



ELEVATED LEVELS OF SERUM BILIRUBIN AS A MARKER IN A SERIES OF CASES OF COMPLICATED APPENDICITIS

Dr. Hridaynath Desai

Associate Professor, Dept. of General Surgery, Shri Vinoba Bhave Civil Hospital, Silvassa, India

Dr. G A Bharath

DNB Trainee, Dept. of General Surgery, Shri Vinoba Bhave Civil Hospital, Silvassa, India

Dr. Krishna Parmar

Consultant Surgeon, Dept. of General Surgery, Shri Vinoba Bhave Civil Hospital, Silvassa, India

ABSTRACT

Background: Appendicitis is one of the commonest causes of abdominal pain requiring emergency surgery. Often, it is difficult to reach a proper diagnosis. There may not be classical symptoms and signs of appendicitis. Accurate diagnosis can be aided by additional testing or expectant management or both. These might delay interventions and lead to appendiceal perforation with increased morbidity, mortality and hospital stay. Studies have shown that simple appendicitis has got mortality of 0.3% and perforated appendicitis 6%. Hyperbilirubinemia is a new diagnostic tool for predicting perforation of appendix. The aim of the study is to establish the role of hyperbilirubinemia as a new diagnostic tool to predict perforated appendicitis. **Methodology:** Prior permission and approval from the ethics committee will be obtained, and an informed written consent to participate in the study will be taken from all the patients. Demographic data of each patient will be recorded including relevant clinical examination findings, blood investigations and findings of conventional radiological imaging **Results:** In our study among Acute appendicitis subjects, 28% had Hyperbilirubinemia and majority were in the age group 21 to 30 years, there was significant association between Duration of symptoms and Hyperbilirubinemia as majority of patients with Hyperbilirubinemia has symptoms for 2 days, there was significant difference in mean LFT parameters between subjects with and without Hyperbilirubinemia, and there was significant difference in mean TLC between subjects with and without Hyperbilirubinemia. **Conclusions:** Total serum bilirubin level as a test for predicting gangrenous or perforated appendicitis is a less sensitive, highly specific with a high negative predictive value. Hence it is a valuable indicator in patients likely to have perforated or gangrenous appendicitis.

KEYWORDS :

INTRODUCTION

The importance of the vermiform appendix in surgery results primarily from its propensity for inflammation, which results in the clinical syndrome known as acute appendicitis¹. Appendicitis remains one of the most common diseases faced by the surgeon in practice². Despite its high prevalence in Western countries, the diagnosis of acute appendicitis can be challenging and requires a high index of suspicion on the part of the examining surgeon to facilitate prompt treatment of this condition, in some cases the sign and symptoms are variable and a firm diagnosis can be difficult³. This is particularly true where the appendix is retrocaecal or retroileal. The percentage of appendectomies performed where appendix subsequently found to be normal varies 15- 50% and postoperative complications can occur in up to 50% of these patients. Early diagnosis of Acute Appendicitis is necessary thereby avoiding the substantial morbidity (and even mortality) associated with perforation².

A safe alternative seems to do appendectomy as soon as the condition is suspected. Although such aggressive approaches mean that up to 30% of procedures are now classified as negative appendectomies, these are associated with negligible mortality and low (10%) morbidity. In cases of negative appendectomy, morbidity is generally related to the risks associated with incisional hernia or lifelong brid ileus; the patient's preoperative health does not represent a vital threat. Delayed diagnosis and treatment of perforated appendix, however, in patients with acute appendicitis may lead to several complications that are potentially life-threatening, such as peritonitis, sepsis, small-bowel obstruction, urinary retention and abdominal abscess formation. The concept of non-operative treatment for appendicitis developed from two lines of observations. First, for patients in an environment where surgical treatment is not available (e.g., submarines, expeditions in remote areas), treatment with antibiotics alone was noted to be effective.

Second, many patients with signs and symptoms consistent with appendicitis who did not pursue medical treatment would occasionally have spontaneous resolution of their illness¹⁰. A timelier and more accurate diagnosis has been attempted by the employment of additional laboratory tests, scoring systems, ultrasound imaging, computed tomography (CT) scan, MRI, and laparoscopy. None of these methods stands alone as they all come in support of, and are secondary to a primary clinical assessment.

Elevated serum bilirubin levels that are not explained by liver disease or biliary obstruction can be observed in many patients with acute appendicitis. A new diagnostic marker for perforation of appendix is Hyperbilirubinemia. Hyperbilirubinemia is the result of imbalance between synthesis and excretion of bilirubin by the liver. Portal blood carries nutrients and other substances absorbed from gut including bacteria and its product (toxins). It is cleared by detoxification and immunological action of the reticuloendothelial system of the liver that acts as first-line defense in clearing toxic substances, bacteria and its products. But when bacterial load overwhelms the Kupffer cell function, it may cause dysfunction or damage to hepatocytes (liver parenchyma). It reflects a rise in serum bilirubin alone or in combination with liver enzymes depending upon the type, severity and site of the lesion.

MATERIAL AND METHODS

The study will be of observational type of study.

Study Population:

Patients with clinically proven will be included with inclusion and exclusion criteria as mentioned below.

Inclusion Criteria:

patients with clinically proven acute appendicitis patients will be included

Exclusion Criteria:

- Patient who underwent Appendectomy previously.
- Alcoholism
- Subjects with appendicular lump formation
- A history of viral hepatitis
- BRIC (benign recurrent intra-hepatic cholestasis)
- Hemolytic or liver diseases (Genetic and acquired) associated with hyperbilirubinaemia.

METHODOLOGY:

Prior permission and approval from the ethics committee will be obtained, and an informed written consent to participate in the study will be taken from all the patients. Demographic data of each patient will be recorded including relevant clinical examination findings, blood investigations and findings of conventional radiological imaging in the Performa attached herewith. Routine blood investigations (Complete blood count), Liver Function Tests (LFTs), Seropositivity for HIV and HbsAg, Urine analysis, USG Abdomen. The results were grouped as "Normal or "Raised (hyperbilirubinemia) if total bilirubin more than 1.0 mg/dl. These cases will be operated and clinical diagnosis will be confirmed per-operatively and post-operatively by Histopathological examination. Final histopathological examination will be considered as a gold standard for diagnosing and categorizing patients as having normal appendix, acute appendicitis and acute appendicitis with perforation and/or gangrene. Based on histopathological examination patients were categorized as negative (acute appendicitis without perforation or gangrene) and positive (acute appendicitis with perforation and/or gangrene).

RESULTS:

In the study among Acute appendicitis subjects, 28% had Hyperbilirubinemia (i.e. Total bilirubin > 1mg/dl). majority were in the age group 21 to 30 years (47.6%) and among subjects without Hyperbilirubinemia, majority were in the age group 21 to 30 years (46.3%). There was no significant association between Hyperbilirubinemia and Age distribution. 61.9% were males and 38.1% were females and among subjects without Hyperbilirubinemia, 59.3% were males and 40.7% were females. There was no significant association between Gender and Hyperbilirubinemia. majority of them had symptoms for 2 days (52.4%) and among subjects without Hyperbilirubinemia, majority of them had symptoms for 1 day (37%). There was significant association between Duration of symptoms and Hyperbilirubinemia. There was significant association between Duration of symptoms and Hyperbilirubinemia.

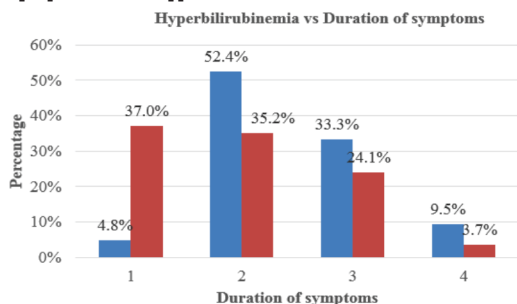


Figure 4: Bar diagram showing Association between Hyperbilirubinemia and Duration of symptoms

among subjects with Hyperbilirubinemia mean Direct bilirubin (mg/dl) was 1.45 ± 0.80 mg/dl, mean Indirect bilirubin (mg/dl) was 0.41 ± 0.30mg/dl, mean SGOT (IU/L) was 42.95 ± 15.62IU/L, mean SGPT (IU/L) was 46.19 ± 16.74IU/L and mean ALP was 98.33 ± 40.98IU/L.

Among subjects without Hyperbilirubinemia mean Direct bilirubin (mg/dl) was 0.51 ± 0.78mg/dl, mean Indirect

bilirubin (mg/dl) was 0.25 ± 0.14mg/dl, mean SGOT (IU/L) was 33.61 ± 11.73IU/L, mean SGPT (IU/L) was 32.72 ± 9.63IU/L and mean ALP was 63.13 ± 30.03IU/L. There was significant difference in mean LFT parameters between subjects with and without Hyperbilirubinemia.

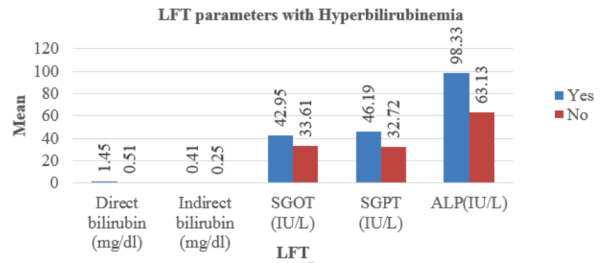


Figure 5: Bar diagram showing Comparison of LFT parameters with respect to Hyperbilirubinemia

52.4% had Acute appendicitis and 47.6% had perforated appendicitis. Among subjects without Hyperbilirubinemia, 100% had Acute appendicitis. There was significant association between Hyperbilirubinemia and Pre-Operative Clinical Diagnosis.

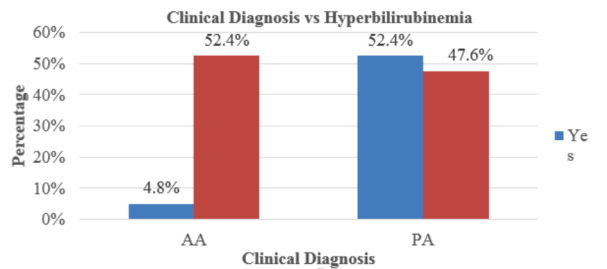


Figure 8: Bar diagram showing Association between Pre-Operative Clinical Diagnosis and Hyperbilirubinemia

among subjects with Hyperbilirubinemia, 52.4% had Acute appendicitis, 14.3% had Gangrenous appendicitis and 33.3% had perforated appendicitis. Among subjects without Hyperbilirubinemia, 94.4% had Acute appendicitis, 5.6% had perforated appendicitis. There was significant association between Hyperbilirubinemia and Per operative findings.

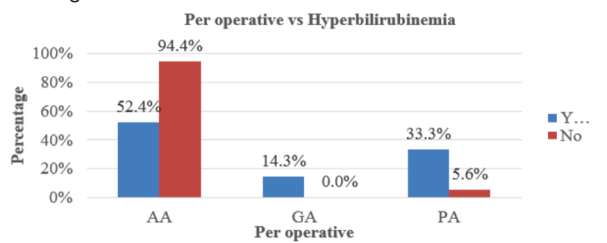


Figure 10: Bar diagram showing Association between Per operative findings and Hyperbilirubinemia

Criterion values and coordinates of the ROC curve

Criterion	Sensitivity	95% CI	Specificity	95% CI	+PV	-PV
≥ 0.2	100.00	75.3 - 100.0	0.00	0.0 - 5.8	17.3	
> 0.5	100.00	75.3 - 100.0	24.19	14.2 - 36.7	21.7	100.0
> 0.6	92.31	64.0 - 99.8	40.32	28.1 - 53.6	24.5	96.2
> 0.7	84.62	54.6 - 98.1	50.00	37.0 - 63.0	26.2	93.9
> 0.8	76.92	46.2 - 95.0	62.90	49.7 - 74.8	30.3	92.9
> 1.5	76.92	46.2 - 95.0	100.00	94.2 - 100.0	100.0	95.4
> 3.8	0.00	0.0 - 24.7	100.00	94.2 - 100.0		82.7

In the study mean Total Bilirubin at > 1.5 had highest sensitivity of 76.92%, specificity of 100%, Positive Predictive value of 100% and Negative Predictive value of 95.4% in diagnosis of complicated acute appendicitis.

DISCUSSION

This study is a single center prospective study conducted in department of general surgery, at Shri Vinoba Bhave Civil Hospital, Silvassa, UT of DNH. over a period of July 2020 to March 2022 on 75 patients admitted for acute appendicitis and underwent emergency appendectomy.

In our study of 75 patients of acute appendicitis, 45 patients (60%) were males while remaining 30 patients (40%) were females. In the study among Acute appendicitis subjects, This observation was similar to other studies. T. Eren et.al⁸ observed that 'of The study group of 162 patients consisted of 97 (60 %) men and 65 (40 %) women.

28% had Hyperbilirubinemia (i.e. Total bilirubin >1mg/dl). This observation was similar to other studies Vineed S et.al³ where Raised total serum bilirubin level (>1mg/dl) was reported in 28% cases and normal in 72 % of total cases.

In the study among subjects with Hyperbilirubinemia, 61.9% were males and 38.1% were females and among subjects without Hyperbilirubinemia, 59.3% were males and 40.7% were females. This observation was similar to Muzna Iftikhar et.al¹ Out of these 185 patients, 100 (54.05%) were male, and 85 (45.95%) were females with a ratio of 1:1.1. There was no significant association between Gender and Hyper bilirubinemia.

In the study among subjects with Hyperbilirubinemia, majority were in the age group 21 to 30 years (47.6%) and among subjects without Hyperbilirubinemia, majority were in the age group 21 to 30 years (46.3%). There was no significant association between Hyperbilirubinemia and Age distribution. This observation was similar to other studies Muzna Iftikhar et.al¹ where Majority of the patients 144 (77.84%) were 12-30 years of age.

In the study among subjects with Hyperbilirubinemia, majority of them had symptoms for 2 days (52.4%) and among subjects without Hyperbilirubinemia, majority of them had symptoms for 1 day (37%). There was significant association between Duration of symptoms and Hyperbilirubinemia. This observation was similar to the study done by Sabyasachi Bakshi et.al⁵, The mean duration of pain was shorter for subjects with an acute uncomplicated appendicitis (9.0 h \pm 5.12 range 6-12 h) compared to those with a gangrenous/perforated appendix (20.2 \pm 1.49 h, range 14-36 h), it reached statistical significance (p < 0.05).

In the study among subjects with Hyperbilirubinemia mean Direct bilirubin (mg/dl) was 1.45 \pm 0.80 mg/dl, mean Indirect bilirubin (mg/dl) was 0.41 \pm 0.30 mg/dl, mean SGOT (IU/L) was 42.95 \pm 15.62 IU/L, mean SGPT (IU/L) was 46.19 \pm 16.74 IU/L and mean ALP was 98.33 \pm 40.98 IU/L. This observation was similar to the study done by Sabyasachi Bakshi et.al⁵, The mean Total Bilirubin Level for all subjects with acute complicated appendicitis was 1.39 \pm 0.26 mg/dl (range being 0.68- 2.20 mg/dl) and the mean direct bilirubin was 0.72 \pm 0.13 mg/dl (range being 0.38-1.10 mg/dl), the mean Indirect Bilirubin was 0.66 \pm 0.14 mg/dl (range being 0.30-1.10 mg/dl), mean ALP 125.85 \pm 5.01 U/l (range 120-146 U/l p value > 0.05), mean AST 32.88 \pm 3.38 U/l (range 26-39 U/l p value > 0.05), mean ALT 32.77 \pm 2.75 U/l (range 28-38 U/l p value > 0.05).

Among subjects without Hyperbilirubinemia mean Direct bilirubin (mg/dl) was 0.51 \pm 0.78 mg/dl, mean Indirect bilirubin (mg/dl) was 0.25 \pm 0.14 mg/dl, mean SGOT (IU/L) was 33.61 \pm 11.73 IU/L, mean SGPT (IU/L) was 32.72 \pm 9.63 IU/L and mean ALP was 63.13 \pm 30.03 IU/L. This observation was similar to the study done by Sabyasachi Bakshi et.al⁵, The mean Total Bilirubin Level for all subjects with acute uncomplicated appendicitis was 0.79 \pm 0.16 mg/dl (range

being 0.45-1.20 mg/dl) and the mean direct bilirubin was 0.43 \pm 0.10 mg/dl (range being 0.20-0.70 mg/dl), the mean Indirect Bilirubin was 0.36 \pm 0.08 mg/dl (range being 0.16-0.60 mg/dl), mean ALP 126.04 \pm 7.42 U/l (range 112- 158 U/l), mean AST 33.70 \pm 2.99 U/l (range 26-39 U/l), mean ALT 33.34 \pm 2.71 U/l (range 27-40 U/l)

There was significant difference in mean LFT parameters between subjects with and without Hyperbilirubinemia.

Mean TLC among subjects with Hyperbilirubinemia was 18890.48 \pm 29126.22 cells/mm³ and among subjects without Hyperbilirubinemia was 10633.33 \pm 2928.97 cells/mm³. There was significant difference in mean TLC between subjects with and without Hyperbilirubinemia. This was similar to the study T. Eren et.al⁸ where WBC count, NEU count, and NEU% were detected to be significantly higher in cases of acute appendicitis when compared to cases having undergone negative appendectomies revealing the diagnostic sensitivity of these parameters (p < 0.01).

In the study among subjects with Hyperbilirubinemia, 52.4% had Acute appendicitis and 47.6% had perforated appendicitis. This was similar to the study Vineed S et.al³ where Raised total serum bilirubin level (>1mg/dl) was reported in 28% cases and normal in 72 % of total cases Of the 29 perforated appendicitis patients 19 (65.5%) patients had elevated bilirubin levels.

Among subjects without Hyperbilirubinemia, 100% had Acute appendicitis. There was significant association between Hyperbilirubinemia and Pre-Operative Clinical Diagnosis.

In the study all patients underwent ultrasonography imaging among subjects with Hyperbilirubinemia, 61.9% had Acute appendicitis, 9.5% had Gangrenous appendicitis, 14.3% had perforated appendicitis and 14.3% had NAD. Among subjects without Hyperbilirubinemia, 79.6% had Acute appendicitis, 3.7% had perforated appendicitis and 16.7% had NAD. There was significant association between Hyperbilirubinemia and Ultrasonography findings.

In the study Pre operative findings among subjects with Hyperbilirubinemia, 52.4% had Acute appendicitis, 14.3% had Gangrenous appendicitis and 33.3% had perforated appendicitis. Among subjects without Hyperbilirubinemia, 94.4% had Acute appendicitis, 5.6% had perforated appendicitis. There was significant association between Hyperbilirubinemia and Per operative findings.

In the study among subjects with Hyperbilirubinemia, on HPE 47.6% had Complicated Acute Appendicitis [Gangrenous or Perforated Appendicitis] and 52.4% had Non-Complicated Acute Appendicitis. Among subjects without Hyperbilirubinemia, on HPE 5.6% had Complicated Acute Appendicitis [Gangrenous or Perforated Appendicitis] and 94.4% had Non-Complicated Acute Appendicitis. There was significant association between Hyperbilirubinemia and HPE Diagnosis.

The sensitivity, specificity, positive predictive value and negative predictive value was calculated for the total serum bilirubin as a test for predicting gangrenous or perforated appendix using 2x2 table. The sensitivity and specificity of Hyperbilirubinemia as a marker in predicting perforated or gangrenous appendicitis with mean Total Bilirubin in >1.5 had highest sensitivity of 76.92%, specificity of 100%, Positive Predictive value of 100% and Negative Predictive value of 95.4% in diagnosis of complicated acute appendicitis.

ROC curve was drawn, area under the curve (AUC) was 0.872, it calculated a cutoff value for total serum bilirubin level >1.5 mg/dL for predicting complicated acute appendicitis. When

total serum bilirubin level was >1.5 mg/dL sensitivity and specificity of the test was 76.92% and 100% respectively.

Our study revealed that there is isolated increase in total serum bilirubin level without significant elevation in liver enzymes, is a significant predictor of perforated or gangrenous appendix ($p < 0.001$). Our study showed total serum bilirubin to have specificity of 100% and sensitivity of 76.92%, The negative predictive value was 95.4% comparable to study done by Poras Chaudhary et.al⁷ which showed 100%. This was also showed by Estrada et.al⁸ where there was three times the risk of having perforated or gangrenous appendix in patients with hyperbilirubinemia (>1.0mg/dL). Sand et.al⁹ showed that hyperbilirubinemia had a specificity of 86% for appendiceal perforation or gangrene. Hence in patients suspicious of perforation or gangrene elevation of serum bilirubin can be used as a test to diagnose and manage perforated or gangrenous appendicitis.

CONCLUSION

Our study concludes that

1. Total serum bilirubin was significantly elevated in patients with gangrenous and perforated appendicitis than those with acute appendicitis.
2. Total serum bilirubin level as a test for predicting gangrenous or perforated appendicitis is a less sensitive, highly specific with a high negative predictive value. Hence it is a valuable indicator in patients likely to have perforated or gangrenous appendicitis.
3. Total serum bilirubin should be used along with clinical examination and other laboratory investigations in the assessment of patients suspected of appendicitis.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgement: None

Authors' Contributions

All authors have equally contributed in designing of the study, data collecting, comparing the results with other publications and drafted manuscript.

REFERENCES

1. Bailey and Love's, Short practice of surgery, 27th edition.
2. Sabiston textbook of Surgery, The biological basis of modern surgical practice, 20th edition.
3. Vineed S, R. K. Hanumanth Naik. Diagnostic accuracy of hyperbilirubinemia in predicting perforated appendicitis, Government. Medical College, Thiruvananthapuram, Kerala, India. International Surgery Journal Vineed S et al. Int Surg J. 2017 Oct.
4. Muzna Iftikhar, Usman Qureshi, Jahangir Sarwar Khan and Salman Shafiqe, Hyperbilirubinemia as an indicator of complicated appendicitis, Holy Family Hospital, Rawalpindi, Pakistan. Research Gate, August 2019.
5. Sabyasachi Bakshil and Nilay Mandal, Evaluation of role of hyperbilirubinemia as a new diagnostic marker of complicated appendicitis, Bakshi and Mandal BMC Gastroenterol 2021.
6. T. Eren, E. Tombalak, I.A. Ozemir, M. Leblebici, S. Ziyade, O. Ekinci, O. Alimoglu. Hyperbilirubinemia as a predictive factor in acute appendicitis, Eur J Trauma Emerg Surg DOI 10.1007/s00068-015-0562-4.
7. Poras Chaudhary, Ajay Kumar, Neeraj Saxena, Upendra C. Biswal. Hyperbilirubinemia as a predictor of gangrenous/perforated appendicitis: a prospective study Postgraduate Institute of Medical Education and Research, Dr Ram Manohar Lohia Hospital (Dr RMLH and PGIMER), New Delhi, India. Annals of Gastroenterology (2013) 26, 325-331
8. Estrada JJ, Petrosyan M, Krumenacker J Jr, Huang S, Moh P. Hyperbilirubinemia in Appendicitis: A New Predictor of Perforation. Journal of Gastrointestinal Surgery 2007.
9. Michael Sand, M.D, Falk G. Bechara, M.D, Tim Holland-Letz, M.S, Daniel Sand, B.S, Gudrun Mehnert, M.D, Benno Mann, M.D. Diagnostic value of hyperbilirubinemia as a predictive factor for appendiceal perforation in acute appendicitis, The American Journal of Surgery (2009) 198, 193-198.
10. Schwartz's, Principles of Surgery, 11th edition.