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Original Research Article

A Prospective Study to Assess the Raised Serum Bilirubin Levels in Cases of Acute Appendicitis and its Role in Predicting Complicated Appendicitis

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Abstract

Background: In this study, we wanted to evaluate the serum bilirubin levels in cases of complicated appendicitis, study the relationship between elevated serum bilirubin levels and acute appendicitis and assess its credibility as a diagnostic marker for acute appendicitis.

Materials and Methods: This was a hospital-based cross-sectional prospective study conducted among 80 patients who presented with right iliac fossa pain to the Department of General Surgery, M S Ramaiah Medical College, Bangalore, from June 2015 to August 2017 after obtaining clearance from the institutional ethics committee and written informed consent from the study participants.

Results: Of the 80 patients in our study who were diagnosed with acute appendicitis, 61 patients had increased serum bilirubin levels. The mean serum bilirubin level in the case of acute appendicitis was 1.28 mg/dl and in cases of complicated appendicitis, it was 2.40 mg/dl. Hence, serum bilirubin was much higher ($P < 0.001$) in cases of gangrenous/perforated appendicitis.

Conclusion: Serum bilirubin levels are significantly elevated in cases of acute appendicitis. Though clinical diagnosis remains the gold standard in diagnosing acute appendicitis, serum bilirubin levels can be used as a useful investigative modality. Serum bilirubin levels in our study have shown a two to three-fold rise compared to the normal range, especially in cases of perforated/gangrenous appendix. Hence, elevated serum bilirubin levels in clinically suspected acute appendicitis cases could be useful in predicting complicated appendicitis.

Keywords: Serum Bilirubin, Acute Appendicitis, Complicated Appendicitis

Introduction

Acute Appendicitis is one of the most common causes of an 'acute abdomen' in young adults.[1] Appendectomy is the most frequently performed urgent abdominal operation and is often the first major procedure performed by a surgeon in training.[1] In the United States, 250,000 cases of appendicitis are reported annually, representing 1 million patient days of admission. There seems to be an increase in the incidence of appendicitis in the first half of this century, particularly in Europe, America and Australasia, with up to 16% of the population undergoing an appendectomy. In the past 30 years, the incidence has fallen dramatically in these countries, such that the individual lifetime risk of appendectomy is 8.6% and 6.7% among males and females respectively. [1] Some familial predisposition exists. Even with all the recent and latest investigative modalities available the diagnosis of appendicitis remains a dilemma. The clinical diagnosis of acute appendicitis is based primarily on symptoms and physical findings. However, this diagnosis is often difficult and up to 50% of the patients hospitalized for possible appendicitis do not have this disorder. Authors of large prospective studies reported a 22% to 30% removal rate of normal appendices at the surgery. [2-5] To supplement the clinical diagnosis and reduce the frequency of unnecessary appendectomy, the importance of laboratory investigations like White Blood Cell (WBC) counts and C-reactive protein (CRP) etc. values has been stressed. [6-8] The use of ultrasonography (USG) as a diagnostic tool for appendicitis has been widely known and studied. [9-12] Various scores combining clinical features and laboratory investigations have also been developed and are good enough to reach the diagnosis. These are the Alvarado score [13] and the Modified Alvarado score. [14] However, to date, there is no confirmatory laboratory marker for the preoperative diagnosis of acute appendicitis and appendiceal perforation. Recently, elevation in serum bilirubin was reported, but the importance of the raised total has not been stressed in acute appendicitis and appendiceal perforation. [15] It is well established that when microbes invade the body, leukocytes defend it. This leads to an increase in the leukocyte count. Bacterial invasion in the appendix leads to the transmigration of bacteria and the release of TNF-alpha, IL6, and cytokines. These reach the liver via the superior mesenteric vein (SMV) and may produce inflammation, abscess or dysfunction of the liver either directly or indirectly by altering the hepatic blood flow. [16-22] In view of the above context, the present study was undertaken to assess the relationship between hyper-bilirubinemia and acute appendicitis and evaluate its credibility as a diagnostic marker for acute appendicitis and also, to see whether elevated bilirubin levels have a predictive potential for the diagnosis of appendiceal perforation.

Aims and Objectives

1) To study the relationship between elevated serum bilirubin levels and acute appendicitis and evaluate its credibility as a diagnostic marker for acute appendicitis.
2) To evaluate whether elevated bilirubin levels have a predictive role in the diagnosis of complicated appendicitis. (Perforated/Gangrenous)

Materials and Methods

This was a hospital-based cross-sectional prospective study conducted among 80 patients who presented with right iliac fossa pain to the Department of General Surgery, M S Ramaiah Medical College, Bangalore, from June 2015 to August 2017 after obtaining clearance from the institutional ethics committee and written informed consent from the study participants.

Inclusion Criteria

- All patients diagnosed with acute complicated or uncomplicated appendicitis clinically on admission, operated upon and confirmed by histopathological examination were included.

Exclusion Criteria

- Patients documented to have a history of jaundice or liver disease.
- Chronic alcoholism (intake of alcohol > 40 gm/day for men and >20 gm/day for women for 10 years)
- Haemolytic disease
- Acquired or congenital biliary disease
- Patients with cholelithiasis
- Patients with positive HBsAg

Sample Size Estimation

The sample size was calculated based on the following formula.

$$n = \frac{Z^2 \times p \times q}{d^2}$$

n = Sample size

Z = 1.96 ≈ 2 (considering confidence as 95%)

p = prevalence (Considered as 50% as exact prevalence is not known)

q = 100 – p that is, 50%

d = Absolute error which was 10%

Statistical Methods

The data obtained were tabulated on a Microsoft Excel spreadsheet and analyzed as below. Patients with a clinical diagnosis of acute appendicitis having hyper bilirubinaemia were expressed in percentage as

$$= \frac{Patients\ with\ clinical\ diagnosis\ of\ acute\ appendicitis\ with\ elevated\ Sr.Bilirubin\ level}{All\ patients\ with\ clinical\ diagnosis\ of\ acute\ appendicitis}$$

The Mean Level of Elevation of Sr. Bilirubin Was Calculated for Patients with A Clinical Diagnosis of Acute Appendicitis.
Patients With A Clinical Diagnosis Of Appendiceal Perforation Having Hyper-Bilirubinaemia Were Expressed In Percentage As;

$$= \frac{Patients\ with\ clinical\ diagnosis\ of\ appendiceal\ perforation\ with\ elevated\ Sr.Bilirubin}{All\ patients\ with\ clinical\ diagnosis\ of\ appendiceal\ perforation}$$

The mean level of elevation of serum bilirubin was calculated for patients with a clinical diagnosis of appendiceal 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 were determined by a 2 x 2 table as below

	Acute Appendicitis	Appendiceal Perforation
Raised Sr. Bilirubin	A	B
Normal Sr. Bilirubin	$\frac{C}{A+C}$	$\frac{D}{B+D}$

$$Sensitivity = \frac{a}{a+c} \times 100$$

$$Specificity = \frac{d}{b+d} \times 100$$

$$Positive\ Predictive\ value = \frac{a}{a+b} \times 100$$

$$Negative\ Predictive\ value = \frac{d}{c+d} \times 100$$

$$Odds\ ratio: \frac{ad}{bc}$$

Results

Table 1: Demographic Distribution

Age in Years	**No. of Patients**	**%**
<20	11	13.8
20-30	50	62.5
31-40	13	16.3
41-50	3	3.8
>50	3	3.8
Total	80	100.0
Age distribution		
Gender	**No. of Patients**	**%**
Female	39	48.8
Male	41	51.3
Total	80	100.0
Sex distribution		

The mean age of presentation was Mean ± SD: 27.41±8.98 yrs. Most of the patients belonged to the age group of 20-30 years.
There was almost an equal distribution between the male and female population.

Table 2: Differential count in acute appendicitis

	Gender		**Total(n=80)**	**P value**
	Females (n=39)	**Males (n=41)**		
Total leukocyte count				
<4000	2(5.1%)	1(2.4%)	3(3.8%)	0.923
4000-11000	26(66.7%)	29(70.7%)	55(68.8%)	
>11000	11(28.2%)	11(26.8%)	22(27.5%)	
Total leukocyte count				
Variables	**Gender**		**Total**	**P value**
	Females	**Males**		
Total leukocyte count	9400.00±3304.70	10319.41±5058.82	9871.20±4292.42	0.341
Neutrophils	73.41±12.03	74.10±12.08	73.76±11.98	0.799
Lymphocytes	23.4±12.85	22.04±11.47	22.70±12.1	0.619
Monocytes	4.22±2.12	3.73±1.84	3.97±1.99	0.272
Basophils	0.00±0.00	0.02±0.16	0.01±0.11	0.333

TLC was found to be elevated in only 22(27.3%) of the patients and within the normal range in 55(68.8%) of the patients. P value was not found to be significant.

Table 3: Histopathological findings

Clinical Diagnosis	Gender		Total
	Female	Male	
Acute appendicitis	35(89.7%)	39(95.1%)	74(92.5%)
Perforated appendix	4(10.3%)	2(4.9%)	6(7.5%)
Total	39(100%)	41(100%)	80(100%)
Clinical diagnosis			
Ultrasound	**Gender**		**Total**
	Female	**Male**	
Normal	18(46.2%)	19(46.3%)	37(46.3%)
Acute appendicitis	21(53.8%)	20(48.8%)	41(51.3%)
Perforated appendix	0(0%)	2(4.9%)	2(2.5%)
Total	39(100%)	41(100%)	80(100%)
Ultrasound findings			
Histopathological	**Gender**		**Total**
	Female	**Male**	
Acute appendicitis	30(76.9%)	27(65.9%)	57(71.3%)
Gangrenous appendix	1(2.6%)	7(17.1%)	8(10%)
Perforated appendix	8(20.5%)	7(17.1%)	15(18.8%)
Total	39(100%)	41(100%)	80(100%)

The mean values of total leukocyte count were found to be within the normal range (4000-1100) and there was a marginal rise in the level of neutrophils (normal <70). The mean values of lymphocytes, basophils and monocytes were found to be within their normal range.

A preoperative clinical diagnosis of acute appendicitis was made in 74(92.5%) of the total 80 patients and that of perforated appendicitis was made in 6(7.5%) of the 80 patients.

Findings of acute appendicitis were seen in 41(51.3%) cases, that of perforated appendicitis in 2(2.3%) patients and that of the normal abdomen in 37(46.3%) patients.

Postop histopathology of the appendix specimen was found to be acute appendicitis in 57(71 %) patients, perforated appendicitis in 15(18.8%) patients and gangrenous appendicitis in 8(10%) of the total 80 patients.

Table 4: Comparison of AST/ALT/ALP in relation to histopathology

Variables	Histopathology		Total	P value
	Acute appendicitis	Complicated appendicitis		
Serum bilirubin	1.28±0.60	2.14±0.89	1.53±0.80	<0.001**
Direct bilirubin	0.68±0.55	1.35±0.81	0.87±0.70	<0.001**
Comparison of serum and direct bilirubin levels with Histopathology report				
Variables	**Histopathology**		**Total**	**P value**
	Acute appendicitis	**Complicated appendicitis**		
AST	28.89±12.47	26.04±17.17	28.08±13.92	0.411
ALT	25.53±12.40	29.39±10.57	26.64±11.97	0.193
ALP	76.88±24.57	82.35±21.92	78.45±23.83	0.356

Table 5: Clinical diagnosis in relation to histopathology

Ultrasound	**Histopathology**		**Total**
	Acute appendicitis	**Complicated appendicitis**	
Normal	25(43.9%)	12(52.2%)	37(46.3%)
Acute appendicitis	31(54.4%)	10(43.5%)	41(51.3%)
Perforated appendix	1(1.8%)	1(4.3%)	2(2.5%)
Total	57(100%)	23(100%)	80(100%)
Ultrasound in relation to histopathology			
p=0.438, Not significant, Fisher Exact test			
Clinical Diagnosis	**Histopathology**		**Total**
	Acute appendicitis	**Complicated appendicitis**	
Acute appendicitis	56(98.2%)	18(78.3%)	74(92.5%)
Perforated appendix	1(1.8%)	5(21.7%)	6(7.5%)
Total	57(100%)	23(100%)	80(100%)
P=0.007**, Significant, fisher Exact test			

The mean serum total bilirubin levels were found to be 1.53 mg/dl, which was above the normal range (≤ 1.0 mg/dl) hence indicating hyper bilirubinemia and the mean was found to be 1.28 in cases of acute appendicitis and 2.14 in cases of complicated appendicitis. Direct bilirubin was also elevated in both acute appendicitis and complicated appendicitis. ALT, AST and ALP were found to be within the normal limits in cases of both acute appendicitis and complicated appendicitis. The p-value was not found to be significant.

Out of the 37 patients who were diagnosed as normal on ultrasound, 25(43%) were diagnosed with acute appendicitis on HPE and 12(52.2%) with complicated appendicitis on HPE. Hence ultrasound when compared to histopathology was not considered to be statistically significant (p=0.438).

All 80 patients were clinically diagnosed with acute appendicitis which was confirmed by intra-op and histopathology. Of the 74 cases that were initially diagnosed as acute appendicitis, 18(78.3%) turned out as complicated appendicitis. P value (0.007) was significant clinically in diagnosing acute appendicitis. Hence, stressing the importance of the need for good clinical examination of all the cases.

Discussion

Acute appendicitis is one of the most frequently encountered "acute abdomen" [1] seen in the General Surgery department. The diagnosis of appendicitis remains a dilemma despite advances in radiological and laboratory investigations. Delay in its diagnosis leads to complications like perforation and peritonitis hence increasing morbidity and mortality. About 8% of people in western countries have appendicitis at some time in their lifetime. [23]

The lifetime rate of appendectomy is 12% for men and 25% for women, with approximately 7% of all people undergoing appendectomy for acute appendicitis during their lifetime. [24,25]

Despite the increased use of sophisticated imaging and non-invasive diagnostic modalities such as graded compression sonography, high-resolution helical

computed tomography (CT) and laparoscopy, the rate of misdiagnosis of appendicitis has remained constant (15%) as the rate of appendiceal perforation (1). In addition, these procedures have several significant limitations including cost, radiation exposure, operator dependency, availability, contrast agent allergy, false positive and false negative diagnoses and exposure to anaesthetics. A new tool to help in the diagnosis of acute appendicitis would thus be a welcome.

Hence, our study was conducted in the Department of General Surgery, Ramaiah Medical College, Bangalore to evaluate the serum bilirubin levels in cases of acute appendicitis and its diagnostic predictive value in cases of the complicated appendix which includes perforated appendicitis and gangrenous appendicitis.

There have been several reports of hyperbilirubinaemia in appendicitis. [6,7] Estrada et al hypothesised that hyperbilirubinaemia may be associated with appendiceal perforation and showed that more patients with a perforated or gangrenous appendix had hyper bilirubinaemia than those with simple acute appendicitis. [26] Sand et al showed that hyper- bilirubinaemia had a specificity of 86% for appendiceal perforation or gangrene, compared with a specificity of only 35% for CRP. The most likely explanation for the rise in SB is therefore circulating endotoxinemia as a result of appendiceal infection. Utile *et al [27] has* shown with *in vitro* infusion of endotoxin into the isolated rat liver that there is a dose-dependent decrease in bile salt excretion from the liver and that Escherichia coli endotoxin may exert direct damage at the cholangiolar level. It was demonstrated by session *et al* in 1971 [28] that in appendicitis mucosal ulceration occurs early and this facilitates the invasion of bacteria into the muscular is propria of the appendix thereby causing classical acute supportive appendicitis. [29] This process is associated with progressive bacterial invasion most likely facilitated by bacterial cytotoxins. The number of organisms isolated from patients with gangrenous appendicitis is five times greater than those with acute supportive appendicitis. Estrada *et al* [26] also found significantly higher peritoneal culture in patients with gangrenous/ perforated appendicitis. This elevated load of bacteria in appendicitis causes either direct invasion or translocation into the portal venous system. Direct invasion of bacteria into the hepatic parenchyma interferes with the excretion of bilirubin into the bile canaliculi by a mechanism that is thought to be caused by bacterial endotoxin and is biochemical rather than obstructive. Indirect evidence of bacterial translocation from the inflamed gastrointestinal tract or peritonitis to the liver via the portal vein was observed by Dieulafoy. [30] These bacteria commonly reach the liver from intra-abdominal organs, commonly from the appendix. Direct evidence of bacterial translocation from inflamed organs was observed in clinical and experimental studies. Recently, in one study, blood samples from the superior mesenteric vein in acute appendicitis showed bacteria in 38% of patients. These findings suggest that bacteria may transmigrate and produce portal bacteraemia, and hepatocellular dysfunction. This low percentage of positive blood cultures cannot explain hepatocellular dysfunction in the majority of cases. Thus, there must be other substances involved. It has been shown that liver dysfunction is caused by cytokines released from the gut due to

injury/inflammation. In a study, rats were subjected to intra-abdominal sepsis from cecalligation and puncture and the following observations were made: 1) the small intestine is an important source of adrenomedullin release during polymicrobial sepsis; 2) norepinephrine-induced hepatocellular dysfunction in early sepsis, mediated by activation of a-2 adrenal-receptors; and 3) TNF produces hepatocellular dysfunction despite normal cardiac output and hepatic microcirculation. [31] Thus, it is concluded that hepatocellular function is depressed during the early stage of sepsis despite the increased cardiac output and hepatic blood flow and decreased peripheral resistance. The depression of hepatocellular function in the early, hyper-dynamic stage of sepsis does not appear to be due to a reduction in hepatic perfusion but is associated with elevated levels of circulating pro-inflammatory cytokines such as TNF and IL-6. Thus, regulation of TNF and/or IL-6 may be responsible for producing hepatocellular dysfunction during the early hyper-dynamic stage of sepsis.

The main finding of our study indicated that patients with perforation were significantly more likely to have hyperbilirubinaemia (elevated total bilirubin levels>1 mg/dl) than those with acute simple appendicitis. Our study included a total of 80 patients who were diagnosed with appendicitis based on clinical, pathological and radiological investigations. Out of the 80 patients, 39 (49%) were males and 41(51%) were females. The mean age of the study group was 27.41 years and 61 patients of the total 80 were of less than 30 years of age. This is 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.

The total leukocyte count was elevated only in 22(27.5%) of the 80 patients with the mean neutrophil count being. [32,33] All the 80 patients in our study underwent ultrasound abdomen and was reported as acute appendicitis in 41(51.3%) patients and perforated appendicitis in 2(2.5%) patients and as normal in 37(46.3%) of the patients. Serum total bilirubin levels were found to be elevated and more than 1 mg/dl in 59(73.7%) of the 80 patients and normal in 21(26.31%) of the 80 patients. SGOT levels were found to be within the normal range in 53(66.3%) patients and elevated in 27(33.8%) patients. SGOT levels were found to be within the normal range in 59(73.8%) patients and elevated in 21(26.3%) of the 80 patients. [34] ALP levels were found to be within the normal range in 71(88.8%) patients and elevated in 9 (11.3%) of the 80 patients. Intra-op and post-op histopathology revealed 57(71.25%) patients as acute appendicitis and 23(28.71%) patients turned out to be the cases of complicated appendicitis which included 19 cases of perforated appendix and 4 cases of gangrenous appendix. The mean serum total bilirubin levels were found to be 1.53 mg/dl, which was above the normal range (≤ 1.0 mg) hence indicating hyperbilirubinemia and the mean was found to be 1.28 in cases of acute appendicitis, 2.14 in cases of complicated appendicitis. Our finding was consistent with hyperbilirubinaemia in a study conducted by Khan S,[15] who found the average level of serum bilirubin in his study population to be 2.38 mg/ld. The sensitivity, specificity, positive predictive value, negative predictive value and odds ratio were calculated from a 2x2 table. The sensitivity of bilirubin in

predicting acute appendicitis and appendiceal perforation diagnosis was 70.17%, Specificity was 8.69%, and the positive predictive value was 76.90%. The negative predictive value was 10.52%. Hence, we see that patients with appendiceal perforation had nearly two times more levels of serum bilirubin as compared to that of acute appendicitis. So we infer that patients with features suggestive of appendicitis with two-three times their normal range of bilirubin are more susceptible to having appendiceal perforation than those with normal or slightly elevated total serum bilirubin. Our study shows that isolated hyperbilirubinaemia without much elevation in the liver enzymes is a significant predictor of appendiceal perforation. This was demonstrated in a study by Estrada *et al* [26] *and* other studies showing nearly a threefold risk of perforated appendicitis in patients with total bilirubin levels greater than 1 mg/dL. The other factors which we studied in this series were age, duration of symptoms, Alvarado score, total leukocyte count, and ultrasonography, which was not significant in any of these criteria.

In conclusion, it seems that assessment of bilirubin levels can help identify patients who are more likely to have appendicitis. It could be used together with clinical findings and other routine laboratory tests to definitively manage patients with acute appendicitis earlier. In addition, hyperbilirubinaemia in patients with appendicitis indicates a higher likelihood of a perforated or gangrenous appendix.

Conclusion

Acute appendicitis is one of the most common clinical entities encountered by general surgeons. Our study has revealed that serum bilirubin levels are significantly elevated in cases of acute appendicitis. Though clinical diagnosis remains the gold standard in diagnosing acute appendicitis, serum bilirubin levels can be used as a useful investigative modality. Serum bilirubin levels in our study have shown a two to three-fold rise compared to the normal range, especially in cases of perforated/gangrenous appendix. Hence, elevated serum bilirubin levels in clinically suspected acute appendicitis cases could be useful in predicting complicated appendicitis.

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