 57.02%, 97.01%, and 15.52%, respectively. In another study by Chaudhary

*et al.*,<sup>14</sup> hyperbilirubinemia was of mixed type (conjugated and unconjugated elevation), but it was total serum bilirubin that was predominantly raised. They noticed that the total bilirubin levels were higher than 3 mg/dL in perforated appendicitis but <3 mg/dL in acute appendicitis. In our study, the mean total bilirubin level was 1.9 mg/dL in perforated cases and 1.4 mg/dL in uncomplicated acute cases. Their findings matched those of another study by Khan.<sup>15</sup>

Hence, in cases of clinical dilemma in diagnosing acute appendicitis, apart from other investigations, serum bilirubin estimation will aid the clinician in decision making for operative intervention to prevent further complications related to untreated acute appendicitis, like appendicular perforation, peritonitis, and sepsis including a remote risk of mortality. White blood cell (WBC) and CRP are being routinely performed for the diagnosis of acute appendicitis with comparable sensitivity, PPV, and NPV, but they lack specificity either alone or in combination. The addition of total serum bilirubin to these tests could be the way forward in helping surgeons owing to a higher specificity than CRP and WBC overall.<sup>16</sup>

Moreover, further studies and reporting based on standards for reporting diagnostic accuracy studies checklist are needed to investigate whether the combined predictive value of total bilirubin, CRP, and WBC would be a more effective and accurate diagnostic tool for surgeons.

#### Limitations of the study

This study was performed in a short duration and with a small sample size. A long duration study with larger sample size and preferably a multicentre study will be better to establish the significance of Estimation of Serum Bilirubin level as a diagnostic laboratory marker of Acute Appendicitis and its role in prediction of appendicular perforation.

## CONCLUSION

We would like to conclude by stating that while diagnosing acute appendicitis, no single laboratory parameter should be considered independently, rather, a combination of various markers should be performed along with clinical judgment and imaging adjuncts. Serum bilirubin level appears to be a promising marker for diagnosing acute appendicitis in view of high specificity. It is a simple and easily available test which can be added to the list of routine investigations at the time of emergency admission. Further multicenter prospective studies would be needed to establish whether total serum bilirubin can be used as an independent marker for the diagnosis of acute or perforated appendicitis.



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The authors declare that there is no conflicts of interest. This is an original cross-sectional and prospective study. Clearance from the Institutional Ethics Committee was taken before commencing the study. Faculties from pediatric and plastic surgery were actively involved in this study. I convey my sincere thanks to other faculties involved in this study for their valuable contributions.

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### Authors' Contributions:

**MG-** Concept and design of the study and prepared first draft of the manuscript; **MPM-** Interpreted the results and reviewed the literature; **VC-** Statistical analysis and revision of the manuscript; **DM-** Correspondence, coordination, and interpretation of data.

### Work attributed to:

Medical College Hospital, 88, College Street, Kolkata - 700 073, West Bengal, India.

### Orcid ID:

Dr. Manoranjan Ghosh - <https://orcid.org/0000-0003-1896-9891>  
Dr. Monali Patole Mukherjee - <https://orcid.org/0000-0002-2636-6524>  
Dr. Vikram Chaturvedi - <https://orcid.org/0000-0002-4098-9445>  
Dr. Dipankar Mukherjee - <https://orcid.org/0000-0003-3068-459X>

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