

Original article:

Diagnostic Role of Hyperbilirubinaemia as a Marker of Acute appendicitis

Laxman yadav*, Pritam Kumar Das, Nitesh kumar

Dept. of General Surgery, Silchar Medical College & Hospital
Srimanta Sankaradeva University of Health Science, Assam, India
Corresponding author*

ABSTRACT:

Introduction: Acute appendicitis is the most frequently encountered abdominal emergency. The diagnosis of acute appendicitis continues to be difficult due to its various clinical presentations. Due to the lack of 100% accurate test for appendicitis, any investigation that can contribute to its diagnosis is valuable. The aim of this study was to determine the diagnostic value of hyperbilirubinaemia as a marker for acute appendicitis.

Materials and Methods: A prospective study was conducted in the Department of General Surgery, Smch, Silchar in which a total of 100 patients with clinical diagnosis of acute appendicitis were studied. Data collected included laboratory and histological results. All patients diagnosed as acute uncomplicated or complicated appendicitis clinically on admission, were operated upon and confirmed by histopathological examination.

Results: The mean bilirubin levels were higher for patients with acute uncomplicated appendicitis compared to those with a non-inflamed appendix ($p < 0.0186$). More patients with acute uncomplicated appendicitis had hyperbilirubinaemia on admission (61% vs 38%) and the odds of these patients having appendicitis were over six times higher (odds ratio: 6.28, $p < 0.001$). Hyperbilirubinaemia had a sensitivity of 61% and specificity of 80% and a positive predictive value of 95% for acute uncomplicated appendicitis. Patients with acute complicated appendicitis (perforated or gangrenous appendix) had higher mean bilirubin levels ($p = 0.01$) and were more likely to have hyperbilirubinaemia ($p < 0.001$). Hyperbilirubinaemia had a sensitivity of 83.3% and specificity of 80% for perforation or gangrenous appendicitis. The specificities of white cell count and C-reactive protein were less than hyperbilirubinaemia for acute uncomplicated appendicitis (60% and 70%) and perforated or gangrenous appendicitis (60% and 70%).

Conclusions: Hyperbilirubinaemia is a valuable marker for acute appendicitis. Patients with hyperbilirubinaemia are also more likely to have appendiceal perforation or gangrene. Bilirubin can be used together with clinical examination and other laboratory investigations in the assessment of patients with suspected acute appendicitis.

INTRODUCTION:

In spite of advances in radiological and laboratory investigations, the diagnosis of appendicitis is still remains a dilemma¹. No single clinical or laboratory test is able to reliably predict acute appendicitis². USG, CT has improved the diagnostic accuracy but is not readily available and costly. Although aggressive surgical approaches reduce complication but leads to increased chances of negative appendicectomies and incurs the cost and potential complication from an unnecessary appendicectomy. So an uncomplicated, cheap biochemical test which can be done easily in emergency situation, may be useful.

Recently, elevation in serum bilirubin was reported, but the importance of the raised total bilirubin has not been stressed in appendicitis³. Jaundice has been associated with appendicitis⁴ and studies have shown hyperbilirubinaemia to be a useful predictor of appendiceal perforation^{5,6}. However, these studies did not focus on the value of bilirubin as a specific marker for acute appendicitis. In view of the above context, the present study was undertaken to assess the diagnostic role of hyperbilirubinemia in acute appendicitis.

MATERIALS AND METHODS:

A hospital based prospective study was conducted in the Department of General Surgery, Smch, Silchar from July 2015 to June 2016 in which a total of 100 patients with clinical diagnosis of acute appendicitis were studied. Data collected included laboratory and histological results. All patients diagnosed as acute uncomplicated or complicated appendicitis clinically on admission, were operated upon and confirmed by histopathological examination

INCLUSION CRITERIA

1. All patients diagnosed as acute appendicitis clinically on admission.
2. All patients diagnosed as appendiceal perforation clinically on admission.
3. For both these groups (1&2), only patients with histopathological report available would be included.

EXCLUSION CRITERIA

1. All patients documented to have a past history of
 - a. Jaundice or Liver disease
 - b. Chronic alcoholism (i.e. intake of alcohol of >40g/day for Men and >20 g/day for women for 10 years).
 - c. Hemolytic disease.
 - d. Acquired or congenital biliary disease
2. All patients with positive HBsAg
3. All patients with cholelithiasis.
4. All patients with cancer of hepatobiliary system.

DATA ANALYSIS

A data sheet (Master Chart) was created using Microsoft Excel 2007. XLSTAT 2016 was used for analysis of data. Microsoft Word was used for creation of tables and graphs.

Sensitivity, specificity, positive predictive value and negative predictive value of bilirubin, WBC and CRP were analysed. Fisher's exact test was done to calculate p value. Diagnostic accuracy of bilirubin, WBC and CRP to diagnose acute uncomplicated and complicated appendicitis were analyzed by calculating area under cover in Receiver-operating characteristic (ROC) curve. A *P* value of <0.05 was chosen to be significant for all tests given the Bonferroni correction conducted among the study cohort.

RESULTS AND OBSERVATIONS

This study included 100 patients of acute appendicitis diagnosed on clinical ground and managed surgically, following parameters were observed.

AGE AND SEX DISTRIBUTION

Table 1 : Distribution of Age and Sex

Age group (in years)	Male (n, %)	Female (n, %)	Total (n, %)
< 10	-	-	-
11--20	14	12	26(26%)
21--30	25	12	37(37%)
31--40	9	9	18(18%)
41--50	3	4	7(7%)
50--60	6	2	8(8%)
>60	1	3	4 (4%)
Total	58	42	100%

From the above table and bar diagram it is seen that out of 100 patients 58 (58%) were males and 42(42%) were females. Male to female ratio was 1.38:1. Most of the patients 37(37%) were in age group of (21 to 30) years followed by 26 (26%) in the (11 to 20) years of age group so majority of the patients presented in 2nd and 3rd decades.

SERUM BILIRUBIN IN PREDICTION OF ACUTE UNCOMPLICATED APPENDICITIS

Group 1 : Normal appendix (non inflamed appendix) = HPE⁻ (n=10)

Group 2 : Acute uncomplicated appendicitis (acute appendicitis without perforation/gangrenous changes) = HPE⁺ (n=72)

Group 3 : Acute complicated appendicitis (perforated/gangrenous appendix) = HPE⁺ (n-18)

Table 2 : 2x2 contingency table (Hyperbilirubinemia & acute uncomplicated appendicitis)

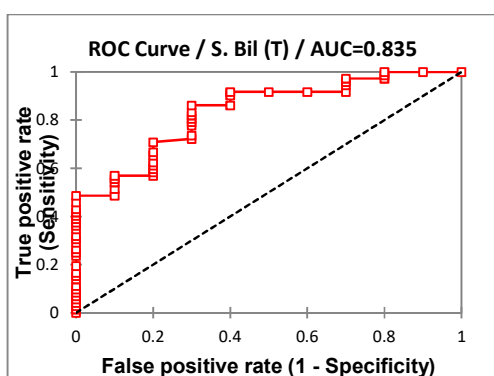
Hyperbilirubinemia	HPE ⁺	HPE ⁻
Present	44	02
Absent	28	08
Total	72	10

Fisher's exact test was done for association between hyperbilirubinemia and Acute uncomplicated appendicitis and data was found to be significant $p < 0.0186$. ($p < 0.05$) Mean serum bilirubin in patients of acute uncomplicated appendicitis was found to be (1.30 ± 0.52) mg/dl. Range (0.47 -2.74)mg/dl.

Table 3 : Sensitivity and specificity (Hyperbilirubinemia & acute uncomplicated appendicitis)

Statistics	Value	95% CI lower bound	95% CI upper bound
Sensitivity	0.611	0.495	0.715
Specificity	0.800	0.478	0.951
Positive predictive value	0.957	0.898	1
Negative predictive value	0.222	0.086	0.358
Relative risk	1.230	1.025	1.476
Odd ratio	6.286	1.422	27.792

C.I. : Confidence interval



Receiver Operating Curve (ROC) of Hyperbilirubinemia & Acute uncomplicated appendicitis

Hyperbilirubinemia had a sensitivity of 61.1% and a high specificity of 80% in prediction of acute uncomplicated appendicitis. Area under the curve (AUC) for serum bilirubin for acute uncomplicated appendicitis was high 0.835. The ROC curve for bilirubin levels in patients with acute uncomplicated appendicitis showed the optimal threshold bilirubin level with the highest sum of sensitivity and specificity was 0.9 mg/dl. The relative risk was 1.23 and Odds of a patient with hyperbilirubinemia having Acute uncomplicated appendicitis were over six times higher (OR : 6.28).

SERUM BILIRUBIN IN PREDICTION OF ACUTE COMPLICATED APPENDICITIS

Table 4 : 2x2 Contingency table (Hyperbilirubinemia and acute complicated appendicitis)

Hyperbilirubinemia	HPE⁺	HPE⁻
Present	15	02
Absent	03	08
Total	18	10

Inference: Fisher’s exact test was done for association between hyperbilirubinemia and acute complicated appendicitis and data was found to be significant $p < 0.0032$.

Mean serum bilirubin in patients of acute complicated appendicitis was found to be (1.88 ± 0.65) mg/dl. Range $(0.82-3.05)$ mg/dl.

Table 5 : Sensitivity and specificity (Hyperbilirubinemia & acute complicated appendicitis)

Statistics	Value	95% CI lower bound	95% CI upper bound
Sensitivity	0.833	0.598	0.948
Specificity	0.800	0.478	0.951
Positive predictive value	0.882	0.729	1.000
Negative predictive value	0.727	0.464	0.990
Relative risk	3.235	1.329	7.877
Odd ratio	20.000	3.221	124.168

C.I. : Confidence interval

WBC count in prediction of Acute uncomplicated Appendicitis :

Table 6 : 2x2 Contingency table (WBC count and acute uncomplicated appendicitis)

WBC count	HPE⁺	HPE⁻
Raised $>11,000/\text{mm}^3$	37	04
Not raised $<11,000/\text{mm}^3$	35	06
Total	72	10

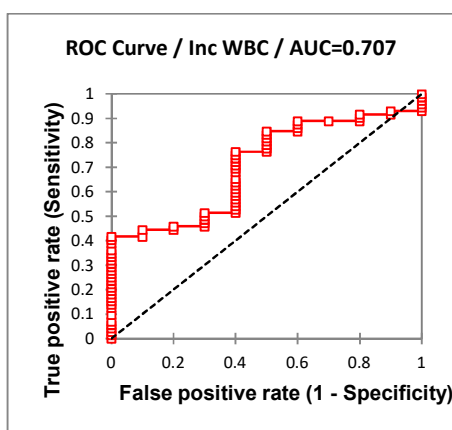
Inference : Fisher’s exact test was done for association between WBC count and Acute uncomplicated appendicitis and data was found to be insignificant $p < 0.7374$. ($p < 0.05$)

Mean WBC count in patients of Acute uncomplicated appendicitis was found to be $13496 \pm 5999/\text{mm}^3$. Range $(3658-24965)/\text{mm}^3$

Table 7 : Sensitivity and specificity (WBC count & acute uncomplicated appendicitis)

Statistics	Value	95% CI lower bound	95% CI upper bound
Sensitivity	0.514	0.401	0.626
Specificity	0.600	0.312	0.831
Positive predictive value	0.902	0.812	0.993
Negative predictive value	0.146	0.038	0.255
Relative risk	1.057	0.901	1.240
Odd ratio	1.586	0.438	5.741

C.I. : Confidence interval



Receiver Operating Curve (ROC) of WBC count & acute uncomplicated appendicitis

WBC count has sensitivity of 51.4% and specificity of 60% in prediction of acute uncomplicated appendicitis. Area under the curve (AUC) for raised WBC count for acute uncomplicated appendicitis was 0.707. The ROC curve for raised WBC count in patients with Acute uncomplicated appendicitis showed the optimal threshold WBC count with the highest sum of sensitivity and specificity was 15339/mm³. No significant relative risk of having appendicitis (RR= 1.05) was found in patients with high WBC count. Odd's ratio was found to be 1.58.

CRP IN PREDICTION OF ACUTE UNCOMPLICATED APPENDICITIS

Table 8 : 2x2 Contingency table (CRP and acute uncomplicated appendicitis)

CRP	HPE ⁺	HPE ⁻
Raised >5mg/L	39	03
Normal <5mg/L	33	07
Total	72	10

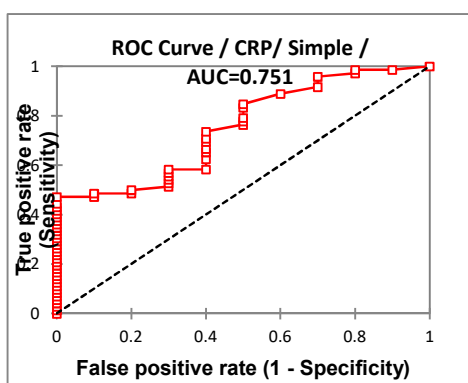
Inference: Fisher’s exact test was done for association between CRP and Acute uncomplicated appendicitis and data was found to be insignificant $p < 0.188$.

Mean CRP in patients of Acute uncomplicated appendicitis was found to be 13.06 ± 11.8 mg/L. Range (1.2-45.6) mg/L

Table 9: Sensitivity and specificity (CRP & acute uncomplicated appendicitis)

Statistics	Value	95% CI lower bound	95% CI upper bound
Sensitivity	0.542	0.427	0.652
Specificity	0.700	0.392	0.894
Positive predictive value	0.929	0.851	1.000
Negative predictive value	0.175	0.057	0.293
Relative risk	1.126	0.956	1.325
Odd ratio	2.758	0.715	10.634

C.I. : Confidence interval



Receiver Operating Curve (ROC) of CRP & Acute uncomplicated appendicitis

CRP had sensitivity of 54.2% and specificity of 70% in prediction of acute uncomplicated appendicitis. Area under the curve (AUC) for CRP for Acute uncomplicated appendicitis was 0.751. The ROC curve for raised CRP in patients with Acute uncomplicated appendicitis showed the optimal threshold CRP with the highest sum of sensitivity and specificity was 8.9mg/L. No significant relative risk of having appendicitis (RR= 1.126) was found in patients with high CRP. Odd’s ratio was found to be 2.75.

DISCUSSION

It is well established that when microbes invade the body, leukocytes defend it. This leads to increase in the leukocyte count. Bacterial invasion in the appendix leads to transmigration of bacteria and the release of pro-inflammatory cytokines such as TNF-alpha, IL6 and cytokines. These reach the liver via Superior mesenteric vein (SMV) and may produce inflammation, abscess or dysfunction of liver either directly or indirectly by altering the hepatic blood flow⁷.

The present study was undertaken to evaluate hyperbilirubinemia as a diagnostic marker for acute appendicitis in Silchar Medical College & Hospital, Silchar, for a period of 1 year.

In the study of 100 case, diagnosed as acute appendicitis on clinical grounds and underwent surgery were studied. After obtaining histopathological reports patients were divided into 3 groups.

Group 1: Normal appendix (non inflamed appendix), other diagnosis.

Group 2: Acute uncomplicated appendicitis (acute appendicitis without perforation/gangrenous changes).

Group 3: Acute complicated appendicitis (perforated/gangrenous appendix)

Table 1 : Cut-off value for various parameters taken for study purpose

Parameters	Total serum bilirubin	WBC count	C-reactive protein
Cut off value	>1 mg/dl	>11,000/mm ³	>5mg/L

Considering the observations obtained in our study, we take the endeavor of discussing our result

HYPERBILIRUBINEMIA AND ACUTE UNCOMPLICATED APPENDICITIS

Table 10: Comparison of different studies for hyperbilirubinemia in prediction of acute uncomplicated appendicitis

Hyperbilirubinemia	Our study	Khan et al ³	Patel et al ¹	Emmanuel et al ⁸	D'souza et al ⁹	Mir et al ¹⁰
Sensitivity (%)	61%	56%	65%	30%	27%	53.64
Specificity (%)	80%			88%	96%	48.1

Higher specificity of hyperbilirubinemia for acute uncomplicated appendicitis of 80% in our study was comparable to Emmanuel et al⁸., and D'souza et al⁹., however both of the study shows low sensitivity.

Sensitivity of 61% of our study was comparable to Mir et al¹⁰, khan et al³ and Patel et al¹.

Table 11: Comparison of different studies for mean serum bilirubin in acute uncomplicated appendicitis

Study	Our study	Mir et al ¹⁰	Patel et al ¹	Ghimire et al ¹¹
Mean serum bilirubin (mg/dl)	1.3±0.52	1.46±0.38	1.3±0.45	1.07±0.24

In our study it was observed that mean serum bilirubin level was increased in patients with acute uncomplicated appendicitis and which is comparable with other studies. Hyperbilirubinemia was significantly associated with acute uncomplicated appendicitis. (P value <0.0186). A high AUC (0.835) in ROC curve in our study for the prediction of acute uncomplicated appendicitis is comparable to Mir et al.¹⁰ (AUC= 0.608). So hyperbilirubinemia had high diagnostic accuracy in prediction of acute uncomplicated appendicitis.

WBC AND ACUTE UNCOMPLICATED APPENDICITIS

Table 12: Comparison of different studies for WBC count in prediction of acute uncomplicated appendicitis

Study	Our study	Emmanuel et al ⁸	D'souza et al ⁹	Mir et al ¹⁰
Sensitivity(%)	51.4	-	68	66.76
Specificity(%)	60	60	71	83.54

Sensitivity observed in our study was comparable to D'souza et al.⁹ and Mir et al¹⁰. Specificity observed in our study was comparable to Emmanuel et al⁸ and D'souza et al.⁹.

Table 13 : Comparison of Mean WBC count in various studies

Study	Our study	Kaser et al ¹²	Beltran et al ¹³
Mean WBC Count(×10 ³ /mm ³)	13.4±5.9	13.2±4	14±3.6

Mean WBC count in our study found to be raised and similar to Kaser et al¹² and Beltran et al.¹³

In our study, AUC (0.707) in ROC curve for the prediction of acute uncomplicated appendicitis was found slightly lower than Mir et al¹⁰ (AUC= 0.86).The association between the WBC count and acute uncomplicated appendicitis was found to be insignificant in our study p<0.7374 and similar results were found by Kaser et al.¹²

CONCLUSION

Hyperbilirubinaemia has a strong association with acute appendicitis. In the diagnosis of acute appendicitis, hyperbilirubinaemia is a simple, reliable, non invasive, safe and cost effective diagnostic modality.

The assessment of serum bilirubin improves diagnostic accuracy and consequently reduces the number of negative appendectomy and its complications.

It is also a valuable indicator of patients more likely to have appendiceal perforation or gangrene and has a predictive potential for the diagnosis of appendiceal perforation. Bilirubin can be used together with clinical examination and other laboratory investigations in the assessment of patients with suspected acute appendicitis.

REFERENCES:

1. Patel D, Nimish J. Shah, Patel B, Mital P, Patel D, Chirag Dalal; Evaluation of hyperbilirubinemia as a new diagnostic marker for acute appendicitis and its role in the prediction of complicated appendicitis *Int J Res Med.* 2014;3:28-33.
2. Ducholm S, Bagi P, Bud M. Laboratory aid in the diagnosis of acute
3. appendicitis. A blinded, prospective trial concerning diagnostic value of
4. leukocyte count, neutrophil differential count, and C-reactive protein. *Dis Colon Rectum* 1989; **32**: 855–859.
5. Khan S. Evaluation of hyperbilirubinemia in acute inflammation of appendix: A prospective study of 45 cases. *KUMJ* 2006; 4(3) 15 : 281-9.
6. Miller DF, Irvine RW. Jaundice in acute appendicitis. *Lancet* 1969;1(7590):321–323.
7. Estrada JJ, Petrosyan M, Krumenacker J Jr, Huang S, Moh P. Hyperbilirubinemia in Appendicitis: A New Predictor of Perforation. *Journal of Gastrointestinal Surgery* 2007; 11: 714–5.
8. Sand M, Bechara F, 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;198:193-198.
9. Beg R B and Garlandton AW: Translocation of certain endogenous bacteria from the GI tract to mesenteric lymph node and other organ in Gonobiotic mouse model. *Infect Immunol* 23; 403-411:1979.
10. Emmanuel A, Murchan P, Wilson I, Balfe P. The value of hyperbilirubinaemia in the diagnosis of acute appendicitis. *Ann R Coll Surg Engl* 2011; 93(3): 213-7.
11. D'souza N, Karim D, Sunthareswaran R, Bilirubin; a diagnostic marker for appendicitis. *Int j surg* 11(2013) 114-117.
12. Mir MA, Haq I, Manzoor F, Diagnostic value of total leukocyte count (TLC), C-reactive protein(CRP) & Bilirubin in patient with suspected acute appendicitis. *Int. j of contemporary Medical research* 2016,3 (5)1249-1253.
13. Ghimire P, Thapa P, Yogi N, - Role of serumbilirubin as a marker of acute gangrenous appendicitis. *Nepal Journal of Medical sciences* 2012;1(2):89-92
14. Kaser SA, Fankhauser F, Willi N, Maurer CA. C-reactive protein is superior to bilirubin for anticipation of perforation in acute appendicitis. *Scand J Gastroenterol* 2010; 45: 885–892.
15. Bletran MA, Almonacid j, Vincencio A, Gutierrez J, Cruces KS, Cumsille MA, Predictive value of white cell count and C-reactive protein in children with appendicitis. *Journal of Pediatric Surgery*(2007) 42, 1208-1214.