

Original Research Article

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Elevated serum bilirubin in acute appendicular perforation as a newer serum marker: a diagnostic validation test

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ABSTRACT

Background: Acute appendicitis is the commonest cause of acute surgical abdomen. Appendicectomy is the most frequently performed urgent abdominal operation and is often the first major procedure performed by a surgeon in training. Delay in diagnosis and treatment results in increased rate of perforation, morbidity, mortality and hospital stay.

Methods: A prospective study where a total of 100 patients with clinical, radiological and histopathological diagnosis of acute appendicitis or appendicular perforation were studied. The liver function tests were carried out in all the patients.

Results: In a study group of 100 patients (74 males and 26 females); 59 cases were acute appendicitis and 41 cases were appendiceal perforation proven histopathological. Out of which 48 cases had elevated serum bilirubin levels i.e., 17 in acute appendicitis group and 31 in appendicular perforation group. The mean serum total bilirubin is 1 ± 0.4 in acute appendicitis cases and 1.9 ± 1.13 in the appendicular perforation cases. Similarly, the sensitivity and specificity of elevated serum bilirubin as a diagnostic marker in appendicular perforation was found to be 75.6% and 71.2% respectively.

Conclusions: Elevated serum bilirubin levels appears to be a promising new supplemental diagnostic serum marker in Appendicular Perforation and perhaps be a decision-making investigation.

Keywords: Acute appendicitis, Appendicular perforation, Hyperbilirubinemia, Serum bilirubin

INTRODUCTION

Acute appendicitis is the commonest cause of “acute surgical abdomen”.¹ Appendicectomy is the most frequently performed urgent abdominal operation and is often the first major procedure performed by a surgeon in training.²

The diagnosis of appendicitis still remains a dilemma in spite of advances in the radiological and laboratory investigations.³ Experienced clinicians accurately diagnose appendicitis based on a combination of history, physical examination and laboratory studies about 80% of

the time.³ Although most patients with acute appendicitis can be easily diagnosed, in some cases the sign and symptoms are variable and a firm diagnosis can be difficult. This is particularly true where the appendix is retrocaecal or retroileal.⁴

Delay in diagnosis and treatment results in increased rate of perforation, morbidity, mortality and hospital stay.⁵ Moreover, radiological modalities like computerized tomography (CT) scan abdomen and ultrasonography (USG) abdomen are effective to supplement the diagnosis of acute appendicitis, both modalities have lower sensitivity in detecting perforated appendicitis.⁶ Thus to

prevent the catastrophic effects of perforated appendix, a surgeon might need a diagnostic aid which can signal perforation at its earliest.⁷

Hyperbilirubinemia is recently postulated as laboratory marker for diagnosing acute appendicitis and determining its severity.⁸ Studies have shown that bacterial infection causes disruption in production and excretion of bile.⁸

In view of the above context, the present study was taken up to assess affiliation between hyperbilirubinemia and to see whether elevated serum bilirubin levels have a predictive potential for the diagnosis of appendiceal perforation.

METHODS

This is a prospective study was conducted in the Department of General Surgery, S. Nijalingappa Medical College, Bagalkot, Karnataka, India for 18 months duration from December 2017 to May 2019.

Source of data

All cases of clinically confirmed acute appendicitis and/or appendiceal perforation coming to Department of General Surgery.

Method of collection of data

Inclusion criteria

All cases of acute appendicitis and appendiceal perforation aged >15 years with suggestive reports.

Exclusion criteria

Patients with appendicular mass, chronic appendicitis, confirmed hepatitis, hemolytic anaemia and liver disease (alcoholic or non) were excluded.

Procedure

After obtaining ethical clearance, patient fitting the inclusion criteria were included. Their demographics were recorded, and were subjected to routine investigations including LFT. Radio-imaging like USG and/or CT to support the diagnosis were done. Patients underwent laparoscopic/open appendicectomy under spinal anesthesia/general anesthesia following which the specimen was sent for histopathological confirmation. Clinical and investigational data were compiled and analysed.

Sample size estimation

A total of 100 patients with clinical diagnosis of acute appendicitis or appendicular perforation were studied. Sample size was calculated as per the procedure adopted by Kumar et al.⁹

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

where, N is the sample size; a is equal to 1.96 i.e., ≈ 2 (considering confidence as 95%); b is the prevalence (prevalence was taken as 50% as exact prevalence was not known); c is $(100 - p)$ that is, 50%; z is the absolute error which was 10%.

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 calculated for patients with clinical diagnosis of acute appendicitis and appendicular perforation. A hypothesis was made based on the observation of the level of the two means. Also, sensitivity, specificity, positive predictive value, negative predictive value and odds ratio was determined by 2×2 as shown in Table 1.

Table 1: Odds ratio.

Level of bilirubin	Appendicular perforation	Acute appendicitis
Raised bilirubin	A	B
Normal bilirubin	C	D

RESULTS

A total of 100 patients with clinical diagnosis of acute appendicitis or appendicular perforation admitted in the Department of General surgery, SNMC and HSK Hospital, Bagalkot were studied. As per the study, the age group 15-24 years is most commonly affected (44%) followed by age group 25-34 years (22%). The youngest patients of this study were of 16 years old while the oldest patient was 70 years. Out of 100 patients enrolled for the study, 74 patients (74%) were males while the remaining 26 patients (26%) were females. The overall mean age of all 100 patients was 30.75 ± 12.8 years. The average age in males and females was 30.7 ± 12.3 years and 30.8 ± 14.2 years respectively.

The mean total bilirubin of all 100 patients was 1.45 ± 0.9 mg/dl while the Direct bilirubin was 0.89 ± 0.77 mg/dl. Mean indirect bilirubin was 0.55 ± 0.37 (Table 2).

52 patients of all 100 patients were found to have normal bilirubin levels (≤ 1.0 mg/dl), while 48 patients had raised bilirubin levels (> 1.0 mg/dl).

Of 59 patients diagnosed as acute appendicitis, 17 patients (28.8%) had raised bilirubin levels (> 1.0 mg/dl), while the remaining 42 patients (71.2%) had normal levels (≤ 1.0 mg/dl). 41 patients diagnosed as Appendicular perforation, 31 patients (75.6%) had raised bilirubin levels (> 1.0 mg/dl), while the remaining 10 patients (24.4%) had normal levels (≤ 1.0 mg/dl) (Table 3).

Table 2: Liver function tests.

Parameter (mg/dl)	Overall mean (SD)	Acute appendicitis mean (SD)	Appendiceal perforation mean (SD)
Total bilirubin	1.45 (0.89)	1 (0.4)	1.9 (1.1)
Direct bilirubin	0.89 (0.77)	0.6 (0.4)	1.2 (0.9)
Indirect bilirubin	0.55 (0.37)	0.4 (0.1)	0.6 (0.4)

Table 3: Comparison of mean serum bilirubin levels in patients with acute appendicitis and appendicular perforation.

Bilirubin (mg/dl)	Diagnosis			
	Acute appendicitis		Appendicular perforation	
	Mean	SD	Mean	SD
Total bilirubin	1.0	0.4	1.9	1.1

Table 4: Comparison of acute appendicitis and appendicular perforation cases diagnosed clinically, radiologically, intra-operatively and histopathologically.

	C/D	R/D	I/O	HPR
Acute appendicitis	75	71	58	59
Appendiceal perforation	25	29	42	41
Total	100	100	100	100

Table 5: Correlation of acute appendicitis and appendicular perforation with total serum bilirubin levels (n=100).

Serum bilirubin (mg/dl)	Diagnosis		
	Appendicular perforation	Acute appendicitis	Total
>1.0	31	17	48
≤1.0	10	42	52
Total	41	59	100

In the study population of 100 patients, 75 patients were diagnosed as acute appendicitis while 25 patients were diagnosed with appendicular perforation clinically. On radio-imaging modalities like USG and CT abdomen, 71 patients were diagnosed as acute appendicitis, 29 patients as appendicular perforation. Intra-operatively, 58 cases of acute appendicitis and 42 cases of appendiceal perforations were diagnosed and sent for histopathological confirmation.

Histopathologically, 59 patients were confirmed as acute appendicitis while 41 patients were diagnosed with appendicular perforation (Tables 4 and 5).

Table 6: Accuracy of serum bilirubin as a marker in predicting appendicular perforation.

Parameters	%
Sensitivity	75.6
Specificity	71.2
Positive predictive value	64.5
Negative predictive value	80.7
Odds ratio	7.6
Positive predictive value	2.6
Negative predictive value	0.34
Diagnostic accuracy	73

DISCUSSION

Appendiceal perforation in patients with acute appendicitis is associated with considerable mortality.¹⁰ A non perforated acute appendicitis can be cured by an appendicectomy without a long recovery period, perforated appendicitis can cause various complications that can be life threatening.¹¹

To decrease mortality a timely diagnosis and initiation of surgical intervention is essential.¹⁰ Clinical assessment and laboratory tests are still acknowledged as being of utmost importance in the diagnosing process, although it remains a complicated task for the surgeon.^{10,11}

A biomarker can be defined as an objectively, measurable characteristic that previous research has validated as a marker of a normal physiology, disease or the disease's response to treatment.¹² Numerous serum markers have been analysed as to predict the severity of appendicitis including CRP, interleukin (IL)-6 and lipopolysaccharide binding protein, procalcitonin.^{13,14}

Miller and Irvine first reported that jaundice was common in patients with severe appendicitis.^{11,15} In patients with abdominal infections bacterial load in portal blood increases beyond the capacity of Kupffer cell function. Additional it may cause damage to hepatocyte which is reflected by the rise in serum bilirubin.¹⁶ Elevated total bilirubin level in acute appendicitis can either be as a result of bacteremia or endotoxaemia, both possible in perforated appendix as well.

In the present study, out of 100 patients 74 patients were male and 26 were females. The mean age of presentation being 30.7 ± 12.2 years in males and 30.8 ± 14.1 years in females respectively, this was consistent with the quoted incidence of Appendicitis in the literature where it is most frequently seen in patients in their second through fourth decades of life.¹⁷

In our study population of 100 patients, 75 patients (75%) were diagnosed as acute appendicitis pre-operatively while 25 patients (25%) were diagnosed with appendicular perforation. On confirmation with histopathological reports (HPR) post-operatively 59 patients (59%) were acute appendicitis case and 41 patients (41%) of appendiceal perforation as diagnosis.

Hyperbilirubinemia was found in 48 patients out of the total 100 cases. 52 patients had normal bilirubin levels (≤ 1 mg/dl). Only 17 in 59 cases (45.8%) of acute appendicitis and 31 in 41 cases (75.6%) of appendiceal perforation had total bilirubin levels more than 1mg/dl. Hence it can be noted that hyperbilirubinemia was associated with most of appendiceal perforation cases.

The mean total serum bilirubin level in cases of appendiceal perforation was 1.9 ± 1.1 which is higher compared to 1 ± 0.4 of acute appendicitis cases. Similar results were found with the study conducted by Mir et al, David et al and Socea et al. This hyperbilirubinemia was mixed in type (both conjugated and unconjugated) in most of the patients and at the same time there was nil to minimal elevation in alanine aminotransferase and aspartate aminotransferase in most cases.^{7,13,14,18}

Appendiceal perforation cases had higher levels of bilirubin compared to acute appendicitis cases. So, it can be stated that patients with features suggestive of acute appendicitis with higher values of serum bilirubin are more vulnerable to appendiceal perforation than those with normal to slightly elevated total serum bilirubin.

Sand et al deciphered that the patients with appendicular perforation had their serum total bilirubin significantly higher than those with uncomplicated appendicitis.¹⁰

Table 7: Elevated serum bilirubin levels in diagnosis of appendicular perforation by various authors.

Authors	Sensitivity (%)	Specificity (%)
Sand et al ¹⁰	70	86
Kaser et al ²²	38	78
Atahan et al ¹⁹	80	84
Emmanuel et al ²¹	60	70
Mir et al ⁷	84.1	83.3
Present study	75.6	71.2

The sensitivity and specificity of hyperbilirubinemia as a marker in predicting appendiceal perforation in acute appendicitis was 75.6% and 71.2% respectively in our study.

The sensitivity in study conducted by Sand et al and Atahan et al were 70% and 77% which was in correspondence to our study.^{10,19} A study by Estrada et al and Emmanuel et al had obtained the specificity of 69% and 70% respectively, where the specificity of our study

is found to be 71.2%.^{20,21} The highest sensitivity and specificity obtained with similar studies is found to be 80% and 90%, a study by Atahan et al and McGowen et al.^{14,19} Similarly the positive predictive value and negative predictive value was 64.5% and 80.7% respectively with the odds ratio as 7.6 (Table 7).

CONCLUSION

In our study appendicular perforation cases were more assured to have elevated serum bilirubin levels than those with acute appendicitis. Estimation of serum bilirubin level is a simple, reasonable and easily available investigation in every laboratory. Although clinical examination aided with radio-imaging remains the cornerstone in diagnosis of appendicitis; evaluation of total serum bilirubin levels can predict a higher probability of perforated appendix.

In conclusion, an elevated serum bilirubin level appears to be a promising new supplemental diagnostic serum marker in appendicular perforation and perhaps be a decision-making investigation.

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