



THE UTILITY OF SERUM BILIRUBIN AS A MARKER IN ACUTE ABDOMEN

General Surgery

P N Sreeramulu Professor General surgery

Dr Shashidhar K N* Professor biochemistry *Corresponding Author

Varsha A Senior Resident General surgery

ABSTRACT

BACKGROUND: Delay in diagnosis leads to various complications like perforation, abscess formation. Evaluation of serum bilirubin helps in diagnosis of complications, like perforation, morbidity, wound infection, prognosis associated with acute abdomen. The aim of the study is to evaluate serum bilirubin levels to predict complications prior to surgery.

METHODS: This is a descriptive cross-sectional study which includes 164 study subjects diagnosed with acute abdomen such as appendicitis, peritonitis, cholecystitis. All study subjects were subjected to clinical evaluation, Laboratory investigations such as liver function tests, ultrasound and x ray abdomen in erect posture. The data was compiled and analysed. The Fisher's exact, Pearson's χ^2 , ANOVA, and Kruskal–Wallis tests while logistic regression for multivariate analysis was performed. $p < 0.05$ was accepted as statistically significant

Results: In our study patients diagnosed with acute appendicitis 35 cases showed elevated WBC count mean $9.81 \pm SD 3.254$. 7 cases showed raised TDB $0.50 SD \pm 0.526$. In acute appendicitis with perforation 25 cases had raised WBC counts mean $12.13 \pm SD 3.764$. 3 cases had increased levels of TDB mean $1.32 \pm SD 0.9333$. WBC, TDB levels are increased among patients with acute appendicitis with perforation compared to patients with acute appendicitis which is statistically significant ($p=0.002$ and 0.001 respectively).

Conclusion: Hyperbilirubinemia, especially with elevated direct bilirubin levels, may be considered as an important marker for the prediction of appendiceal gangrene/perforation which is cost effective in a rural set up where CT scan cannot be performed.

KEYWORDS

Acute abdomen, Perforation, cholecystitis, appendicitis

INTRODUCTION

Appendicitis is a result of a bacterial infection in the appendix and is a frequent cause of abdominal pain and of hospital admissions. Usually, clinical symptoms are enough to hint the diagnosis; however, a diagnosis can only be confirmed upon surgery with subsequent pathological evaluation. Several blood markers, including bilirubin, C-reactive protein (CRP), and white blood cell (WBC) count may be increased in patients with appendicitis and even more in patients suffering from perforated appendicitis.¹⁻⁶ Identifying perforated clinical appendicitis depends on clinical examination supported by raised inflammatory and biochemical markers. An early diagnosis of perforation improves outcomes, allowing the surgeon to prepare for a relatively difficult procedure.⁷

A biological marker or biomarker can be defined as an objectively, measurable characteristic that previous research has validated as a marker of a normal physiology, disease or the disease's response to treatment.⁸ The use of biomarkers in basic and clinical research as well as in clinical practice has become so commonplace that their presence as primary endpoints in clinical trials is now accepted almost without question.⁹ The use of clinical biomarkers is easier and less expensive than direct measurement of the final clinical endpoint, and biomarkers are usually measured over a shorter time span. They can be used in disease screening, diagnosis, characterization, and monitoring; as prognostic indicators; for developing individualized therapeutic interventions; for predicting and treating adverse drug reactions; for identifying cell types; and for pharmacodynamic and dose–response studies.¹⁰

There has been much research into hyperbilirubinaemia in cases of perforated appendicitis, but these studies do not extend to also include CRP levels, which is interesting considering that it remains a part of many work–up investigations.¹¹⁻¹³ An investigation by Kaser *et al.* looking at the usefulness of CRP and bilirubin in predicting a perforated appendix revealed that both CRP and bilirubin are raised significantly in perforations, but that CRP was more useful in predicting perforations. While this research highlighted the usefulness (or lack thereof) of measuring the white cell count, it did not investigate the individual differentiated white cell counts and their ability to predict appendicitis.¹⁴

Hyperbilirubinemia has often been noted not only in appendicitis but also in other inflammatory conditions of the abdomen, suggesting that a certain relationship might exist between bacteria and serum bilirubin.^{15,16} Hence in the present study we aimed to establish the role of hyperbilirubinemia to predict of either gangrenous/perforated

appendicitis and gall bladder as well as to compare other parameters in a similar role.

MATERIALS AND METHODS:

We performed a prospective study of various surgical patients presenting with acute abdomen to the emergency department of R L Jalappa hospital from 2017 to 2018. A total of 164 study subjects are included in study diagnosed with appendicitis, hollow viscus perforation and cholecystitis. Patient with chronic liver disease, HbsAg positive were excluded from the study. The study was approved by the Ethics Committee of our institution, and signed informed consent forms were obtained from all patients.

The patients were subjected to complete general physical examination, relevant laboratory investigations such as, complete blood count, renal function tests, qualitative hBsAg test and liver function test and ultrasonography. WBC, normal range $4000-10,000/mm^3$, Total bilirubin (normal range $0.0-1.2$ mg/dL), direct bilirubin (normal range $0.0-0.2$ mg/dL), indirect bilirubin (normal range $0.2-1.0$ mg/dL) levels were used as reference range. The patients diagnosed as appendicitis, perforation or cholecystitis were subjected to prompt surgery within 8 hours of admission. The appendectomy was performed via open or laparoscopic approach, graham's omental patch closure for hollow viscus perforation and open/ laparoscopic cholecystectomy for cholecystitis. The specimen removed was sent for histopathological examination, and the report obtained is treated as the definitive diagnosis and the postoperative histopathological findings of the patients were recorded and evaluated.

RESULTS:

A total of 164 patients with a preoperative diagnosis of acute appendicitis peritonitis secondary to hollow viscus perforation and acute cholecystitis and were included in study and divided into the three groups based on histological and clinical findings.

Among the 164 patients who presented with acute abdomen 86 patients were females, 78 were males. Further 84 (51%) patients were diagnosed with acute appendicitis. 38 (23%) were with appendicitis with perforation. 26 (15%) with peritonitis secondary to hollow viscus perforation grouped (9.7%) with acute cholecystitis. Among 86 females 49 (56%) were diagnosed with appendicitis, 16 (18.6%) were diagnosed with appendicitis with perforation 10 (11.6%). 12 (13.9%) with acute cholecystitis, 10 (13.9%) with peritonitis due to perforation.

In patients diagnosed with acute appendicitis 35 cases showed elevated WBC count mean (9.81) $SD \pm 3.254$. 7 cases showed raised TDB $0.50 SD \pm 0.526$. In acute appendicitis with perforation 25 cases

had raised WBC counts mean $12.13 \pm SD 3.764$. 3 cases had increased levels of TDB mean $1.32 \pm SD 0.9333$. Patients with peritonitis 11 cases had increased WBC counts mean $10.19 \pm SD 5.923$ and 3 cases had raised TDB mean $1.31 \pm SD 2.892$. Patients with acute cholecystitis 4 cases had raised WBC count mean 10.44 , 4 cases had raised TDB

Table 1 The comparison of the mean values of the preoperatively assessed blood test parameters among the three groups of patients according to their postoperative histopathological results

Preoperative parameters	Postoperative histopathological findings			
	Group 1 Acute appendicitis	Group 2 appendicitis with complications	Group 3 Bowel with Perforation	Group 4 cholecystitis
	Mean \pm SD	Mean \pm SD	Mean \pm SD	Mean \pm SD
WBC	9.81 \pm 3.254	12.13 \pm 3.764	10.44 \pm 3.959	10.19 \pm 5.924
TDB	0.50 \pm 0.526	1.32 \pm 0.933	0.96 \pm 1.207	1.31 \pm 2.892
SDB	0.31 \pm 0.465	0.45 \pm 0.602	0.40 \pm .577	0.13 \pm .342

The difference in mean WBC, TDB between groups is statistically significant. Whereas the difference in SDB across histopathological groups is not statistically significant.

WBC, TDB levels are increased among patients with acute appendicitis with perforation compared to patients with acute appendicitis which is statistically significant ($p=0.002$ and 0.001 respectively).

The mean difference in TDB levels among patients with acute appendicitis with perforation and acute cholecystitis also statistically significant ($p=0.011$).

The mean SDB levels among patients with acute appendicitis with perforation and acute cholecystitis also statistically significant ($p=0.035$).

DISCUSSION

Acute appendicitis is the most common suspected diagnosis of abdominal pain in the emergency department, and the single most common illness requiring emergency surgery.^{17,18} Despite the increase in diagnostic modalities such as ultrasonography and computed tomography, the rates of appendicitis misdiagnosis (15%) and appendiceal rupture have remained constant.¹⁹

In our study majority patients were diagnosed with acute appendicitis, and others were presented with appendicitis with perforation and female patients were more prevalent than males. These results were contrast with study by Mubashir M et al. where males were in majority than females.²⁰ Hyperbilirubinemia has been studied in various infectious disease including intra-abdominal infections. Hyperbilirubinemia in cases of appendicitis is hypothesized to be due to bacteraemia or endotoxemia causing impaired excretion of bilirubin from the bile canaliculi.²¹

Ambre SR et al. found that hyperbilirubinemia can be considered as a supportive index to diagnose the acute appendicitis²² where as in our study WBC, TDB levels were increased among patients with acute appendicitis with perforation compared to patients with acute appendicitis which is statistically significant ($p=0.002$ and 0.001 respectively). Present study results matched with study by Sand M et al. as they found that Patients with appendiceal perforation, however, had a mean bilirubin level of $1.5 \text{ mg/dL } (+/- .9 \text{ SD mg/dL; range, } 4.4\text{-}3 \text{ mg/dL; median, } 1.4 \text{ mg/dL})$, which was significantly higher than those with a nonperforated appendicitis ($P < .05$) and concluded that 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.²³ Similarly Eren T et al. study showed according to multivariate analysis elevated direct bilirubin levels were associated with 36 times greater risk for appendiceal gangrene/perforation ($p < 0.01$, $p < 0.05$, $p < 0.01$, respectively).²⁴ Hong YR et al. multivariate analysis demonstrated that total bilirubin (odds ratio, 1.772; 95% confidence interval, 1.320 to 2.379; $P = 0.0001$) and SIRS score (odds ratio, 1.583; 95% confidence interval, 1.313 to 1.908; $P < 0.0001$) had statistically significant diagnostic value for perforated appendicitis.²⁵ Also another prospective study results gave alike findings that Hyperbilirubinemia with a cutoff point of $>1.3 \text{ mg}\%$ for appendiceal perforation had a sensitivity of 80%, specificity of 89%, a positive predictive value of 93%, and a negative

predictive value of 96%. By which a conclusion was drawn that hyperbilirubinemia with bilirubin levels more than $1.3 \text{ mg}\%$ were highly predictive of appendiceal perforation.²⁶ These findings from previous literature were in favour of the present study findings.

CONCLUSION

We conclude that Hyperbilirubinemia, especially with elevated direct bilirubin levels, should be considered as an important marker for the prediction of appendiceal gangrene/perforation which is cost effective in a rural set up where CT scan cannot be performed. Patients with hyperbilirubinemia and having clinical symptoms of appendicitis should be identified as having a higher probability of appendiceal perforation than those with normal bilirubin levels since clinical diagnosis and hyperbilirubinemia go hand in hand with each other.

REFERENCES

- Lau WY, Teoh-Chan CH, Fan ST, Yam WC, Lau K, Wong S. The bacteriology and septic complication of patients with appendicitis. *Ann surg.* 1984;200(5):576.
- Bennion RS, Baron EJ, Thompson Jr JE, Downes J, Summanen P, Talan DA, et al. The bacteriology of gangrenous and perforated appendicitis-revisited. *Ann surg.* 1990;211(2):165.
- Chen C-Y, Chen Y-C, Pu H-N, Tsai C-H, Chen W-T, Lin C-H. Bacteriology of acute appendicitis and its implication for the use of prophylactic antibiotics. *Surg infect.* 2012;13(6):383-90.
- Humes D, Simpson J. Acute appendicitis. *Bmj.* 2006;333(7567):530-4.
- Andersson R. Meta-analysis of the clinical and laboratory diagnosis of appendicitis. *Br J Surg.* 2004;91(1):28-37.
- Lintula H, Kokki H, Pulkkinen J, Kettunen R, Gröhn O, Eskelinen M. Diagnostic score in acute appendicitis. Validation of a diagnostic score (Lintula score) for adults with suspected appendicitis. *Langenbeck's archives of surgery.* 2010;395(5):495-500.
- Korner H, Sondenaa K, Soreide JA, Andersen E, Nysted A, Lende TH, et al. Incidence of acute nonperforated and perforated appendicitis: age-specific and sex-specific analysis. *World J Surg.* 1997;21(3):313-7.
- Group BDW, Atkinson Jr AJ, Colburn WA, DeGruttola VG, DeMets DL, Downing GJ, et al. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin Pharmacol Ther.* 2001;69(3):89-95.
- Strimbu K, Tavel JA. What are biomarkers? *Curr Opin HIV AIDS.* 2010;5(6):463.
- Aronson JK, Ferner RE. Biomarkers-A General Review. *Curr Protoc Pharmacol.* 2017;76:9.23.1-9.17.
- Khan S. Elevated serum bilirubin in acute appendicitis: a new diagnostic tool. *Kathmandu Univ Med J.* 2008;6(2):161-5.
- Sand M, Bechara FG, 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(2):193-8.
- Estrada JJ, Petrosyan M, Barnhart J, Tao M, Sohn H, Towfigh S, et al. Hyperbilirubinemia in appendicitis: a new predictor of perforation. *J Gastrointest Surg.* 2007;11(6):714-8.
- Kaser SA, Fankhauser G, Willi N, Maurer CA. C-reactive protein is superior to bilirubin for anticipation of perforation in acute appendicitis. *Scand J Gastroenterol.* 2010;45(7-8):885-92.
- Ger R. Hyperbilirubinemia due to intraperitoneal sepsis. *N Y State J Med.* 1972;72(19):2407-13.
- Nishida T, Fujita N, Megawa T, Nakahara M, Nakao K. Postoperative hyperbilirubinemia after surgery for gastrointestinal perforation. *Surg Today.* 2002;32(8):679-84.
- Gaitini D, Beck-Razi N, Mor-Yosef D, Fischer D, Ben Itzhak O, Krausz MM, et al. Diagnosing acute appendicitis in adults: accuracy of color Doppler sonography and MDCT compared with surgery and clinical follow-up. *AJR Am J Roentgenol.* 2008;190(5):1300-6.
- Kearney D, Cahill RA, O'Brien E, Kirwan WO, Redmond HP. Influence of delays on perforation risk in adults with acute appendicitis. *Dis Colon Rectum.* 2008;51(12):1823-7.
- Akai M, Iwakawa K, Yasui Y, Yoshida Y, Kato T, Kitada K, et al. Hyperbilirubinemia as a predictor of severity of acute appendicitis. *J Int Med Res.* 2019;47(8):3663-9.
- Mubashir M, Raman A. Evaluation of Prevalence of Appendicitis at Surgery Department: A Descriptive Study. *Journal of Advanced Medical and Dental Sciences Research.* 2019;7(4):109-11.
- Franson TR, Hierholzer WJ, Jr., LaBrecque DR. Frequency and characteristics of hyperbilirubinemia associated with bacteremia. *Rev Infect Dis.* 1985;7(1):1-9.
- Ambre SR, Chavan S. Hyperbilirubinemia as a diagnostic marker for acute appendicitis. *International Surgery Journal.* 2018;5(6):2091-6.
- Sand M, Bechara FG, 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(2):193-8.
- Eren T, Tombalak E, Ozemir IA, Leblebici M, Ziyade S, Ekinci O, et al. Hyperbilirubinemia as a predictive factor in acute appendicitis. *Eur J Trauma Emerg Surg.* 2016;42(4):471-6.
- Hong YR, Chung C-W, Kim JW, Kwon CI, Ahn DH, Kwon SW, et al. Hyperbilirubinemia is a significant indicator for the severity of acute appendicitis. *J Korean Soc Coloproctol.* 2012;28(5):247.
- Kumar BA, Kalyan K, Rehman M. Perforation in acute appendicitis: evaluation of hyperbilirubinemia and elevated C reactive protein as a predictive factor. *IAIM.* 2017;4:18-23.