



EVALUATION OF HYPERBILIRUBINEMIA AS A DIAGNOSTIC MARKER FOR ACUTE APPENDICITIS AND ITS ROLE IN THE PREDICTION OF APPENDICULAR PERFORATION

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ABSTRACT

Background: Acute appendicitis being the most common condition that needs urgent intervention, has to be diagnosed and evaluated at the earliest. It is found that a correlation exists between appendicular perforation and high serum bilirubin level. In the absence of radiological investigations, patients with clinical signs and symptoms of appendicitis and with hyperbilirubinemia might have a higher probability of appendicular perforation.

Method: This is a prospective study of patients admitted in ESI PGIMSR & Model Hospital, Basaidarapur,

New Delhi, who underwent appendectomy for acute appendicitis from October 2016 to January 2018. A study population of 100 cases with the diagnosis of acute appendicitis with or without appendicular perforation were selected.

Results: In our study, appendicular perforation patients had significant increase in serum bilirubin. 27 % of patients with appendicitis had elevated bilirubin level, where as in perforated appendicitis patients 93 % of the patients had elevated bilirubin level, this difference was statistically found to be significant (P<0.001). The serum bilirubin as a predictor for appendicular perforation revealed Sensitivity of 93.3%, Specificity of 72.3%, with the Positive Predictive value 37.8%, Negative Predictive value 98.4%.

Conclusion: The present study suggests that serum bilirubin level estimation, a simple cheap and easily available test in every laboratory, can be added to the routine investigation list of clinically suspected case of acute appendicitis or perforated appendix for the confirmation of diagnosis.

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INTRODUCTION

Acute appendicitis is the most common cause of an “acute abdomen”^{1,2}. Appendectomy is the most frequently performed urgent abdominal operation and is often the first major procedure performed by a surgeon in training¹. The diagnosis is mainly clinical but appendicitis can mimic a variety of acute medical and surgical abdomino-thoracic conditions. Early diagnosis of appendicitis is important to prevent morbidity and mortality due to its complications. The usual picture of appendicitis is often not classical, leaving many cases as diagnostic problems.

Those with the typical symptoms and signs of acute appendicitis, or suspected cases with definite findings of peritonitis are promptly indicated for surgery. In patients with questionable findings, the aggressive surgical approach has been “when in doubt take it out,” and the price paid was the frequent removal of normal appendices which varies up to 15-50%.

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In order to improve the diagnostic accuracy, a number of diagnostic modalities have been proposed, including clinical signs which includes scoring systems³, ultrasonography⁴⁻⁷, CT scans⁸, MRI⁹ and laparoscopy. Among imaging modalities, graded compression ultrasonography is an inexpensive, fast and non-invasive method. However, ultrasonography is operator dependent modality, and hence its diagnostic utility varies. Serum bilirubin levels appear to be a promising new laboratory marker for diagnosing acute appendicitis and also promises to have a predictive potential for the diagnosis of appendicular perforation.

Patients with clinical signs and symptoms of appendicitis and with hyperbilirubinemia should be identified as having a higher probability of appendicular perforation suggesting, serum bilirubin levels have a predictive potential for the diagnosis of appendicular perforation. However since paucity of studies from India exploring the potential of bilirubin as diagnostic marker for acute appendicitis and its role in predicting appendicular perforation lead us to take up the study.

METHODS

This is a prospective study of patients admitted under various surgical units in ESI PGIMSR & Model Hospital, Basaidarpur, New Delhi, who underwent appendectomy for acute appendicitis in the emergency setting, from October 2016 to January 2018. A study population of 100 cases with the diagnosis of acute appendicitis with or without appendicular perforation were selected.

Data Collection

Patients were evaluated by detailed history and clinical examination. Thorough investigations were carried out. Records of operative interventions and the findings as well as histopathology reports were also maintained. The investigations included: Complete blood count, Liver function test, Viral hepatitis markers, Urine examination (routine & microscopy), Kidney function test, Random blood sugar, Ultrasonography of abdomen, ECG (as indicated), X-ray chest. The patients diagnosed as acute appendicitis were subjected to prompt surgical intervention within 12 hours of admission. The appendectomy was performed via an open approach using McArthur-McBurney's incision. Laparoscopic appendectomy was avoided to prevent undue handling of the appendicular specimen during extraction, for more accurate histopathological analysis.

Inclusion Criteria: All diagnosed cases of appendicitis with or that without perforation.

Exclusion Criteria

- Appendicular lump,
- All patients documented to have a past history of Jaundice or Liver disease in last 6 months duration,
- Chronic alcoholism (i.e. intake of alcohol of >40g/day for Men and >20g/day in Women for 10 years)
- Hemolytic disease
- Acquired or Congenital biliary disease
- Hbs Ag positive
- Cholelithiasis
- Cancer of hepato-biliary system were excluded from the study.

Statistical Analysis

The eligible patients were categorized into the following groups based on the final pathologic reports for the appendix.

Group 1: Acute appendicitis with mucosal inflammation

Group 2: Perforated appendix

These groups were clinically divided into two groups i.e., acute appendicitis without perforation which involves group 1 and perforated appendix involving group 2. Laboratory values were compared based on the reference values mentioned below:

Serum total bilirubin	0.0-1.0 mg/dl
Serum direct bilirubin	0.0-0.2 mg/dl
Alkaline phosphatase (ALP)	80-200 IU/L
Aspartate transaminase (AST/SGOT)	0-45 IU/L
Alanine transaminase (ALT/SGPT)	0-50 IU/L

Statistical analysis was performed by the SPSS program for Windows, version 17.0. Continuous variables were presented as mean \pm SD, and categorical variables were presented as

absolute numbers and percentage. Data was checked for normality before statistical analysis. Normally distributed continuous variables were compared using the unpaired t test, whereas the Mann-Whitney U test was used for those variables that could not be normally distributed. Categorical variables were analyzed using either the chi square test or Fisher's exact test. A receiver operating characteristics analysis was calculated to determine optimal cut-off values for serum bilirubin, TLC, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP). The area under the curve, the sensitivity, and the specificity were calculated to analyze the diagnostic value of all these markers. For all statistical tests, a P value less than 0.05 was considered statistically significant.

The efficacy of liver function tests (bilirubin and liver enzymes) to determine the presence of complicated appendicitis was evaluated under the parameters of sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy.

RESULTS

A total of 100 patients with clinical diagnosis of acute appendicitis or appendicular perforation were included in the study. The study population constituted 38% of patients aged more than 35 years of age (Fig. 1), 41% were females. Average age of patients suffering from appendicitis in this study was 30.45 ± 12.39 years. 79% of the patients whose ultrasonogram was suggestive of appendicitis had inflammation of appendix histopathologically. Out of 100 patients 99 underwent appendectomy and one underwent both appendectomy and hemicolectomy. 27% of patients with appendicitis had elevated bilirubin level, whereas in perforated appendicitis patients 93% of the patients had elevated bilirubin level, this difference was statistically found to be significant ($P < 0.001$).

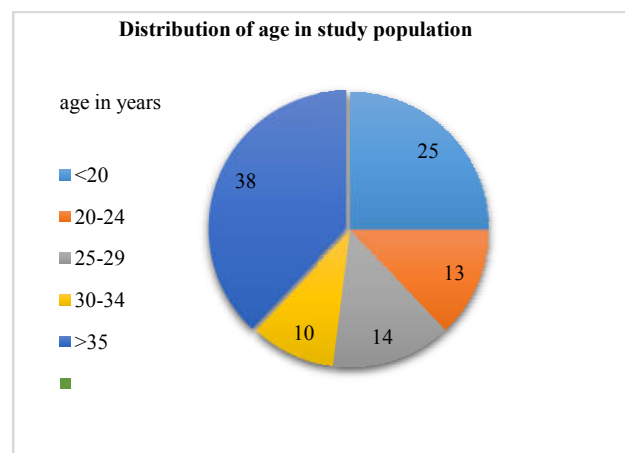


Fig 1 Age distribution in acute appendicitis

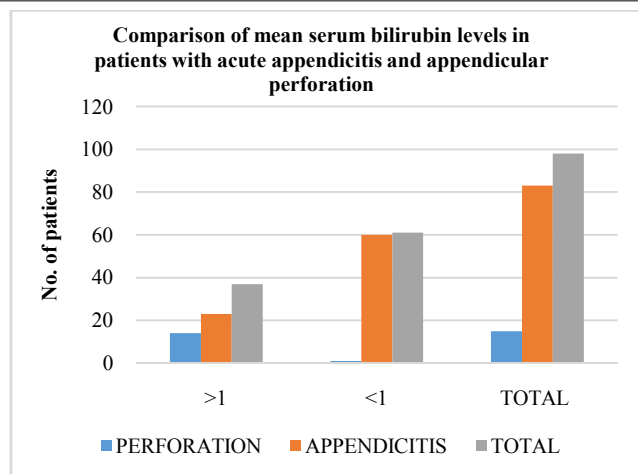


Fig 2 Comparison of mean serum bilirubin levels in patients with acute appendicitis and appendicular perforation

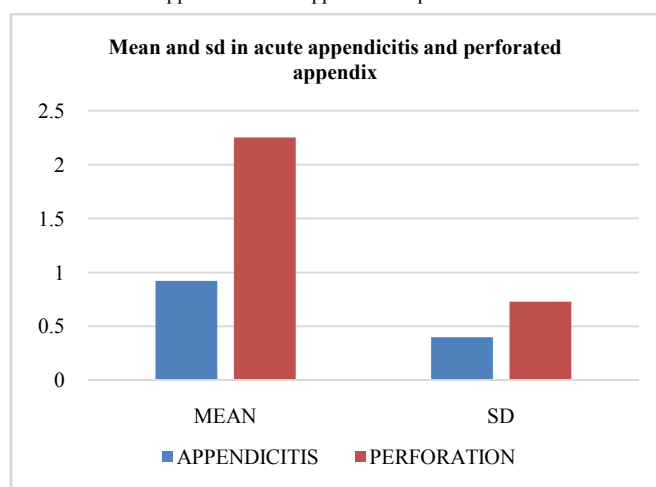


Fig 3 Mean and SD in acute appendicitis and perforated appendix

Appendicular perforation patients had significant increase in serum bilirubin. (Fig. 2&3). The serum bilirubin as a predictor for appendicular perforation revealed Sensitivity of 93.3%, Specificity of 72.3%, with the Positive Predictive value 37.8%, Negative Predictive value 98.4%.

Table 4 Comparing Mean and SD of serum bilirubin in acute appendicitis and perforated appendix

S.bilirubin	Diagnosis		t= 9.965, df=96 P<0.001
	Appendicitis	Perforation	
Mean	0.923±0.40	2.25±0.73	

Mean serum bilirubin level in appendicitis patients was 0.92±0.4 mg/dl when compared to perforated appendicitis which was 2.25±0.73 mg/dl. The difference in mean serum bilirubin level was found to be statistically significant.

DISCUSSION

Acute Appendicitis is the most common general surgical emergency, and early surgical intervention improves outcome. It is estimated that about 07% of the general population will develop appendicitis during their lifetime.

Acute appendicitis can be cured by an appendicectomy without a long recovery period, whereas perforated appendicitis can cause various complications that can result in life- threatening conditions. Recent developments in the diagnosis of acute appendicitis with the assistance of radiological tools such as ultrasonography and CT have reduced the rate of negative

appendectomies. Because of the development of helical CT, the effectiveness and the accuracy of diagnosing appendicitis have already overcome the limitation of sonography, with sensitivities of 90 to 99% and specificities of 91 to 99%. However, a recent analysis by Pritchett *et al*¹⁰, showed that the increasing use of CT scanning in acute appendicitis increases the cost of care and the staying time in the emergency department, and delays the time to surgery. Because physical examinations and laboratory tests are still acknowledged as being of the utmost importance in the diagnostic process, this study tries to find key laboratory tests that would allow us to anticipate the severity of acute appendicitis.

In the present study of 100 patients, hyperbilirubinemia was found in 37 cases, of which 14 patients were diagnosed with perforated appendix (true positives), i.e. either grossly perforated, or with microscopic evidence of the same. The average value for the two groups AA and PA was 0.92mg/dL (±0.4 SD) and 2.25 mg/dl (±0.73 SD), respectively. This hyperbilirubinemia was mixed in type (both conjugated and unconjugated) in most of the patients.

For perforated appendicitis, the p-value of total serum bilirubin was <0.001. Sensitivity, specificity and negative predictive value of serum bilirubin as a marker of perforated appendix was found to be as high as 93.3%, 72.3 % and 98.3% respectively. While the values for positive predictive value was modest at 37.8%. The implications being that elevated bilirubin levels are strongly indicative of appendicular perforation, though normal levels do not rule out the same.

A retrospective analysis by Sand M *et al*¹¹, involving 538 patients with histologically confirmed acute appendicitis had the mean bilirubin level of 0.9 mg/dl (±0.6 SD mg/dl; range 0.1 to 4.3 mg/dl; median 0.7 mg/dl). Patients with Appendicular perforation, however had a mean bilirubin level of 1.5 mg/dl (±0.9 SD mg/dl; range 0.4 to 4.3 mg/dl; median 1.4 mg/dl). The Specificity of hyperbilirubinemia for appendicular perforation was 0.86 compared with 0.55 white blood count and 0.96 for C- reactive protein⁷³. The study concluded that the Patients with hyperbilirubinemia and clinical symptoms of appendicitis should be identified as having probability of appendicular perforation than those with normal bilirubin levels. A retrospective analysis by Emmanuel A *et al*¹², whereby retrospective analysis of appendicectomies performed in two hospitals (n=472). They found that the mean bilirubin levels were higher for patients with simple appendicitis compared to those with a non-inflamed appendix. Hyperbilirubinemia had a specificity of 88% and a positive predictive value of 91% for acute appendicitis. Patients with appendicitis who had a perforated or gangrenous appendix had higher mean bilirubin levels and were more likely to have hyperbilirubinemia (p<0.001). The specificity of hyperbilirubinemia for perforation was 70%. The specificities of white cell count and C-reactive protein were less than hyperbilirubinemia for simple appendicitis and perforated or gangrenous appendicitis. They concluded that hyperbilirubinemia is a valuable marker for acute appendicitis. Patients with hyperbilirubinemia are also more likely to have appendicular perforation. Bilirubin should be included in the assessment of patients with suspected appendicitis.

A prospective analytical study conducted on 100 patients with acute appendicitis by Mallikarjuna MN *et al*¹³, in their study concluded that Specificity and negative predictive value of serum bilirubin as a marker of complicated appendicitis was found to be high 96.38% and 97.56 %. While the values for sensitivity and positive predictive value were modest at 82.23% and 83.33% respectively.

Our study shows that isolated hyperbilirubinemia is a significant predictor of appendiceal perforation. The other factors which we studied in this series were age, sex, total leukocyte count, ultrasonography, urea and creatinine. P value was not significant in any of these. The Sensitivity, Specificity and negative predictive value of SB in our study is 93.3%, 72.3% and 98.4 % respectively, comparable to other published studies. The positive predictive value of SB was 37.8% in our study. Therefore, in suspected cases of appendicitis elevation of SB can be used as a criterion to diagnose and manage acute appendicitis, especially when there is doubtful differential diagnosis were considered like right ureteric colic, mesenteric adenitis, right salpingitis. Both sensitivity and specificity of elevated total SB level in acute appendicitis with perforation and/or gangrene is higher as compared to TLC, urea and creatinine. This finding is similar to other reported studies.

CONCLUSION

The present study suggests that serum bilirubin level estimation, a simple cheap and easily available test in every laboratory, can be added to the routine investigation list of clinically suspected case of acute appendicitis or perforated appendix for the confirmation of diagnosis. Serum bilirubin levels appears to be a promising new laboratory marker for diagnosing acute appendicitis, however diagnosis of appendicitis remains essentially still is clinical. Patients with clinical signs and symptoms of appendicitis and with hyperbilirubinemia higher than the normal range should be identified as having a higher probability of appendicular perforation, since the rise in SB level was significantly higher in patients with appendiceal perforation in the study.

Serum bilirubin has a definite predictive potential in these cases suggesting, serum bilirubin levels have a predictive potential for the diagnosis of appendicular perforation. Therefore, obtaining SB values upon admission can be used in conjunction with more modern diagnostic tests such as ultrasonography, CT scan to help determine the presence of perforation and thus aid in prompt clinical management. Serum bilirubin levels may be considered as one more positive factor for strong suspicion of appendicitis or perforated appendix in differential diagnosis of right iliac fossa pain.

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