

Original Research Article

Hyperbilirubinemia as a diagnostic tool in patients with perforated appendicitis: a prospective study

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Received: 24 March 2020

Revised: 28 April 2020

Accepted: 29 April 2020

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ABSTRACT

Background: This study was conducted to determine the effectiveness of hyperbilirubinemia as diagnostic tool to predict perforated appendicitis.

Methods: Patients presenting to department of general surgery of SS Medical College and Hospital during the period from June 2017 to June 2019 with features of appendicitis and liver function tests on admission undergoing laparoscopic or open appendectomy were included in this study. Age, duration of symptoms, temperature, white blood cell counts, bilirubin levels and histological data were collected. Culture and sensitivity of peritoneal fluid was done. Patients were grouped according to histological examination of appendectomy specimens and comparison was made between the groups.

Results: The mean bilirubin level of all patients was 0.95 mg/dl (range, 0.1-4.3 mg/dl). The mean bilirubin levels were higher for patients with simple appendicitis compared to those with a non-inflamed appendix (0.8 mg/dl and 0.5 mg/dl, $p < 0.001$). Hyperbilirubinaemia had a specificity of 88% and a positive predictive value of 88.89% for acute appendicitis. Patients with appendiceal perforation, however, had a mean bilirubin level of 1.5 mg/dl and were more likely to have hyperbilirubinaemia ($p < 0.001$). The specificity of hyperbilirubinaemia for perforation or gangrene was 70%.

Conclusions: patients with hyperbilirubinemia and clinical symptoms of appendicitis should be identified as having a higher probability of appendiceal perforation than those with normal bilirubin levels. Hyperbilirubinemia alone is not a strong enough predictor, but might be more useful when integrated into a scoring system.

Keywords: Acute appendicitis, Gangrenous appendix hyperbilirubinemia, Perforated appendicitis, WBC

INTRODUCTION

Acute appendicitis is one of the commonest causes for acute abdomen in any general surgical practice.¹ From the time that it was first described by Reginald Heber Fitz in 1886, it has remained a topic of serial research works for various factors ranging from its aetiology, to its management options.²

Appendicitis is one of the commonest acute conditions manifesting as pain abdomen in the emergency room.

The life time rate for appendectomy is 12% for men and 25% for women, with approximately 7% of all people undergoing appendectomy in their lifetime. Most commonly affected age group is second to fourth decades of life, with mean age of 31.3 years and median age of 22 years. Both sexes are affected, with a slight male to female predominance, about 1.2-1.3:1.³

So much has been stressed about the various methods of diagnosis, only because the same is extremely important. Appendicitis, which if caught early and managed

appropriately can be the most uneventful surgery, while the other end of the spectrum is also true, that when missed, appendicitis can turn into a disease with great morbidity and mortality.

Objective of study was to determine the effectiveness of hyperbilirubinemia as diagnostic tool to predict perforated appendicitis.

METHODS

This was a tertiary care hospital based prospective study conducted in the department of general surgery at SS institute of medical sciences and research centre who presented with clinical features of appendicitis between June 2017 to June 2019.

Inclusion criteria

Patients aged more than 18 years presenting to department of general surgery at SS institute of medical sciences with features of acute appendicitis were included in the study if they underwent appendectomy (laparoscopic or open) and liver function tests performed on admission.

Exclusion criteria

Patients were excluded if they had documented liver disease, history of alcoholism, hemolytic disease, and other acquired or congenital biliary disease.

A total of 156 appendectomies were performed during the study period of which 140 patients were included in our analysis. We excluded 16 cases because appendectomy was performed as part of another procedure. The 140 patients analyzed were stratified into four groups based on histopathology result:

Group 1 comprised patients with non-inflamed appendices, group 2 comprised those with acute appendicitis, group 3 included patients with appendicitis with an inflammatory infiltrate extending through the full thickness of the appendiceal wall to the serosa and group 4 comprised patients with a perforated or gangrenous appendix.

The relevant preoperative laboratory results were analyzed for diagnostic properties which included the preoperative white blood count (WBC), total bilirubin level, and liver transaminase levels of glutamic-oxaloacetic transaminase (GOT) and glutamic-pyruvic transaminase (GPT). Total bilirubin levels greater than 1 mg/dl were defined as hyperbilirubinemia. The other normal values were defined as $4-11 \times 10^9$ cells for WBC, and 10 to 35 u/l for GOT and GPT.

Microbiological specimens, including aerobic and anaerobic cultures, were obtained from the blood in 52

patients preoperatively and from the peritoneal cavity in 81 patients at the time of appendectomy.

The diagnostic value of WCC, bilirubin was predicted with sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for the above groups either for each individual test or when combined. Comparisons were made between three broad groups of patients: those with non-inflamed appendices were compared with those with acute but not perforated or gangrenous appendicitis (simple acute appendicitis) and those with appendiceal perforation or gangrene were compared with those with simple acute appendicitis.

Statistical analysis

Categorical variables were presented as frequency and percentages. To study the association between categorical variables chi-square test was used. P value of <0.05 is considered as significant. Statistical analyses were performed with IBM SPSS program for windows version 22.

RESULTS

Among 140 patients included in this study, 74 patients (53%) were females, 66(47%) were males. The mean age was 32 years (range: 18-70 years).

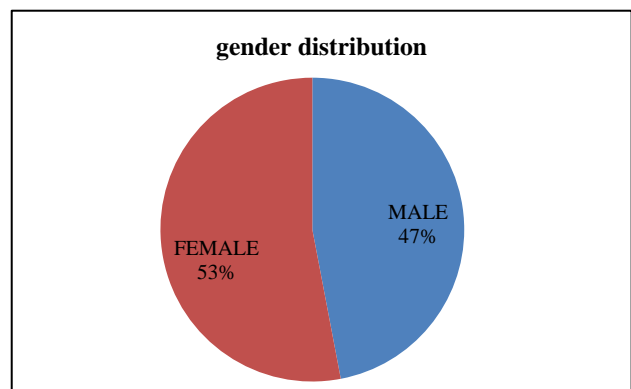


Figure 1: Gender distribution of patients with acute appendicitis.

Table 1 shows the distribution of patients by histology group. Twenty-five patients (18%) had a noninflamed appendix. The mean bilirubin levels were higher for patients with simple acute appendicitis (group-2) compared to those with a non- inflamed appendix (group-1), (0.8 mg versus 0.5 mg, $p < 0.001$) and more patients in group-2 had hyperbilirubinaemia on admission (30% versus 12%, $p < 0.001$). The odds of a patient with hyperbilirubinaemia having simple acute appendicitis were over three times higher than those without hyperbilirubinaemia [odds ratio (or): 3.1429]. The specificity of hyperbilirubinaemia for simple acute appendicitis was 88% and its positive predictive value was 88.89% (Table 3).

Table 1: Distribution of patients into groups based on histology.

Group	Description	Total N (%)	Number of patients with hyperbilirubinaemia N (%)
1	No acute inflammation	25 (18)	3 (12)
2	Acute appendicitis	80 (53)	24 (30)
3	Acute appendicitis with inflammatory infiltrate Extending through full thickness of appendiceal wall	21 (15)	8 (40)
4	Perforated or gangrenous appendix	14 (10)	10 (70)
Total		140	46

Table 2: Levels of bilirubin.

Group	Description	Mean bilirubin (mg) (range)
1	No acute inflammation	0.5 (0.1-0.7)
2	Acute appendicitis	0.8 (0.1-4)
3	Acute appendicitis with inflammatory infiltrate extending through full thickness of appendiceal wall	1 (0.2-2.5)
4	Perforated or gangrenous appendix	1.5 (0.4-4.3)

Patients with a perforated or gangrenous appendix (group-4) had higher mean bilirubin levels than those with simple acute appendicitis (1.5mg versus 0.8 mg, $p=0.01$). More patients with a perforated or gangrenous appendix had hyperbilirubinaemia than those with simple acute appendicitis (70% versus 30%, $p<0.001$) and the

odds of a patient with hyperbilirubinaemia having a perforated or gangrenous appendix were over five times higher (or 5.83).

The specificity of hyperbilirubinaemia for a perforated or gangrenous appendix was 70% (Table 4).

Table 3: Values of bilirubin and WBC for differentiating simple acute appendicitis from non-inflamed appendix.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Likelihood ratio +ve (95% CI)	Likelihood ratio -ve (95% CI)	Prevalence (%)	Accuracy (%)
Bilirubin	30	88	88.89	28.21	2.50	0.80	76.19	43.81
WBC	78	80	87	36	2	0.25		

Table 4: Values of bilirubin and WBC for differentiating simple acute appendicitis from perforated or gangrenous appendix.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Likelihood ratio +ve (95% CI)	Likelihood ratio -ve (95% CI)	Prevalence (%)	Accuracy (%)
Bilirubin	71.43	70	29.41	93.33	2.38	0.41	14.89	70.21
WBC	91	15.8	11	93	1.02	0.28		

The specificity of WBC for simple acute appendicitis was 80% and for appendiceal perforation or gangrene was 15.8%.

No significant difference in the mean levels of any of the other LFT's between patients with simple acute appendicitis and those with non-inflamed appendices, or between patients with a perforated or gangrenous appendix and those with simple acute appendicitis was noted.

Bacterial cultures

A positive blood culture was detected in 11 of the 52 patients (20%). The prevalence of elevated bilirubin was significantly higher in those patients with a positive blood culture compared to those with a negative blood culture ($p=0.008$)

A total of 81 intraperitoneal fluid swabs were taken intraoperatively for bacterial culture, of which 30 (37%)

yielded a positive culture. The common organisms cultured were *Escherichia coli* and bacteroides present in 66% and 34% of positive cultures respectively.

DISCUSSION

Appendicitis is most often uncomplicated. Whereas nonperforated acute appendicitis can be treated by appendectomy followed by a short recovery period, a perforated appendicitis may be a life-threatening condition. Hence early diagnosis of perforation improves outcome, and allows the surgeon to operate early and prepare for a potentially difficult procedure.

Hyperbilirubinemia in sepsis is well recognised entity and has been associated with a variety of causative bacteria, gram-negative bacteria being most commonly implicated.^{4,5}

Several mechanisms leading to hyperbilirubinaemia in systemic infections have been described. Sisson et al demonstrated that mucosal ulceration in appendicitis occurs early in the evolution of the disease before dilation of the appendix.⁶ This facilitates invasion of the bacteria into muscularis propria of the appendix, causing classical acute suppurative appendicitis. Subsequent events cause a nonspecific host immune response, which leads to edema, elevated intraluminal pressure, and subsequent ischemic necrosis of mucosa, causing tissue gangrene and perforation.^{7,8}

Elevated levels of bacteria in the appendix cause either the 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 the bacterial endotoxin and is biochemical in nature rather than obstructive.

Table 5: Data from studies, sensitivity and specificity of hyperbilirubinemia as marker of appendix perforation.

Study	Patients with perforated appendix	Sensitivity (%)	Specificity (%)
Estrada ⁹	41	-	-
Sand ¹⁰	97	70	86
Atahan ¹¹	45	77	87
Emmanuel ¹²	45	60	70
Present study	14	71.43	70

This study shows that hyperbilirubinemia is an independent predictor of appendiceal perforation, with nearly a fivefold risk of perforated appendicitis in patients with total bilirubin levels greater than 1.5 mg/dl. In addition, specificity and positive predictive value of bilirubin were considerably higher compared with WBC.

Sensitivity was slightly lower, however, it still was acceptable compared with WBC.

There have been several reports of hyperbilirubinaemia in appendicitis (Table 5).⁹⁻¹² Estrada et al hypothesised that hyperbilirubinaemia may be associated with appendiceal perforation and showed that more patients with a perforated or gangrenous appendix had hyperbilirubinaemia than those with simple acute appendicitis. Sand et al showed that hyperbilirubinaemia had a specificity of 86% for appendiceal perforation or gangrene, compared with a specificity of only 35% for CRP.¹³ Present study results are in consistent with above mentioned studies.

CONCLUSION

No single clinical or laboratory test is able to reliably predict appendicular perforation therefore, obtaining serum bilirubin values upon admission in conjunction with history, clinical examination and laboratory and radiological investigations is used to make the diagnosis and decide appropriate management. Also hyperbilirubinemia alone is not a strong enough predictor, but might be more useful when integrated into a scoring system.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Gopalreddy D, Jadhav DL, Kannavar S. Hyperbilirubinemia as a diagnostic tool in patients with perforated appendicitis: a prospective study. *Int Surg J* 2020;7:1728-32.