

# Hyperbilirubinemia as a New Diagnostic Marker for Acute Appendicitis and its Role as a Predictor of Complicated Appendicitis: A Prospective Study

Shaik Khader Basha, RG Santhaseelan, PK Baskaran\*

Department of General Surgery, Sree Balaji Medical College & Hospital Affiliated to Bharath Institute of Higher Education and Research, Chennai, Tamil Nadu, India

## ABSTRACT

**Aim:** The present study was done to assess the relationship between hyperbilirubinemia and acute appendicitis and to evaluate its credibility as a diagnostic marker for acute appendicitis and its predictive potential in diagnosis of complicated appendicitis.

**Methodology:** This one-year cross sectional study was conducted in the department of general surgery, Sree Balaji Medical College and Hospital during the period of April 2018 to April 2019. A total of 100 patients with clinical diagnosis acute appendicitis or complicated appendicitis were studied. The serum bilirubin and liver function tests were carried out in all the patients.

**Results:** In this study, male (58%) outnumbered females (42%) and overall, the mean age was 29. The mean total serum bilirubin of all 100 patients was  $1.491 \pm 1.0319$  mg/dl which was above the normal range ( $>1.0$  mg/dl) considered for the study, hence indicating the presence of hyperbilirubinemia. The mean of direct bilirubin was  $1.290 \pm 0.7483$  mg/dl while that of indirect bilirubin was  $0.504 \pm 0.2494$  mg/dl. Among the patients with inflamed appendix, 26 patients (34.66%) were found to have elevated bilirubin ( $>1.0$  mg/dl). In patients diagnosed with appendicular perforation (n=25), 19 patients (76%) had bilirubin elevated ( $>1.0$  mg/dl), while only 6 patient (24%) had normal level ( $<1.0$  mg/dl). Thus, hyperbilirubinemia was seen in 34.66% of patients with acute appendicitis and 76% of patients with complicated appendicitis. Sensitivity and specificity of bilirubin in diagnosing acute appendicitis and appendiceal perforation was 76% and 65.33% respectively. Similarly positive predictive value and negative predictive value of bilirubin was 42.22% and 89.09%.

**Conclusion:** Serum bilirubin routinely added to the blood investigation can be useful laboratory investigation for aiding in the diagnosis of acute appendicitis. Can be easily done and cheaply available. Patients with three times the normal bilirubin value and clinical signs of appendicitis and appendicular perforation have higher probability of having complicated appendicitis.

**Key words:** Acute appendicitis, Appendicular perforation, Hyperbilirubinemia, Bilirubin

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**Corresponding author:** PK Baskaran  
**e-mail** ✉: drpkbaskaran@yahoo.co.in  
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## INTRODUCTION

Acute appendicitis is one of the most common case presenting as a surgical emergency [1,2]. Appendicitis has been evolving through ages depicting its importance of early diagnosis and appropriate management. The diagnosis of appendicitis is more of a clinical even with latest advances in the diagnostic modalities. Misdiagnosis of appendicitis is 15.3% even in the hands of an experienced surgeon [3]. There are 36 negative appendicectomies done globally to prevent one case of appendicitis per se as per main got. And it can be potentially life threatening to the patient if the diagnosis is late or delayed leading to perforation, peritonitis, abscess,

sepsis. Hence appendicitis should be diagnosed early and negative appendicectomies have to be avoided to prevent unnecessary surgical morbidity. surgical exploration can lead to anaesthetic complications, future hernias can develop because of abdominal wall muscle weakness, it also causes post-operative adhesion and in pregnant women it can lead to fetal loss and lastly an abdominal scar.

Even well experienced surgeons make their diagnosis based on history, clinical Examination and findings, and laboratory investigations which are only 80% positive [4]. As ultrasonography and CT is unavailable in the rural areas and with an intention to reduce negative appendicectomies and delay in diagnosis of complicated appendicitis, there arises a gap for available diagnostic markers. Even Though Alvarado scoring, WBC count and CRP are used as laboratory markers. Recent studies on rise

in bilirubin value suggest high specificity and comparable sensitivity than former it can be easily done laboratory marker [5,6].

Acute Appendicitis is mostly polymicrobial in nature, causes bacterial translocation into the gut. These bacteria in turn releases endotoxins and stimulates production of pro inflammatory cytokines like TNF and IL1. These molecules reach the liver via portal venous system leading to hepatocyte dysfunction and prevent the release of bilirubin and produces cholestatic type of jaundice. Based on these observation, present study was done to empathize the predictive value of hyperbilirubinemia in appendicitis and potential to detect complicated appendicitis [7-9].

## MATERIALS AND METHODS

The current study was performed in the department of general surgery at Sree Balaji Medical College Hospital during the period of April 2018 to April 2019.

### Place of study

The present study was conducted in the department of surgery, Sree Balaji medical college hospital, Chromepet, Chennai.

### Source of data

Patients admitted with clinical diagnosis and planned for emergency surgery under the department of general surgery, Sree Balaji Medical College and Hospital during the study period.

### Sample size

A total of 100 patients with pre-operative clinical diagnosis of appendicular pathology were included.

### Selection criteria

#### Inclusion criteria

All patients clinically diagnosed as acute appendicitis and gangrenous appendicitis which were taken up for emergency surgery in surgical department. In both the group histopathological report were considered.

#### Exclusion criteria

Prior history of jaundice, Prior history of liver disease, Prior history of pancreatitis, Chronic alcoholism, Patients

with hepatitis B, A and C and Taking drugs increasing liver parameters like rifampicin.

### Procedure

The study was conducted after obtaining ethical committee clearance of Sree Balaji Medical College and hospital, Chromepet, Chennai. Based on the criteria patient admitted and underwent emergency appendectomy for acute and complicated appendicitis in Sree Balaji Medical College and hospital were included. All eligible patients were informed about the purpose and usefulness of study. Then after obtaining informed consent as per consent form submitted in annexure.

All relevant clinical finding and history recorded in predesigned Patient proforma submitted in annexure. All patients clinically diagnosed as acute and complicated appendicitis were submitted to battery of blood investigation, then emergency appendectomy and histopathological report attached.

### Statistical analysis

The collected data were analysed with IBM.SPSS statistics software 23.0 Version. To describe about the data descriptive statistics frequency analysis, percentage analysis were used for categorical variables and the mean & S.D were used for continuous variables. To find the significant difference between the bivariate samples in independent groups the Unpaired sample t-test was used. To assess the efficacy of the tools the Sensitivity, Specificity, PPV and NPV was used. To find the significance in categorical data Chi-Square test was used similarly if the expected cell frequency is less than 5 in 2x2 tables then the Fisher's Exact was used. In all the above statistical tools the probability value .05 is considered as significant level.

## RESULTS

In our study conducted on "hyperbilirubinemia as a new diagnostic marker for acute appendicitis and its role as a predictor of complicated appendicitis: a prospective study" conducted from April 2018 to April 2019 at Sree Balaji Medical College and Hospital, Chromepet, Chennai. 100 cases of acute appendicitis undergoing emergency appendectomy were included in our study. Patients included in our study were resuscitated adequately before taken up for study. Patient's details were collected and documented using the standard proforma. The details and values were compiled into a master chart and following observations were made (Table 1 to Table 10) and (Figure 1 to Figure 7).

**Table 1: Sex distribution.**

| Sex distribution |           |         |
|------------------|-----------|---------|
|                  | Frequency | Percent |
| Female           | 42        | 42      |
| Male             | 58        | 58      |
| Total            | 100       | 100     |



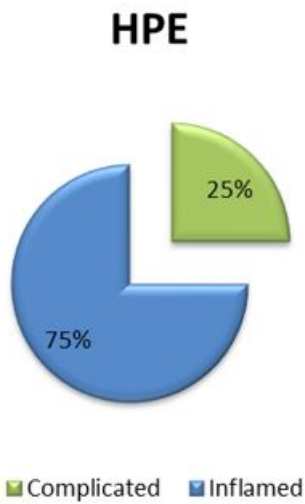


Figure 4: Figure 4: Histopathological diagnosis.

Table 4: Total bilirubin levels.

| Total Bilirubin |           |         |
|-----------------|-----------|---------|
|                 | Frequency | Percent |
| >1 mg/dl        | 45        | 45      |
| <=1 mg/dl       | 55        | 55      |
| Total           | 100       | 100     |

Table 5: Descriptive statistics of LFTS.

| Descriptive Statistics | N   | Minimum | Maximum | Mean  | S. D    |
|------------------------|-----|---------|---------|-------|---------|
| Total bilirubin        | 100 | 0.4     | 4.5     | 1.491 | 1.0319  |
| Direct Bil             | 100 | 0.4     | 3.6     | 1.29  | 0.7483  |
| Indirect Bil           | 100 | 0.1     | 1.1     | 0.504 | 0.2494  |
| SGOT                   | 100 | 10      | 53      | 27.08 | 9.6804  |
| SGPT                   | 100 | 11      | 47      | 26.87 | 9.1537  |
| ALP                    | 100 | 33      | 141     | 97.16 | 23.4373 |

Table 6: Total leucocyte count.

| Total count |           |         |
|-------------|-----------|---------|
|             | Frequency | Percent |
| < 10000     | 29        | 29      |
| >= 10000    | 71        | 71      |
| Total       | 100       | 100     |

## Neutrophils

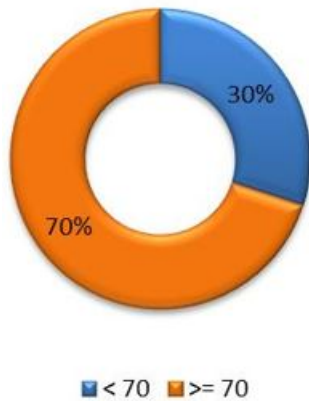


Figure 5: Differential leucocyte count.

Table 7: Descriptive statistics of differential leucocyte count.

| Descriptive statistics |     |         |         |       |          |
|------------------------|-----|---------|---------|-------|----------|
|                        | N   | Minimum | Maximum | Mean  | S.D      |
| Total count            | 100 | 6800    | 18700   | 11784 | 2718.798 |
| Neutrophils            | 100 | 54      | 91      | 73.26 | 8.8929   |
| Lymphocytes            | 100 | 8       | 44      | 21.89 | 7.8159   |
| Monocytes              | 100 | 0       | 11      | 3.99  | 2.8832   |
| Eosinophils            | 100 | 0       | 5       | 1.06  | 1.1443   |

The mean total bilirubin levels in patients diagnosed as inflamed appendicitis was  $1.08 \pm 0.48$ , in patients with complicated appendicitis was  $2.74 \pm 1.24$ . The direct and indirect bilirubin levels in patients with inflamed appendicitis was  $1.04 \pm 0.41$  and  $0.44 \pm 0.19$ , respectively. The direct and indirect bilirubin levels in patients with

complicated appendicitis was  $2.04 \pm 1.01$  and  $0.70 \pm 0.30$  respectively (Table 8 and Figure 6).

Table 8: Comparison of mean serum bilirubin levels in patients with acute appendicitis (Inflamed) and appendicular perforation/ gangrene (Complicated).

| Comparison with Unpaired t-test |             |    |      |      |          |          |
|---------------------------------|-------------|----|------|------|----------|----------|
| Groups                          |             | N  | Mean | S. D | t- value | P-value  |
| Total bilirubin                 | Complicated | 25 | 2.74 | 1.24 | 9.705    | 0.0005** |
|                                 | Inflamed    | 75 | 1.08 | 0.48 |          |          |
| Direct BIL                      | Complicated | 25 | 2.04 | 1.01 | 4.836    | 0.0005** |
|                                 | Inflamed    | 75 | 1.04 | 0.41 |          |          |
| Indirect BIL                    | Complicated | 25 | 0.7  | 0.3  | 4.021    | 0.0005** |
|                                 | Inflamed    | 75 | 0.44 | 0.19 |          |          |

\*\*Highly Significant at P<0.01 level

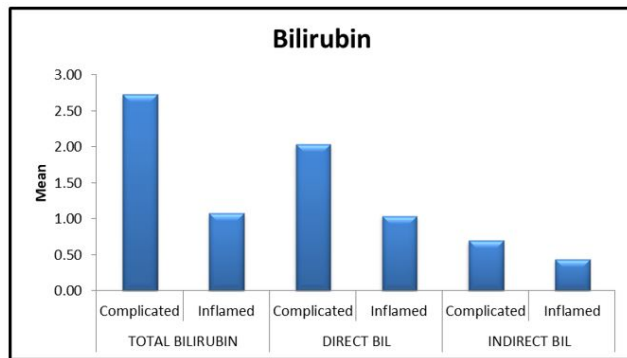


Figure 6: Comparison of mean serum bilirubin levels in patients with acute appendicitis (Inflamed) and appendicular perforation/gangrene (Complicated).

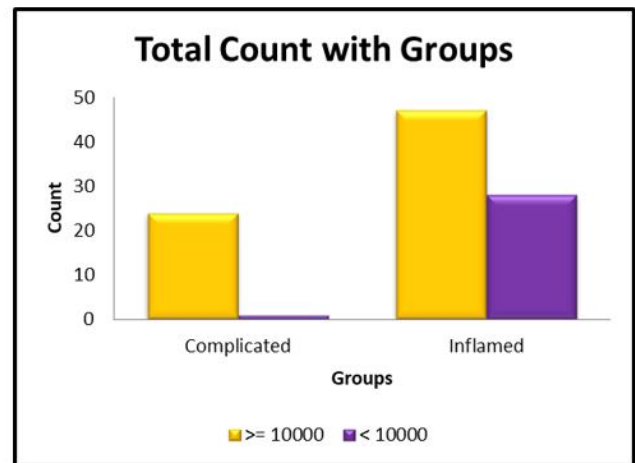


Figure 7: Total count with groups.

Table 9: ROC curve.

| Groups   | Valid N (listwise) |
|----------|--------------------|
| Positive | 25                 |
| Negative | 75                 |

Table 10: Area under the curve.

| Area  | P-value | Area under the curve |       |
|-------|---------|----------------------|-------|
|       |         | 95% C.I              |       |
|       |         | LB                   | UB    |
| 0.707 | 0.002** | 0.59                 | 0.823 |

\*\*Highly Significant at P<0.01

**DISCUSSION**

Acute appendicitis remains the most common acute surgical condition of the abdomen, it is also most misdiagnosed condition. Appendectomy is the most performed emergency procedure for acute appendicitis in the world. The lifetime risk of developing acute appendicitis is 8% for the people in western countries. The highest incidence of acute appendicitis is in the 2nd and 3rd decade of life. It occurs commonly in childhood and early adult life, rarely in infancy. It occurs equally among males and females before puberty. Male to female ratio increases to 3:2 by age of 25 in young adults [10]. The lifetime rate of appendectomy is 12% for males and 25% for females, about 7% of all people undergoing appendectomy for acute appendicitis during their lifetime. Majority of appendicitis is believed to be caused by appendicular luminal obstruction. Fecolith is the usual cause of this luminal obstruction. Less common causes include hypertrophy of the lymphoid tissue, intestinal parasites, and tumours. appendix contains bacterial flora normally like that present in normal large intestine. Escherichia coli and Bacteroides fragilis are the most common organisms observed in normal appendix, acute appendicitis, perforated appendicitis, and gangrenous appendicitis [11,12].

However, a broad variety of both anaerobic and facultative bacteria may be present. Acute appendicitis is diagnosed mainly by the clinical examination. It is often difficult to diagnose as classical signs and symptoms suggesting acute appendicitis may not be present in all patients. Different presenting symptoms and clinical signs mimic the diagnosis of acute appendicitis, especially in women. The decision to operate on clinical suspicion alone can lead to removal of normal appendix, it happens in 15 -50% of cases. Precise diagnosis can be made by additional tests and expectant management or both. The above delay in diagnosis may lead to perforation or gangrene of the appendix leading to increased morbidity. Safe alternative is to do appendectomy as soon as the condition is suspected, but this strategy leads to unnecessary appendectomy [13].

There is still ongoing debate regarding the optimal management of acute appendicitis with several studies proposing conservative and nonoperative management. To achieve an accurate and early diagnosis many additional tests, scoring systems, imaging modalities like ultrasonography, CT, MRI is done and laparoscopy can be employed. None of the above tests alone will diagnose acute appendicitis, these tests are always inferior to clinical examination and signs unless combined. [14].

Hyperbilirubinemia is a new diagnostic marker for perforated and gangrenous appendicitis which is postulated recently. These results due to an imbalance in synthesis and excretion of bilirubin by the liver. This study has been designed to verify the association of hyperbilirubinemia in cases acute appendicitis and its complications. This study is a single centre cross sectional, observational study conducted in the department of general surgery, Sree Balaji Medical College and Hospital, Chromepet, Chennai over a period of one year from April 2018 to April 2019 on 100 patients admitted for acute appendicitis and underwent emergency appendectomy. In our study of 100 patients, 58 patients (58%) were males while remaining 42 patients (42%) were females. This observation was like other studies. [15]. The 71 patients, 37 (52.10%) were male and 34 (47.90%) were female' [16-19]. Stated in his study that 'Of 50, 40 cases were male and 10 females' Most of the patients in our study was found to be in young adults aged between 21 to 30 yrs age group. 43 % of patients are from this age group. Mean age of presentation was 29 years. The mean and standard deviation in males were 29 and 11.3814. The mean and standard deviation in females were 29 and 7.7520, respectively. The mean age of distribution in our study population corresponds to other studies [20] stated that 'The average was 27.1 years.

Mean age -26.93±9.33'. 'Out of the 964 patients included in study, the mean age reported was 28.7 years' Our studies have shown that appendicitis is more common in males and in younger age groups. Majority of female patients were from age group 21 to 30 years. After the age of 30 years the ratio decreases with equal or greater incidence in females. This is also supported by the below journal [21,22] where he states 'The disease is slightly more common in males, with a male: female ratio of 1.4:1, In teenagers and young adults, the male-female ratio increases to 3:2 at age 25; thereafter, the greater incidence in males' declines. In Our study we observed that out of 100 patients 55 of them had normal total bilirubin value of < 1.0mg/dL (55%) while hyperbilirubinemia was found in 45 patients (45%). This corresponds to the below studies conducted [23] found that 'Of the 71 patients, total serum bilirubin was elevated in 41 (57.70%) of them', observed that 'Among 50 cases, total SB (TSB) was raised in 38 (76%) cases whereas 12 (24%) cases had normal TSB level' [24] had found hyperbilirubinemia in 59 (38%) of 157 patients studied with acute appendicitis. The mean total serum bilirubin of all 100 patients was 1.491 ±1.0319 mg/dL, which is minimally above normal range (≤1.0 mg/dL).

The mean in inflamed (uncomplicated) appendicitis was 1.08±0.48. The mean in perforated or gangrenous appendicitis (complicated) was 2.74±1.24 which is well above the normal range, indicating hyperbilirubinemia. The direct bilirubin and indirect bilirubin in patients diagnosed with acute appendicitis were 1.04±0.041mg/dl and 0.44±0.1941mg/dl respectively. Similarly, direct bilirubin and indirect bilirubin in patients diagnosed with complicated appendicitis were

2.04±1.01mg/dL and 0.70±0.30 mg/dL respectively. The total serum bilirubin was significantly elevated in gangrenous or perforated appendix than those in acute appendicitis (P<0.001). This was consistent with the studies done [25,26] who found average level of serum bilirubin in his study population to be 2.38 mg/dL. found a mean of 3.62mg/dL in his study population of complicated appendicitis. All patients were found to have SGOT and SGPT within normal limits, thus fulfilling our exclusion criteria. The mean SGOT and SGPT were 27.080± 9.6804 U/L and 26.870±9.1537U/L. The mean ALP values were 97.160±23.4373/L.

In our study all patients underwent ultrasonography imaging, 59(59%) patients were diagnosed as acute appendicitis, and 25 (25%) patients were diagnosed as having perforated or gangrenous appendix and 16 (16%) patients with normal appendix. Ultrasound was highly sensitive for detecting complicated appendicitis. We observed in our study that total leucocyte count was elevated in 71% of all the patients diagnosed as appendicitis. The mean TLC count of all patients was 11784±2718/mm<sup>3</sup>, in which majority of cells are neutrophils 73.260 ±8.8929 % followed by lymphocytes 21.890±7.8159 %. These were consistent with other study like [27,28] stated in study 'Of the 71 patients Total leukocyte count was found to be elevated in 33 (46.5%) patients. Regarding mean TLC stated that 'Mean WBC was 16.4 × 10<sup>3</sup>/μL (SD, ±5.2; 3.1 to 32.0 ×10<sup>3</sup>/μL) for all patients. Mean WBCs in the simple and complicated groups were elevated respectively, with significantly higher levels in the complicated group'.

Among the patients diagnosed with uncomplicated acute appendicitis (n=75), 49 patients (65.33%) were having normal total serum bilirubin levels (≤1.0mg/dL), 26patients (34.66%) had elevated total serum bilirubin levels. In patients with perforated or gangrenous appendicitis (n=25), only 6(24%) patients had total serum bilirubin within normal limits, rest of 19(76%) patients had elevated total serum bilirubin levels. Hence hyperbilirubinemia is found in most of the patients with perforated or gangrenous appendicitis (76%). The sensitivity, specificity, positive predictive value, negative predictive value was calculated for the total serum bilirubin as a test for predicting gangrenous or perforated appendix using 2×2 table. The sensitivity and specificity of serum bilirubin as a marker in predicting perforated or gangrenous appendicitis was 76% and 65.33% respectively. Similarly, the negative predictive value and positive predictive value for the test is 89.09% and 42.22% respectively. ROC curve was drawn, area under the curve (AUC) was 0.707. Our study revealed that there is isolated increase in total serum bilirubin level without significant elevation in liver enzymes, is a significant predictor of perforated or gangrenous appendix (p<0.001). Our study showed total serum bilirubin to have low specificity of 65.33% and high sensitivity of 76.00%. The negative predictive value was 89.09% comparable to which showed 100% [29] where there was three times the risk of having perforated or gangrenous appendix in patients with

hyperbilirubinemia (>1.0mg/dL) [30] showed that hyperbilirubinemia had a specificity of 86% for appendiceal perforation or gangrene. Hence in patients suspicious of perforation or gangrene elevation of serum bilirubin can be used as a test to diagnose and manage perforated or gangrenous appendicitis.

### CONCLUSION

Total serum bilirubin was significantly elevated in patients with complicated (gangrenous or perforated) appendicitis than those with acute appendicitis. Total serum bilirubin level as a test for predicting complicated (gangrenous or perforated) appendicitis is an overly sensitive, less specific with a high negative predictive value. Hence it is a valuable indicator in patients likely to have complicated (gangrenous or perforated) appendicitis. Total serum bilirubin should be used along with clinical examination and other laboratory investigations in the assessment of patients suspected of appendicitis.

### FUNDING

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### ETHICAL APPROVAL

The study was approved by the Institutional Ethics Committee.

### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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