# **Original Research Article**

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# Evaluation of hyperbilirubinemia as an innovative diagnostic marker for acute appendicitis and its role in the prediction of appendicular perforation

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### **ABSTRACT**

**Background:** Acute appendicitis is one of the most common causes of acute abdomen in surgical practice. Despite advances in the radiological and laboratory investigations, the diagnosis of appendicitis remains dilemma. The negative appendicectomy rate varies 15-50%, with up to 50% postoperative complications in these patients. Hence we conducted a study to assess the role of hyperbilirubinemia in diagnosing acute appendicitis and to foresee appendicular perforation.

**Methods:** It was a prospective study conducted in the Department of General Surgery, M.R. Medical College, Gulbarga, Karnataka, India for 18 months duration from December 2010 to May 2012. Only histopathologically confirmed cases of acute appendicitis and/or appendicular perforation were included in the study. Demographic data, history and clinical findings were recorded on a predesigned proforma. Investigations included complete blood count, reticulocyte count, platelet count, peripheral smear, serum haptoglobulin, liver function tests, HbsAg, urine analysis (routine and microscopy).

**Results:** The sensitivity and specificity of serum bilirubin as a marker in predicting acute appendicitis and appendicular perforation was 78.6% and 8.6% respectively. Similarly, the positive predictive value and negative predictive value for the same was 77.5% and 9.1% respectively. The Odds ratio was 0.344.

**Conclusions:** Serum bilirubin level appears to be a promising new laboratory marker for diagnosing acute appendicitis and would be a decision-making investigation. Patients with clinical appendicitis and with hyperbilirubinemia are to be suspected of having a higher risk for appendicular perforation.

Keywords: Acute appendicitis, Appendicular perforation, Serum bilirubin

## INTRODUCTION

Acute appendicitis is one of the most common causes of acute abdomen in surgical practice, and appendicectomy is the most frequently performed urgent abdominal operation.<sup>1</sup> Despite advances in the radiological and laboratory investigations, the diagnosis of appendicitis remains dilemma. Although most patients can be diagnosed on clinical background, it may become very

difficult to diagnose in cases where symptoms and signs are unusual. The negative appendicectomy rate varies 15-50%, with up to 50% postoperative complications in these patients.<sup>2</sup>

Total Leukocyte counts, C-reactive protein and other laboratory investigations have been used to complement the clinical diagnosis and to reduce the frequency of negative appendicectomy.<sup>3</sup> Till date, ultrasonography

(USG) is used as the most common diagnostic tool for appendicitis.<sup>2</sup> Various scores combining clinical features and laboratory investigations such as modified Alvarado score<sup>4</sup> have been developed. And all these are not confirmatory markers.<sup>5</sup>

A few studies show that there is an association between the presence of hyperbilirubinemia and appendicitis and its complications. Hence we conducted a study to assess the role of hyperbilirubinemia in diagnosing acute appendicitis and to foresee appendicular perforation.

### **Objectives**

- To study the correlation between hyperbilirubinemia and acute appendicitis, and to assess its consistency as a marker for acute appendicitis.
- To assess whether elevated bilirubin levels have a prognostic potential for the diagnosis of Appendicular perforation

### **METHODS**

It was a prospective study conducted in the Department of General Surgery, M.R. Medical College, Gulbarga, Karnataka, India for 18 months duration from December 2010 to May 2012.

### Sample size and method

A total of 175 patients with clinical diagnosis of acute appendicitis or appendicular perforation were studied.

The minimal sample size (100) was calculated based on the following formula.

$$N = (a^2 x b x c) \div (z^2)$$

Where,

N = Sample size;  $a = 1.96 \approx 2$  (considering confidence as 95%); b = prevalence (prevalence was taken as 50% as exact prevalence was not known); c = 100 - p that is, 50%; z = Absolute error which was 10%

### Inclusion criteria

All patients with diagnosis of acute appendicitis or appendicular perforation were included in the study.

### Exclusion criteria

- Histopathological diagnosis negative for acute appendicitis or appendicular perforation were excluded.
- Patients with a history of hemolytic disease, jaundice or liver disease, hepatobiliary malignancy, congenital or acquired biliary disease, chronic alcoholism (intake of alcohol of >45g/day for Men and >30g/day

in women for ten years) and HBsAg positive patients were excluded from the study.<sup>6</sup>

### Procedure

Ethical clearance was obtained. Patients were recruited as per eligibility criteria. Demographic data, history and clinical findings were recorded on a predesigned proforma. Investigations included complete blood count, reticulocyte count, platelet count, peripheral smear, serum haptoglobulin, liver function tests, HbsAg, urine analysis (routine and microscopy). The results were grouped as 'normal' or 'raised' (hyperbilirubinemia) as per the standard reference values (Table 1).<sup>7</sup>

Table 1: Reference range of serum bilirubin and liver enzymes.

Test	Normal range		
Serum bilirubin			
Total	0.3-1.0mg/dl		
Direct	0.1-0.3mg/dl		
Liver enzymes			
SGPT	0-35U/L		
SGOT	0-35U/L		
ALP	30-120U/L		

### Statistical analysis

Patients with histological diagnosis of acute appendicitis and appendicular perforation having hyperbilirubinemia were expressed in percentages. Mean of the level of elevation of serum bilirubin was considered for patients separately for both the groups (acute appendicitis and appendicular perforation). The positive predictive value, negative predictive value, sensitivity, specificity, and odds ratio were determined by 2 x 2 table as below.

Table 2: 2 x 2 contingency table.

	Acute appendicitis	Appendicular perforation
Raised Sr. bilirubin	A	В
Normal Sr. bilirubin	С	D

### **RESULTS**

A total of 175 patients were included in the study. Most of the patients belonged to 11 to 20 years age group (48%) with a mean age of 20.1±10.9 years. 95 (54%) were males. Clinically 147 (84%) patients had acute appendicitis, and 28 (16%) had appendicular perforation. As per ultrasonography, 117 (67%) patients had acute appendicitis, 21 (12%) patients had appendicular perforation, and 37 (21%) patients were normal. But histopathologically, 35 (20%) patients were found to have appendicular perforation, while 140 (80%) had nonperforated appendicitis. Total leukocyte count (TLC) was raised more than 11,000/mm³ in 65 (37%) patients.

Table 3: Liver function tests of the study population.

Parameters	Mean	SD
Total bilirubin (mg/dL)	1.6	0.8
Direct bilirubin (mg/dL)	1.1	0.7
Indirect bilirubin (mg/dL)	0.5	0.2
SGOT (U/L)	28.8	12.7
SGPT (U/L)	25.6	11.6
ALP (U/L)	81.2	20.4

Liver functions tests are tabulated in Table 3. A total of 142 (81%) patients had serum total bilirubin raised more than 1mg/dL. Among 140 uncomplicated appendicitis patients, 110 (78.6%) had raised bilirubin levels whereas 32 (91.4%) out of 35 patients with appendicular perforation had raised bilirubin levels. Patients with appendicular perforation had a higher percentage as well as mean total and direct bilirubin levels as compared to patients with simple acute appendicitis (Table 4 and 5).

Table 4: Comparison of mean serum bilirubin levels in patients with acute appendicitis and appendicular perforation.

	Diagno	sis		
Bilirubin levels (mg/dL)	Acute appendicitis		Appendicular perforation	
	Mean	SD	Mean	SD
Total bilirubin	1.3	0.65	2.1	1.2
Direct bilirubin	0.8	0.57	1.3	1.1
Indirect bilirubin	0.5	0.21	0.80	0.3

Table 5: Correlation of acute appendicitis and Appendicular perforation with total serum bilirubin levels.

C	.75)			
bilirubin	(n-140)		Appendicular perforation (n=35)	
(mg/dL)	Number	<b>%</b>	Number	<b>%</b>
>1.0	110	78.6	32	91.4
≤1.0	30	21.4	03	8.6
Total	140	100.00	35	100.00

The sensitivity and specificity of serum bilirubin as a marker in predicting acute appendicitis and appendicular perforation was 78.6% and 8.6% respectively. Similarly, the positive predictive value and negative predictive value for the same is 77.5% and 9.1% respectively. The odds ratio was 0.344.

### **DISCUSSION**

For several years, the appendix was thought as an organ with no function. But now we all know that the appendix is an immunologic organ that participates in the secretion of immunoglobulins, particularly immunoglobulin A (IgA).<sup>7</sup>

The famous pathologist Reginald Webber Fitz (1843-1913) established acute appendicitis as a definitive lesion and explained the pathophysiology of peritonitis secondary to acute appendicitis.<sup>8</sup>

Acute appendicitis is the most common general surgical emergency, and early surgical intervention improves outcomes. The lifetime risk of acute appendicitis in western literature is 8%. The appendicitis occurs most commonly in the second and third decade of life. 12% men and 25% women are at risk of appendicectomy in his/her lifetime. 10

Obstruction of the lumen is believed to be the major cause of acute appendicitis. Faecoliths are the frequent cause of obstruction. Other causes include hypertrophy of lymphoid tissue, tumors, intestinal parasites. The principal organisms seen in the normal appendix, in acute appendicitis, and in perforated appendicitis are *Escherichia coli* and *Bacteroids fragilis*.

Till date, the diagnosis of acute appendicitis is primarily clinical; which has led to a negative appendicectomy rate of 15 to 50%.<sup>2</sup> The logic of removing a normal appendix to avoid the complications of delayed diagnosis can be morbid, particularly in the elderly as it is associated with upto 50% post-operative complications in in this age group.<sup>1,2</sup> Hence, the accurate diagnosis of appendicitis is a must.

The importance of hyperbilirubinemia and its association in acute appendicitis has been postulated recently. There is scarce literature that speaks of hyperbilirubinemia in patients with acute appendicitis.<sup>11</sup> It is hypothesized that an association exists between hyperbilirubinemia and acute appendicitis and its complications.<sup>11</sup>

In present study, out of 175 patients, 95 patients (54%) were males while the remaining 80 patients (46%) were females. The mean age in our study population (175 patients) was 20.1±10.9 years. This is consistent with the literature. In present study hyperbilirubinemia (>1 mg/dL) was found in 142 patients (81%), while 33 patients (19%) had normal bilirubin levels (≤1.0 mg/dL). Estrada et al had found hyperbilirubinemia in 59 (38%) of 157 patients studied with acute appendicitis. 11 The mean total serum bilirubin of the study group was 1.6±0.8 mg/dL (range, 0.8-2.4mg/dL). The mean of Direct bilirubin was 1.1±0.7mg/dL (range, 0.4-1.8mg/dL) and Indirect bilirubin was 0.5±0.2mg/dL (range, 0.3-0.7mg/dL). This is similar to study conducted by Khan S, who found average level of serum bilirubin in his study population to be 2.38 mg/dL.12 The mean SGOT and SGPT were  $28.8\pm12.7$ U/L and  $25.6\pm11.6$ U/L. The mean ALP values were 81.2±20.4U/L.

In present study population, nine patients were excluded from the study as they were found to have normal appendix on histopathological examination. Amongst the patients diagnosed with uncomplicated acute appendicitis (n=140), 110 patients (78.6%) were found to have increased bilirubin (>1.0 mg/dL), and only 30 patients (21.4%) had normal bilirubin levels ( $\leq$ 1.0 mg/dL). In patients diagnosed with Appendicular perforation (n=35), 32 patients (91.4%) had bilirubin elevated (>1.0 mg/dL), while only 3 patients (8.6%) had normal levels ( $\leq$ 1.0 mg/dL). Hence, Hyperbilirubinemia was associated with most of the patients diagnosed with acute appendicitis (78.6%) or appendicular perforation (94.1%).

The total leukocyte count was found elevated in just 65 patients (37%). The mean of TLC was  $10109\pm3701/\text{mm}^3$ , in which the highest percentage constituted neutrophils with 70.8% followed by 24.3% by lymphocytes.

On ultrasonography, 117 patients (67%) were diagnosed as Acute appendicitis, 21 patients (12%) as Appendicular perforation and 37 patients (21%) were reported as normal ultrasonographic findings. Literature shows ultrasonography was 82% sensitive for appendicitis and/or appendicular perforation, hence ultrasonography is a helpful tool in diagnosing appendicitis or perforation.

The mean bilirubin levels in Acute appendicitis was  $1.3\pm0.65$ mg/dL (range, 0.65-1.95 mg/dL) while in Appendicular perforation was  $2.1\pm1.2$ mg/dL (range, 0.9-3.3mg/dL). Hence, we see that patients with Appendicular perforation had higher levels of bilirubin than that of acute appendicitis. So we conclude that patients with features suggestive of appendicitis with greater values of bilirubin are more vulnerable of having Appendicular perforation than those with normal or slightly elevated total serum bilirubin.

Sand et al also found that the patients with Appendicular perforation had their mean bilirubin levels significantly higher than those with a non-perforated appendicitis. The sensitivity and specificity of serum bilirubin as a marker in predicting acute appendicitis and appendicular perforation was 78.6% and 8.6% respectively. Similarly, the positive predictive value and negative predictive value for the same is 77.5% and 9.1% respectively. The odds ratio was 0.344.

# CONCLUSION

Serum bilirubin level appears to be a promising new laboratory marker for diagnosing acute appendicitis and would be a decision-making investigation. Patients with clinical appendicitis and with hyperbilirubinemia are to be suspected of having a higher risk for appendicular perforation.

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### REFERENCES

- O' Connel PR. The Vermiform Appendix. In: Williams NS, Bulstrode CJK, O'Connell PR, eds. Bailey and Love's Short practice of surgery. 25 ed. London: Arnold; 2008:1204-1208.
- 2. Wijesuriya LI. Imaging as an aid to the diagnosis of acute appendicitis. Malaysian Fam Phys. 2007;2(3):106-9.
- Beltrán MA, Almonacid J, Vicencio A, Gutiérrez J, Cruces KS, Cumsille MA. Predictive value of white blood cell count and C-reactive protein in children with appendicitis. J Pediatr Surg. 2007;42(7):1208-14
- Kanumba ES, Mabula JB, Rambau P, Chalya PL. Modified Alvarado scoring system as a diagnostic tool for acute appendicitis at Bugando Medical Centre, Mwanza, Tanzania. BMC Surg. 2011;11(4):1-5.
- Atema JJ, Gans SL, Beenen LF, Toorenvliet BR, Laurell H, Stoker J, et al. Accuracy of white blood cell count and c-reactive protein levels related to duration of symptoms in patients suspected of acute appendicitis. Acad Emerg Med. 2015;22(9):1015-24.
- Ghany M, Hoofnagle JH. Approach to the patient with liver disease. In: Kasper DL, Braunwald Braunwald E, Fauci AS, Hauser SL, Longo DL and Jameson JL, et al, eds. Harrison's Principles of Internal Medicine. 17th ed. McGraw Hill; 2008:1920.
- Jaffe BM, Berger DH. The Appendix. In: Brunicardi F, Andersen D, Billiar T, Dunn D, Hunter J, Matthews J, et al, eds. Schwartz's Principles of Surgery. 9th ed. New York: McGraw Hill; 2009:1073-1092.
- 8. Fitz RH. Perforating inflammation of the vermiform appendix, with special reference to its early diagnosis and treatment. Trans Ass Amer Phys. 1886;1:107-44.
- Maa J. The Appendix. In: Townsend CM, Beauchamp RD, Evers BM, Mattox KL, eds. Sabiston Textbook of Surgery. 18th ed. Philadelphia, Pa: Saunders Elsevier; 2008:1333-1347.
- 10. Flum DR, Morris A, Koepsell T, Dellinger EP. Has misdiagnosis of appendicitis decreased over time? A population-based analysis. JAMA. 2001;286(14):1748-53.
- 11. Estrada JJ, Petrosyan M, Krumenacker J Jr, Huang S, Moh P. Hyperbilirubinemia in Appendicitis: A new predicator of perforation. J Gastrointest Surg. 2007;11:714-5.

- 12. Khan S. Evaluation of hyperbilirubinemia in acute inflammation of appendix: A prospective study of 45 cases. KUMJ. 2006;4(3)15:281-9.
- 13. Sand M, Bechara GF, Holland-Letz T, Sand D, Mehnert G, Mann B. Diagnostic value of Hyperbilirubinemia as a predictive factor for Appendiceal perforation in Acute Appendicitis. Am J Surg. 2009;198(2):193-8.

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