

# Evaluation of hyperbilirubinaemia as a new diagnostic marker for acute appendicitis & its role in prediction of appendicular perforation

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## Abstract

**Introduction:** Acute appendicitis is the most common general surgical emergency and early surgical intervention improves outcomes. The diagnosis of appendicitis can be elusive, and a high index of suspicion is important in preventing serious complications from this disease. The present study was undertaken to assess relationship between hyperbilirubinemia and acute appendicitis to evaluate its credibility as a diagnostic marker for acute appendicitis. **Material & methods:** The case control study was carried out on 60 patients who were clinically diagnosed as having acute/perforated appendicitis and on 60 healthy volunteers from the community having no signs and symptoms of acute appendicitis. The evaluation of acute appendicitis was done by history taking, clinical examination and investigations including CBC, Ultrasonography and confirmed by histopathological examination of appendectomy specimen. For the final analysis various statistical methods like descriptive, crosstabs, chi-square test were applied using the SPSS (version 20.0). **Results:** Total serum bilirubin level was raised in 43 patients (71.7%) out of the total sample of 60 cases. Of these, 42(70%) cases were positive for appendicitis on HPE (True Positive), and 1(1.7%) was negative on HPE (false positive). Among the 17(28.3%) cases in whom serum bilirubin was not raised, in 3(5%) cases HPE was negative (True Negative), and in 14 (23.3%) cases HPE was positive (False Negative). In 60 healthy individuals mean serum bilirubin was  $0.7 \pm 0.3$  mg%. In 46 cases of histopathologically proved acute appendicitis (non-perforated) the mean serum bilirubin was  $1.3 \pm 0.7$  mg% while in perforated group it was  $2.5 \pm 1.1$  mg% (P value was significant i.e.  $<0.001$ ). **Conclusion:** Serum bilirubin is an important adjunct in diagnosing the presence of gangrenous/perforated appendicitis. Our findings confirm that hyperbilirubinaemia has a high specificity for distinguishing acute appendicitis.

**Keywords:** Acute appendicitis, Appendiceal perforation, Hyperbilirubinemia

## Introduction

Appendicitis remains the most common abdominal surgical emergency, with an incidence between 55.3 (females) and 68.8 to 88(males) per 100, 000[1]. In the continued absence of a 100% accurate test for appendicitis, any investigation that can contribute to its diagnosis is valuable. Diagnosis of acute appendicitis, clinically still holds a central place. Delay in laparotomy can lead to appendiceal perforation with increased morbidity and hospital stay [1-3]. A safe alternative seems to be appendectomy as soon as the condition is suspected, a strategy that increases the number of unnecessary appendectomies [4,5]. A timelier and more accurate diagnosis has been attempted by the employment of additional laboratory tests [6-11], scoring systems [12-

15], ultrasound imaging [16,17], computed tomography (CT) scan [18,19], scintigraphy [20], MRI [21], and laparoscopy [22-24]. None of these methods stands alone as they all come in support of, and are secondary to a primary clinical assessment.

Appendiceal perforation in patients with acute appendicitis may cause a variety of potentially life-threatening complications. Escherichia coli endotoxin has been shown to impact physiological bile flow in vivo. This had led to the theory that hyperbilirubinemia in patients with appendicitis may have a predictive potential for the preoperative diagnosis of appendiceal perforation [27]. Patients with hyperbilirubinemia combined with symptoms and signs consistent with acute appendicitis should be considered for early appendectomy [28].

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Hyperbilirubinaemia is a valuable marker for acute appendicitis. Patients with hyperbilirubinaemia are also more likely to have appendiceal perforation or gangrene. Bilirubin should be included in the assessment of patients with suspected appendicitis [29].

Jaundice has been associated with appendicitis and studies have shown hyperbilirubinaemia to be a useful predictor of appendiceal perforation [28,29]. However, these studies did not focus on the value of bilirubin as a specific marker for acute appendicitis.

The aim of this prospective study was to investigate the diagnostic value of hyperbilirubinemia as a laboratory marker for appendiceal perforation in patients with acute appendicitis.

## Material and Methods

The present case control study was carried out on patients who were clinically diagnosed as having acute/perforated appendicitis and were posted for emergency appendectomy in department of General Surgery, Indira Gandhi Medical College, Shimla over a period of one year.

**Study design** – prospective case control study.

**Inclusion criteria-** All patients diagnosed clinically to have acute appendicitis and perforated appendicitis, subjected for emergency appendectomy and 60 healthy volunteers having no signs and symptoms of acute appendicitis, hemolytic diseases, jaundice, hepatobiliary diseases and chronic alcoholism were taken as controls, were included in this study.

**Exclusion Criteria-** All patients documented to have a past history of Jaundice or Liver disease, Chronic alcoholism, Hemolytic disease. Acquired or Congenital biliary disease, positive for HBV and HCV, Cancer of hepatobiliary system, patients managed conservatively for acute appendicitis or admitted for interval appendectomy were excluded from study.

**Collection of data-**

## Results

As per the study, age of the patients ranged from 9 years to 84 years, with a mean age of  $31.717 \pm 14.818$  years. In case of control group (healthy volunteers) age ranged from 6 years to 73 years, with a mean age of  $32.32 \pm 14.211$  years.

In the study, most commonly affected age group was 21-30 years (33.3%) followed by 31-40 years (20%). Least number of patients were found in age group >60 years (3.3%). The youngest patient of this study was 9 years old while the oldest patient was 84 years.

**Sample size:** (1) 60 cases of acute appendicitis  
(2) 60 healthy volunteers as controls

**Sampling method:** Consecutive Sampling

Detailed history and examination was taken. Once the diagnosis of acute appendicitis was suspected, the patients were subjected to routine investigation as per hospital protocol e.g. complete haemogram (CHG), urea, creatinine, electrolytes, X-ray chest, urine microscopy, ultrasonography, ECG and screening for HIV, hepatitis B & C by kit method.

Serum Bilirubin level measurement was done in all patients by fully automatic analyzer machine available in the hospital. Serum bilirubin  $>0.8\text{mg/dl}$  was considered significant for acute/perforated appendicitis. Ultrasonography of abdomen was done in all cases to confirm the diagnosis and to rule out all other causes of pain abdomen. After obtaining informed consent, the patients were operated, operative findings were noted, and the appendectomy specimens were sent for histopathological examination. The histopathology reports suggestive of appendicitis were considered as gold standard for diagnosis.

Among the histopathologically proved cases, those with raised serum bilirubin i.e.  $>0.8\text{mg}\%$ , were considered true positive, while those in whom bilirubin was not raised were considered false negative. Among the histopathologically negative cases, those with raised bilirubin were considered as false positive, while those in whom bilirubin is not raised were considered as true negative. Similarly classification of true positive, false positive, true negative and false negative after correlating with histopathological report was done for perforated appendicitis.

**Statistical analysis:** The data collected were entered and analysed using the SPSS statistical software (version 20.0) by methods like descriptive statistics, cross- tabs, and chi-square test. The sensitivity, specificity, predictive value of positive test and predictive value of negative test were calculated for serum Bilirubin for acute/perforated appendicitis as per requirement of the study objectives.

**Table-1: Age distribution of study subjects**

Age group	Acute/Perforated appendicitis	Healthy volunteers	P Value
1-10	1(1.7%)	2(3.3%)	
11-20	11(18.3%)	12(20%)	
21- 30	20(33.3%)	18(30%)	
31- 40	12(20%)	14(23.4%)	
41- 50	10(16.7)	10(16.7%)	
51- 60	4(6.7%)	2(3.3%)	
> 60	2(3.3%)	2(3.3%)	
Total	60(100%)	60(100%)	
			0.821

In control group, maximum number of volunteers were taken in age group 21-30(30%) followed by 31-40(23.4%)

**Table-2: Gender Distribution of Study Subjects**

Age group	Acute/perforated appendicitis		Healthy volunteers	
	Male	Female	Male	Female
1-10	<b>1(2.6%)</b>	<b>0(0%)</b>	<b>1(3.1%)</b>	<b>1(3.6%)</b>
11-20	8(20.5%)	3(14.3%)	6(18.8%)	6(21.4%)
21- 30	13(33.3%)	7(33.3%)	8(25%)	10(35.7%)
31- 40	7(17.9%)	5(23.8%)	7(21.9%)	7(25%)
41- 50	6(15.4%)	4(19%)	6(18.8%)	4(14.3%)
51- 60	3(7.7%)	1(4.8%)	2(6.2%)	0(0%)
> 60	1(2.6%)	1(4.8%)	2(6.2%)	0(0%)
Total	39(100.0%)	21(100%)	32(100%)	28(100%)

p value=0.821(NS)

In the present study, out of 60 cases, 39 (65%) cases were males, and 21 (35%) cases were females. The male to female ratio in the present study was 1.8:1 In control group (healthy volunteers), the male to female ratio in the present study was 1.1:1. In males most common age group of presentation was between 21- 30years of age (25%), The pattern of age distribution observed among females, with the highest incidence in age groups: 21-30 years (35.7%).

**Table-3: Distribution of cases as per Histopathology Report**

Sr No	HPE	No. of cases	%
1	Positive	56	93.3%
2	Negative	4	6.7%
	<b>Total</b>	60	100%

In the present study, in 56 (93.3%) cases histopathological reports were positive for acute appendicitis and in 4 (6.7%) cases histopathological reports were negative for acute appendicitis. Therefore the rate of negative appendicectomy in the present study is 6.7%.

**Table-4: Distribution of the types of appendix on HPE**

HPE finding	Number	Percentage (%)	P Value
Normal appendix	4	6.6%	
Acute appendicitis	46	76.7%	
Perforated appendicitis	10	16.7%	
<b>Total</b>	60	100%	0.05 (S)

Hence, in our study there were 46 (76.7%) cases of acute appendicitis, 10(16.7%) cases of perforated appendicitis, and 4 cases i.e. 6.6% were found normal.

**Table-5:** Role of hyperbilirubinemia in the Diagnosis of acute appendicitis/perforated appendicitis by Correlation with HPE

Hyperbilirubinemia	HPE Positive	HPE Negative
Positive	42 (TRUE POSITIVE)	1 (FALSE POSITIVE)
Negative	14 (FALSE NEGATIVE)	3 (TRUE NEGATIVE)

Total serum bilirubin level was raised in 43 patients (71.7%) out of the total sample of 60 cases. Of these, 42(70%) cases were positive for appendicitis on HPE (True Positive), and 1(1.7%) was negative on HPE (false positive). Among the 17(28.3%) cases in whom serum bilirubin was not raised, in 3(5%) cases HPE was negative (True Negative), and in 14 (23.3%) cases HPE was positive (False Negative).

**Table-6:** Bilirubin levels in healthy volunteers:

Total serum bilirubin (mg/dl)	Distribution in healthy volunteers (n=60)	
	Number	Percentage
≤0.8	47	78.3%
>0.8	13	21.7%
Total	60	100%

In the present study, 47 cases (78.3%) serum bilirubin was normal i.e. ≤ 0.8mg% and in 13 cases (21.7%) serum bilirubin was raised in healthy volunteers.

**Table-7:** Comparison of total serum bilirubin levels in patients with acute appendicitis, appendicular perforation and in healthy volunteers:

Bilirubin levels(mg/dl)	Diagnosis					
	Acute appendicitis		Appendicular perforation		Healthy volunteers	
	Number	%	Number	%	Number	%
>0.8	33	71.7%	9	90%	13	21.7
≤0.8	13	28.3%	1	10%	47	78.3
<b>Total</b>	<b>46</b>	<b>100%</b>	<b>10</b>	<b>100%</b>	<b>60</b>	<b>100%</b>

In this study, serum bilirubin was raised in maximum cases of acute perforated appendicitis i.e. in 9 cases (90%), out of 10 cases of histopathologically proved acute perforated appendicitis and in 1 case (10%) it was normal.

In acute appendicitis (non-perforated), out of 46 cases of histopathologically proved acute appendicitis, in 33 cases (71.7%) it was raised and in 13 cases (28.3%) it was normal.

In healthy individual group, it was raised in just 13 cases (21.7%) and in 47 cases (78.3%) the level of serum bilirubin was normal.

## Discussion

The incidence of acute appendicitis varies, but it is highly prevalent, occurring from in 7 to 22 out of 10,000 people [30,31]. Whereas non-perforated acute appendicitis can be cured by an appendectomy without a long recovery period, perforated appendicitis or suppurative appendicitis can cause various complications that can result in life-threatening conditions [32].

As per the study, mean age of presentation was 31.717±14.818years. Most commonly affected age group was 21-30 years (33.3%) followed by 31-40 years (20%). This is because there are more lymphoid follicles in this age group. Least number of patients were found in age group >60 years (3.3%). The youngest patient of this study was 9 years old while the oldest patient

was 84 years. Cardall et al [33] reported a mean age of presentation 30.8 yrs, West et al [34] reported it to be 26.5 yrs and Guraya et al [35] reported the mean age of patients with acute appendicitis to be 23.7 years.

In this study of 60 patients, acute appendicitis and perforated appendicitis was suspected clinically in 47 and 13 patients respectively. The clinical diagnosis was confirmed with histopathological examination report. Out of 47 cases of acute appendicitis on clinical diagnosis acute appendicitis was present in 43 cases (91.5%) and in 4 cases (8.5%) it was normal. This is consistent with Khan S study 2008 [36] and Salman Khan study 2009 [37]. In 13 cases diagnosed clinically as perforated appendicitis, histopathological examination report was positive for perforated appendicitis in 10 cases (76.9%) and in 3 cases (23.1%) histopathological examination report was suggestive of acute appendicitis. So finally, 46(76.7%) cases of acute appendicitis, 10(16.7%) cases of perforated appendicitis and 4 (6.6%) normal cases (HPE -VE) were included in the study. These figures are consistent with Atahan et al [38] study.

Hyperbilirubinemia was observed in most of the patients with acute appendicitis and perforated appendicitis. But it was more in patients with perforated appendicitis (90%) than patients with acute appendicitis (71.7%).

In case of healthy volunteers serum bilirubin was normal in 78.3% cases and was increased in 21.7% cases. The mean serum bilirubin level in patients diagnosed as **acute appendicitis** was as follows:

1. Total=1.3±0.7mg/dl (range 0.6-2.0mg/dl)
2. Direct=0.4±0.2mg/dl (range 0.2-0.6mg/dl)
3. Indirect=0.9±0.5mg/dl (range 0.4-1.4mg/dl)

The findings corresponds with Sand M et al [39](0.9±0.6mg/dl), Poras Chaudhary et al [40] (1.52mg/dl), Khan S (2.02±0.7mg/dl) 2009 [36], Young Ran Hong [41] (0.83±0.46mg/dl)

In patients diagnosed perforated appendicitis mean serum bilirubin was as follows

1. Total = 2.5±1.1 mg/dl (range, 1.4 – 3.6 mg/dl).
2. Direct= 0.8±0.5 mg/dl (0.3-1.3mg/dl)
3. Indirect= 1.7± 0.6mg/dl (1.1-2.3mg/dl).

These findings are in accordance with Poras Chaudhary et al [39] (3.62mg/dl), Sand M et al [39] (1.5±0.9mg/dl), Emmanuel et al [42] (1.35mg/dl), Atahan et al (1.28±0.44mg/dl) [38].

#### Comparison of hyperbilirubinemia in diagnosis of acute/perforated appendicitis with other Studies:

Name of study	Sensitivity	Specificity	(PPV)	(NPV)
Atahan et al [38]	77%	87%	47%	97%
Sand M et al [39]	70%	86%	51%	93%
Kaser et al [43]	38%	78%	32%	82%
Emmanuel et al [42]	30%	88%	91%	24 %
Salman Khan [36]	80%	100%	100%	14%
Khan S [37]	82%	100%	100%	17.3%
<b>Present study</b>	<b>75%</b>	<b>75%</b>	<b>97.7%</b>	<b>17.6%</b>

Thus, in this study it was observed that patients with perforated appendicitis had markedly higher levels of bilirubin (2.5± 1.1 mg/dl) as compared to that of acute (non-perforated) appendicitis (1.3±0.7mg/dl). Also it was observed that, bilirubin level in acute appendicitis patients (1.3±0.7mg/dl) was slightly higher as compared to healthy volunteers (0.7± 0.3mg/dl).

The rise in serum bilirubin in acute appendicitis and perforated appendicitis was mixed type i.e. Direct and Indirect.

Bilirubin levels may be high, but remain within normal range, in cases of appendicitis. Therefore, bilirubin levels may be a useful measurement when investigating a patient with suspected appendicitis. Hyperbilirubinaemia is highly specific with regards to perforation, a finding supported by other studies. However, possibly because of the few perforated cases in this study, we cannot recommend that hyperbilirubinaemia be used to predict perforation [44].

So, it is inferred from the study that, the patients with features suggestive of acute appendicitis with higher levels of serum bilirubin, are more susceptible of having appendicular perforation than those with normal or slightly elevated serum bilirubin.

## Conclusion

Acute appendicitis is the most common general surgical emergency, and early surgical intervention improves outcomes. Accurate diagnosis of acute appendicitis needs careful history, physical examination, laboratory and imaging investigations as there is a diagnostic dilemma, especially in women and at extremes of age.

A serum bilirubin level appears to be a promising new laboratory marker for diagnosing acute appendicitis, and its level come out to be a **credible aid** in diagnosis of acute appendicitis, its complications and would be helpful investigation in decision making.

So we recommend Bilirubin should be included in the assessment of patients with suspected appendicitis but further studies are required for its role in appendicitis complications.

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