Original Research Article

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Diagnostic value of serum bilirubin in appendicular perforation

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ABSTRACT

Background: Hyperbilirubinemia has been well documented in relation to acute appendicitis. This study tries to establish the diagnostic value of this parameter in determining the severity of acute appendicitis.

Methods: This is a prospective analytical study conducted on 100 patients with acute appendicitis. All patients were subjected to clinical evaluation and investigations; including liver function tests. The diagnosis was confirmed perioperatively and postoperatively by histopathological examination. The data was compiled and analysed.

Results: The incidence of complicated appendicitis was found to be 18%, defined as evidence of gangrene, or microscopic or gross perforation on histopathological examination. Among these total serum bilirubin (TSB) was raised in 17 cases (17%) and statistically significant correlation was established by p-value <0.001. The mean of TSB level was higher in perforated appendicitis than in cases of acute appendicitis (0.57±0.26 mg/dL; range 0.1-1.2 versus 1.68±1.09 mg/dL; range 0.8-4.8 mg/dL). TSB was shown to have specificity of 96.4%, sensitivity 88.2%, PPV 83.3% and NPV was 97.6%. The diagnostic accuracy of raised bilirubin for diagnosis of appendicular perforation was calculated to be 95.0%. The rise in bilirubin was mixed in type (both indirect and direct). There could not be established any correlation between the liver enzymes and appendicitis or its complications.

Conclusions: This study ascertains the predictive value of serum bilirubin in acute appendicitis patients as an indicator of severity. Raised bilirubin in the setting of acute appendicitis identifies higher probability of appendicular perforation.

Keywords: Appendicitis, Appendicular perforation, Bilirubin, Jaundice

INTRODUCTION

Acute appendicitis is the most common acute abdominal condition in young adults.¹ It is estimated that as much as 6% to 7% of the general population will develop appendicitis during their lifetime, with the incidence peaking in the second decade of life.² Despite its high prevalence, the diagnosis of acute appendicitis remains challenging and requires a high index of suspicion on the part of the examining surgeon to facilitate prompt treatment of this condition. Symptomatology, physical examination findings, a variety of laboratory tests, ultrasonography and computed tomography (CT) scans have all been employed in the diagnosis of acute appendicitis, with accuracies up to 85 to 99%.³

Any delay in diagnosis and surgery for a complicated appendicitis results in significant morbidity and mortality. The mortality rate in non-perforated appendicitis is less than 1%, but it may be as high as 5% when perforation occurs.⁴ It is because of this fear of progression to perforation, surgeons historically have accepted a certain rate of "negative" appendectomies to ensure that they do not fail to operate on patients, especially those with atypical presentations, in a timely fashion.

For this purpose, various inflammatory markers such as WBC count, C-reactive protein, amyloid, interleukin-6 and bilirubin have been investigated as adjuncts for the

diagnosis of appendicular perforation, with inconclusive results.^{5,6}

Jaundice in the context of appendicitis has been well described in the literature over 60 years ago, but it is only recently that hyperbilirubinemia has emerged as a new diagnostic tool for the perforation of appendix.7 High bilirubin levels have often been noted not only in appendicitis but also in other inflammatory conditions of the abdomen, suggesting a relationship might exist between severity of infection/inflammation and serum bilirubin. It is postulated that elevated serum bilirubin occurs as a result of portal sepsis or empyema resulting in liver hepatocytes dysfunction or damage.^{8,9} This is thought to be caused by bacterial endotoxins or cytokines. The result is either a direct damage to hepatocytes, cholestasis, both leading or hyperbilirubinemia. Furthermore, endotoxins are shown to result in hemolysis, which then adds further increase in bilirubin levels.

This recognition of an easy and widely available diagnostic aid for the identification of the dreaded complications of appendicitis warrants further research and quantification before its application as a routine tool for driving management decisions in appendicitis can be justified. The present study has been designed to evaluate the association between hyperbilirubinemia in cases of acute appendicitis in a tertiary care centre and evaluate its credibility as a diagnostic marker for appendicular perforation.

METHODS

This is a prospective study of patients admitted under various surgical units in Victoria Hospital and Bowring and Lady Curzon Hospital, who underwent appendectomy for acute appendicitis in the emergency setting, from November 2014 to October 2016. Of the 105 patients recruited in the study, 5 were excluded (1 patient found to be HbsAg positive, 3 patients with history of chronic alcoholism, and 1 patient with finding of cholelithiasis in USG), thus leading to the final sample of 100 patients.

Data collection

The patients are subjected to complete general physical examination, relevant laboratory investigations such as complete blood count, renal function tests, qualitative HBsAg test and liver function tests and ultrasonography. The patients diagnosed as acute appendicitis were subjected to prompt surgical within 8 hours of admission. The appendectomy was performed via an open approach using McAurthur-McBurney's incision. Laparoscopic appendectomy was avoided to prevent undue handling of the appendicular specimen during extraction, for more accurate histopathological analysis. The specimen thus removed is sent for histopathological examination, and the report obtained is treated as the definitive diagnosis.

5 patients with possible hyperbilirubinemia of other origins were excluded after application of exclusion criteria

Exclusion criteria

- All patients documented to have a past history of:
- a) Jaundice or liver disease
- b) Chronic alcoholism (i.e. intake of alcohol of >40 g/day for men and >20 g/day in women for 10 years)
- c) Hemolytic disease
- d) Acquired or congenital biliary disease
- All patients with positive HBsAg
- All patients with cholelithiasis on USG
- All patients with cancer of hepato-biliary system.

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 intraluminal and mucosal inflammation (A)
- Group 2: acute appendicitis with transmural infiltration and microscopic perforation (MP)
- Group 3: gangrenous and/or necrotic appendicitis (G)
- Group 4: perforated appendicitis (P).

Clinically, these four groups were simplified into two groups i.e., non-perforated (group 1) and perforated (groups 2, 3 and 4).

The clinic-pathological characteristics and laboratory values for each group were compared to each other. The standard values were given based on the reference of our institute as follows (Table 1).

Table 1: Normal laboratory values.

Serum Bilirubin	
Total	0.0- $1.0 mg/dL$
Direct	0.0- 0.2 mg/dL
Liver enzymes	
Alkaline phosphatase (ALP)	80-200 IU/L
Aspartate transaminase (AST/SGOT)	0-45 IU/L
Alanine transaminase (ALT/SGPT)	0-50 IU/L

Continuous variables are presented as mean±SD, and categorical variables are presented as absolute numbers and percentage. Data were checked for normality before being subjected to statistical methods like mean, standard deviation, proportion, percentage calculation using Microsoft Excel® (Microsoft, Redmond, WA, US). All statistical analysis was performed using SPSS Software v.20. Factors potentially presenting the severity of acute appendicitis were assessed using one-way analysis of variance and included the total bilirubin, direct bilirubin, ALP, AST and ALT. For the analysis of significance, the

four groups were dichotomized into non-perforated (group 1) and perforated (groups 2, 3 and 4) groups and the data were evaluated using the chi-square test. Results were compared using the chi-square test. In case of global relevance, the Mann-Whitney U test was used to compare different groups of non-normal data. All analyses were two-sided, with significance set at P-value less than 0.05.

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

Among the 100 patients who underwent an appendectomy due to acute appendicitis, 60 patients were men (60%) and 40 were women (40%). The incidence of complicated appendicitis was found to be 21.67% in males and 14.28 % in females. The range of age distribution was 15 years to 65 years. Majority of the patients were in the age group of 15-30 years, with mean age as 29.42 ± 11.89 years. The median for age was found to be more representative at 25 years.

Of all cases diagnosed as acute appendicitis preoperatively, 82 had acute appendicitis, 4 showed evidence of microscopic perforation, 2 had gangrenous appendix, 12 cases had perforated appendix. Thus, on the basis of histopathological examination 82 cases were designated as group 1 and 18 cases as group 2 (complicated appendicitis) (Figure 1 and 4).

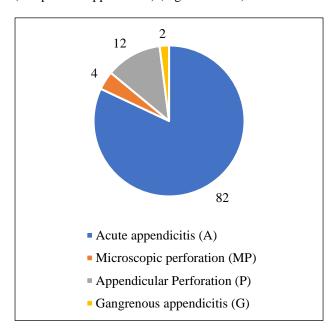
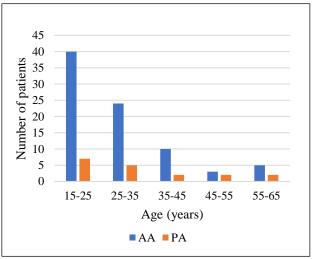


Figure 1: Distribution of histopathology groups.

The male and female patients were found to be evenly distributed among the two groups, i.e. complicated and uncomplicated appendicitis. However, a higher incidence of appendicular perforation was found in the older age group (33% in age group > 45 years) (Figure 2).



(AA): Acute appendicitis; (PA): Complicated appendicitis

Figure 2: Age distribution in the two groups.

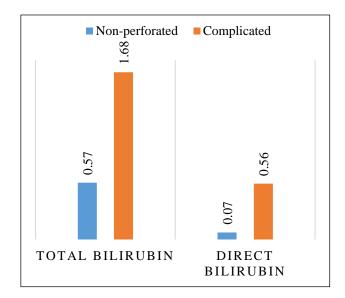


Figure 3: Average values of Bilirubin in AA versus PA (in md/dL).

Liver enzymes and bilirubin levels were correlated with the existing pathology. ALP levels were found to be normal or minimally elevated. No significant rise in ALT and AST levels was noted. Evaluation with chi-square test failed to show any statistically significant correlation for all the three enzymes (p >0.05) (Table 2).

Among 100 cases, total Serum Bilirubin (TSB) was raised in 17 cases whereas 83 cases had normal TSB level. The mean of TSB for the entire population was found to be 0.77 mg/dL (SD 0.67, range 0.0 to 4.8). the values were higher in group 2 complicated appendicitis (microscopic perforation + gangrenous appendix + perforation) than those in acute appendicitis. The mean of TSB in AA cases was 0.57 mg/dL (SD 0.26; range 0.1-

1.2) and the mean of TSB in PA was 1.68 mg/dL (SD 1.09; range 0.8-4.8 mg/dL). Using Man-Whitney U test, the relation between elevated total bilirubin levels and

perforation in acute appendicitis was found to be statistically significant (P < 0.001) (Figure 3).

Table 2: Mean values of liver enzymes.

(In IU/L)	AA	PA	Total
ALP	88.82 (SD 49.40)	154.67 (SD 82.38)	100.67 (SD 62.15)
AST	26.88 (SD 9.09)	33.28 (SD 12.76)	28.03 (SD 10.15)
ALT	26.88 (SD 9.05)	21.61 (SD 7.27)	24.2 (SD 8.83)

For diagnosis of PA, total serum bilirubin showed the specificity of 96.38%, sensitivity of 88.23%, and positive predictive value of 83.34% and negative predictive value of 97.56%. The diagnostic accuracy was calculated to be 95.0%.

In the study group, 4 cases of microscopic perforation, defined as the presence of transmural infiltration and microscopic breach in mucosa and serosa, were noted. In three of these cases, increase in total bilirubin was noted. This yielded a sensitivity and specificity of 75 % and 97.56 % for differentiating between AA and cases of impending perforation. However, the statistical correlation using chi-square test was not found to be significant (p \sim 0.29).

DISCUSSION

Acute appendicitis is a common surgical emergency. Non-perforated acute appendicitis can be cured by an appendectomy without a long recovery period, whereas perforated appendicitis or suppurative appendicitis can cause various complications that can result in lifethreatening 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. Although the reported diagnostic accuracy of sonography varies depending on the patient population studied, a metaanalysis showed an overall sonographic sensitivity of 85% and a specificity of 92%. 10 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%. 3,10 However, a recent analysis by Pritchett et al, 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.¹¹

In the present study of 100 patients, hyperbilirubinemia was found in 17 cases, of which 15 patients were

diagnosed with complicated appendicitis (true positives), i.e. either grossly perforated or gangrenous, or with microscopic evidence of the same. The average value for the two groups AA and PA was 0.57 mg/dL (±0.26 SD) and 1.68 mg/dL (±1.09 SD), respectively. This hyperbilirubinemia was mixed in type (both conjugated and unconjugated) in most of the patients. At the same time, there was no elevation or minimal elevation in ALT and AST in most of the cases. Similarly, ALP was either within the normal range or was minimally elevated.

For gangrenous/perforated appendicitis, the P-value of total serum bilirubin was <0.001 (CI 95%, highly significant correlation). 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. The implications being that elevated bilirubin levels are strongly indicative of appendicular perforation/gangrene, though normal levels do not rule out the same. The overall diagnostic accuracy being 95.0%.

The level of TSB was higher than 1 mg/dL in cases of gangrenous/perforated appendicitis while in cases with acute appendicitis it was lower than 1 mg/dL (P<0.05). Broadly, we can say that it was predominantly isolated hyperbilirubinemia.

Miller et al. first reported that jaundice was common in patients with severe appendicitis. 12 Recently, Sand et al. reported a relatively high incidence of hyperbilirubinemia (24.9%) from an analysis of 538 acute appendicitis patients, of whom 50.7% were verified as having perforated appendicitis. 13 Present data showed a relatively lower incidence of perforation (18%) among the appendicitis patients. The incidence hyperbilirubinemia among the perforated patients was found to be high at 84%. Since these findings were documented at the time of admission, it is unlikely that liver injury because of anaesthetic agents, blood transfusion, or medication was the cause of elevated bilirubin levels. Moreover, as per the exclusion criteria patients with alcoholic liver disease, viral hepatitis, haemolytic or congenital liver diseases were excluded from the study.

Concerning the pathophysiology of hyperbilirubinemia in acute appendicitis, there are some hypotheses. The most likely explanation of the rise in TSB is circulating endotoxemia as a result of appendicular infection.¹² It was demonstrated by Sisson et al. in 1971 that in appendicitis mucosal ulceration occurs early and this facilitates invasion of bacteria into the muscularis propria of the appendix thereby causing classical acute suppurative appendicitis.¹⁴ Subsequent events lead to ischemic necrosis of mucosa, causing tissue gangrene and perforation. It is postulated that portal sepsis or empyema results in either a direct damage to hepatocytes, cholestasis, or both leading to hyperbilirubinemia. The depression of is associated with elevated levels of circulating pro-inflammatory cytokines such as TNF and IL-6. Furthermore, endotoxins are shown to result in hemolysis, which then adds further increase in bilirubin levels.

Present study shows that isolated hyperbilirubinemia without much elevation in the liver enzymes is a significant predictor of appendicular perforation. This was demonstrated by a study by Estrada et al. and other studies showing nearly a threefold risk of perforated appendicitis in patients with total bilirubin levels greater than 1 mg/dL.^{8,15,16}

CONCLUSION

The present study investigated hyperbilirubinemia as a predictive marker for appendicular perforation. It was deduced that patients with appendicular perforation have significantly higher bilirubin levels than patients with uncomplicated appendicitis. Serum bilirubin estimation, a routinely available and cost-effective test can prove valuable for the preoperative identification of appendicular perforation. There is sufficient evidence to support its addition to the routine panel of investigations for acute appendicitis, to be used as a guide to clinical assessment and decision making.

Furthermore, in an era that is inclining towards more conservative management of simple appendicitis cases, the intent is to develop a tool to help in the diagnosis of appendicular complications and prompt targeted early operative intervention.¹⁷

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Ethical approval: The study was approved by the

institutional ethics committee

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