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# Hyperbilirubinemia : A predictor for perforated appendicitis

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#### ABSTRACT

Background: Acute appendicitis is one of the most common surgical emergencies. The diagnosis of acute appendicitis done by clinically and aided by blood investigation and imaging techniques. To avoid life threatening complications early diagnosis and treatment necessary. The physiological obstruction of the bile flow associated with appendicular pathology leads to hyperbilirubinemia. Aims and objectives: To study serum bilirubin level in cases of acute appendicitis and its complications like appendicular perforation. Methods: A retrospective study was carried out for 4 years at two tertiary care hospitals from 2015 to 2018 to evaluate the serum bilirubin levels in acute appendicitis and appendicular perforation. Patients having acute appendicitis and appendicular perforation, confirmed on histopathology, with no other medical or surgical comorbidity were included in the study. Results: Total 420 patients which contain 105 patients had appendicular perforation amongst these, 78 (74%) had hyperbilirubinemia and 315 patients having acute appendicitis only 91(29%) had hyperbilirubinemia. Average, lower and higher serum bilirubin levels of this study were 1.5 mg/dl, 0.5 mg/dl and 3.2 mg/dl respectively. Average, lower and higher serum bilirubin of patients diagnosed to be having acute appendicitis were 1.3 mg/dl, 0.5mg/dl and 2.4 mg/dl respectively. Average, lower and higher serum bilirubin of the patients diagnosed to be having appendicular perforation were 1.8 mg/dl, 0.8mg/dl and 3.2 mg/dl respectively. Conclusions: Hyperbilirubinemia was more seen in appendicular perforation than in acute appendicitis, so pre-operatively serum bilirubin estimation may help us with other diagnostic modality in diagnosing appendicular perforation.

Keywords: Appendicitis, Serum Bilirubin, Appendicular Perforation, Hyperbilirubinemia

## **INTRODUCTION**

Acute appendicitis is one of the commonest surgical emergencies and appendectomy is a commonly performed surgical procedure. Many an acute abdomen pathology have similar clinical signs and symptoms always mimic the diagnosis of acute appendicitis causes accurate clinical diagnosis difficult<sup>[1]</sup> and there are a number of causes leading to pain in right iliac fossa particularly in female patients. Diagnosing acute appendicitis clinically still remains a common surgical problem. Accurate diagnosis can be aided by additional testing or expectant management or both. The disease characteristics and management of appendicitis has evolved a lot since the first historical report of appendectomy from Europe over the past years<sup>[2,3]</sup>.

Clinical evaluation is most common and the best diagnostic tool for diagnosing any appendicular pathology over a world <sup>[4]</sup>. The currently available

blood investigations and imaging modalities do help in diagnosing acute appendicitis but are not very specific about its sequelae or the pathology involved<sup>[5]</sup>.

Delay in diagnosing acute appendicitis may lead to complications such as intra-abdominal abscess, perforation, generalized peritonitis appendicular lump formatin, etc. Due to the availability of radiological imaging techniques like x rays, ultrasonography and computerized tomography, having accuracies of 85-90% for diagnosing acute appendicitis<sup>[6-8]</sup>. These diagnostic modalities are costly, may not available in remote area, require maintenance, time consuming. So it requires finding out cost effective, easily available and fairly accurate investigations to diagnose acute appendicitis and it's complications in time.

Recent studies have shown that elevated bilirubin levels are associated with acute appendicitis and appendicular perforation. These studies emphasized that hyperbilirubinemia can be used as a marker for appendicitis both and appendicular acute perforation<sup>[9-12]</sup>.Hyperbilirubinemia is the result of imbalance between production and excretion of bilirubin by the liver. It may be because of hepatocellular, cholestatic or hemolytic diseases. Liver receives blood mainly through the portal venous system, which receives blood from abdominal organs. Portal blood carries nutrients and other substances absorbed from gut including bacteria and its product (toxins). In a small percentage, even in normal healthy people, bacteria are found in portal blood. It is commonly 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 kuffer cell function, it may causes 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. Recently, another substance known as cytokines e.g. interleukin (IL)-6, tumor necrosis factor (TNF), has also been considered to be responsible for depressed excretory function of the liver and may lead to increase in serum bilirubin levels without a rise in liver enzymes.

Aim and Objectives: To study serum bilirubin level in cases of acute appendicitis and its complications like appendicular perforation.

#### METHODS

A retrospective study conducted for evaluating serum bilirubin levels in acute appendicitis and appendicular perforation. It was conducted at two tertiary care hospitals after permission from institutational head at GMERS Medical College and Hospital, Vadanagar and Smt SCL hospital affiliated with Smt NHL Municipal Medical College Ahmedabad over a period of 4 years from January 2015 to December 2018. Total 420 patients included who came to emergency surgery department and investigated and diagnosed appendicitis was confirmed to have acute appendicitis and perforation appendicular by histopathology examination. Patients documented to have a past history of liver disease, positive hepatitis B virus surface antigen (HBsAg), cholelithiasis, hepatopancreatobiliary gastrointestinal or malignancy, jaundice, chronic alcoholism, hemolytic disease, congenital or acquired biliary disease, drug intake causing cholestasis, age below 12 years, appendectomy performed incidentally or for other indication and conservatively managed for appendicitis were excluded. All the routine investigations, complete blood counts, renal function test, electrocardiogram, chest x-ray, blood sugar levels and liver function tests were sent at the time of admission in the pre-operative period before any surgical or anesthetic intervention was done.

The normal bilirubin range in adults was taken as direct bilirubin 0.1-0.3 mg%, indirect bilirubin 0.2-0.8 mg%, and total bilirubin 0.3-1.0 mg%. At the time of admission patients were started on intravenous fluids. antibiotics (ceftriaxone+ cefoperazone +salbactum sulbactum or and metronidazole), opioid analgesics, proton pump inhibitors and antipyretics (as and when requires). All the patients gave an informed consent for the surgery beforehand. The patients were then operated upon under general anaesthesia or spinal anaesthesia and an appendectomy was done by open or laparoscopy methods. Patients were managed as per their specific needs and condition in the post- operative period.

RESULTS

A total of 420 patients were enrolled as study patients in this present study. In the study average age of patients 30 years with youngest and the eldest patients were 14 and 60 years old respectively.



#### **Chart 1: Gender Distribution.**

There were 218(52%) male and 202 (48%) females in this study group.

|                                 | Numbe   | Number of        | Averag   |
|---------------------------------|---------|------------------|----------|
|                                 | r of    | patients with    | e serum  |
|                                 | patient | Hyperbilirubinem | bilirubi |
|                                 | S       | ia               | n        |
|                                 |         |                  | [mg/dl]  |
| Acute<br>appendicitis           | 315     | 91               | 1.3      |
| Appendicula<br>r<br>perforation | 105     | 78               | 1.8      |
| Total                           | 420     | 169              | 1.5      |

Table 1: Serum bilirubin levels in acuteappendicitisandappendicularperforationpatients.

315 patients had acute appendicitis and 105 had appendicular perforation. The diagnosis was confirmed on the histopathological examination. 169 (40%) out of 420 patients had Hyperbilirubinemia present which include 91 (21%) had acute appendicitis and 78 (19%) had appendicular perforation. Hyperbilirubinemia was present in 78 (74%) patients out of 105 of appendicular perforation while only 91 (29%) patients out of 315 of acute appendicitis. In this study an average serum bilirubin of 1.5 (SD±0.20) mg/dl with lower and the higher levels were 0.5 and 3.2 mg/dl respectively. In this study lower serum bilirubin level of 0.5 mg/dl was found in a male patient having acute appendicitis and

the higher was 3.2 mg/dl in a male patient having appendicular perforation.



## Chart 2: Number of patients with Hyperbilirubinemia in acute appendicitis and appendicular perforation.

Patients diagnosed as acute appendicitis had an average 1.3 (SD $\pm$ 0.2) mg/dl serum bilirubin with lower and higher levels were 0.5 and 2.4 mg/dl, respectively. Patients diagnosed as appendicular perforation had an average 1.8 (SD $\pm$ 0.30) mg/dl serum bilirubin with lower and higher levels were 0.8 and 3.2 mg/dl respectively.

Liver enzyme AST was within normal range in 386 (92%) cases, minimally elevated in 29(7%) cases, and moderately elevated in 5(1%) cases. ALT was within normal range in 378 (90%) cases, and minimally elevated in 33 (8%) cases and moderately in 9 (2%) cases. ALP was within normal range in 394 (94%) cases, minimally elevated in 16 (4%) cases, moderately elevated in 10(2%) case.

## DISCUSSION

Whereas non-perforated acute appendicitis can be cured by an appendectomy without a long recovery period, perforated appendicitis or suppurative appendicitis can cause various complications that can result in life-threatening conditions<sup>[13]</sup>. Recent developments in the diagnosis of acute appendicitis with the assistance of radiological tools, such as ultrasonography and computed tomography (CT) have reduced the rate of negative appendicectomies. Although the reported diagnostic accuracy of ultrasonography varies depending on the patient population studied, a meta-analysis showed an overall ultrasonographic sensitivity of 85% and a specificity of 92%<sup>[14]</sup>. Pritchett et al.<sup>[15]</sup> 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 intervene surgically.

Atahan et al.<sup>[16]</sup> concluded that the assessment of preoperative total bilirubin is useful for the differential diagnosis of perforated versus acute suppurative appendicitis, whereas a white blood cell (WBC) assessment is effective for diagnosing the presence versus absence of appendicitis. Symptom duration, WBCs, and total bilirubin should be used as independent parameters in the early diagnosis of appendix perforation. Previous research articles have concluded that there is a significant association between hyperbilirubinemia and appendicular perforation<sup>[1,10-12]</sup>. Serum bilirubin levels estimation used in conjunction with other diagnostic modalities like ultrasonography and computerized tomography scans lead to better aid in diagnosing appendicular perforation pre operatively<sup>[11,12,17]</sup>.

The total 420 patients included, out of which 218 (52%) were males and 202 (48%) were females which correlated with Hong YR et al, in their study of 1195 patients had 51% males and 49% females<sup>[6]</sup>. Poras C et al, had 80% males and 20% females in their study<sup>[17]</sup>. These differences in the gender distribution of this study and the studies quoted above may be due to the different number of study patients in the sample size. Youngest and the oldest patient of this study were 14 and 60 years respectively with an average age 30 years, which correlated with Khan S et al reported an average age of 27.2 years of their study sample<sup>[10]</sup>.

The total 420 patients included, out of which 315 (75%) had acute appendicitis and 105 (25%) had appendicular perforation which correlate with Estrada JJ et al, who include total 157 patients, out of which 116 (74%) had acute appendicitis and 41 (26%) had perforated or gangrenous appendicitis on final histopathological report<sup>[11]</sup> while Poras C et al, who include total 50 patients, out of which 42 (84%) had acute appendicitis on final histopathological report<sup>[17]</sup>. The difference can be due to sample size.

The total 420 patients included, out of which 169 (40%) had Hyperbilirubinemia which correlate with Bali R S et. al. who include total 927 patients, out of which 412 (40%) had hyperbilirubinemia was found in their study<sup>[12]</sup>, while Sand et al<sup>[18]</sup> who include total 538 patients, out of which 24.9% had

hyperbilirubinemia. Hyperbilirubinemia was present in patients having appendicular perforation and acute appendicitis were 74% and 29% which correlate with Ramasamy Ramu T et al in the form of 90% and 29% respectively<sup>[19]</sup>, indicate that bacteria and TNF- alpha in endotoxin mediated cholestasis causes decreased excretion of bile in canaliculi demonstrated by  $al^{[20]}$ . Whiting et The pathogenesis of hyperbilirubinemia in severe intra abdominal infections. as associated with appendicular perforation, is hypothesized to be due to bacteremia or endotoxemia causing impaired bilirubin excretion from bile canaliculi<sup>[21,22]</sup>. In severe abdominal infections hyperbilirubinemia seen due to above mechanism<sup>[11,23-25]</sup>.</sup>Septicaemia due to gastrointestinal perforation there is an association between pro inflammatory cytokine and nitric oxide triggered cholestasis was seen<sup>[26-27]</sup>.

In our study, the mean value of serum bilirubin was 1.5mg%, in acute appendicitis 1.3 mg% and in perforated appendicitis 1.8mg% correlate with previous study Bali RS et al<sup>[12]</sup> and Mir Ma et al<sup>[28]</sup>.

It was demonstrated by Sisson et al in 1971<sup>[29]</sup> 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. Subsequent events lead to edema, elevated intraluminal pressure, and ischemic necrosis of mucosa, causing tissue gangrene and perforation<sup>[30-31]</sup>. This process is associated with progressive bacterial invasion most likely facilitated by bacterial cytotoxins. The number of organisms isolated from patients with gangrenous appendicitis is five times greater than those with acute suppurative appendicitis. Estrada et al<sup>[32]</sup> also found significantly higher peritoneal culture in patients with gangrenous/perforated appendicitis. This elevated load of bacteria in appendicitis causes either 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.

Majority (92%) of these study patients had normal liver enzymes (AST, ALT, ALP). Similar findings also reported by Khan S in their research and observed that hyperbilirubinemia in acute

appendicitis and its complications was probably due to hepatocyte dysfunction because of deranged hepatocyte permeability to bilirubin or the depressed ductule enzyme (Na-K ATPase) causing cholestasis<sup>[10]</sup>. Thus, it is concluded that hepatocellular function is depressed during the early stage of sepsis despite the increased cardiac output and hepatic blood flow and decreased peripheral resistance. The depression of hepatocellular function in the early, hyperdynamic stage of sepsis does not appear to be due to reduction in hepatic perfusion but is associated with elevated levels of circulating pro inflammatory cytokines such as TNF and IL-6. Thus up regulation of TNF and/ or IL-6 may be responsible for producing hepatocellular dysfunction during the early hyperdynamic stage of sepsis.

# CONCLUSIONS

Serum bilirubin estimation routinely performed a simple cheap and easily available test in every laboratory. Hyperbilirubinemia predominantly seen in appendicular perforation compare acute appendicitis. Therefore, obtaining serum bilirubin values upon admission can be used in conjunction with the other available investigative modalities like ultrasonography or computerised tomography scan may better help to diagnose and management of appendicular perforation.

## REFERENCES

- Ramaswami YB, Prakash HS, TC RP, Jabbar FA. Hyperbilirubinemia: a new diagnostic marker for appendicular perforation. Inter Surg J. 2017 Aug 24;4(9):3024-7.
- 2. Kumar BA, Kalyan KA, Rehman MM: Perforation in acute appendicitis: evaluation of hyperbilirubinemia and elevated C reactive protein as a predictive factor. IAIM. 2017, 4:18-23.
- 3. Amyand C. VIII. Of an inguinal rupture, with a pin in the appendix coeci, incrusted with stone; and some observations on wounds in the guts. Philosoph Trans Royal Soci London. 1736 Oct;39(443):329-42.
- 4. Panagiotopoulou IG, Parashar D, Lin R, Antonowicz S, Wells AD, Bajwa FM, et al. The diagnostic value of white cell count, Creactive protein and bilirubin in acute appendicitis and its complications. Annal Royal Coll Surg Eng. 2013 Apr;95(3):215-21.

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- 5. Kumar BA, Kalyan KA, Rehman MM. Perforation in acute appendicitis: evaluation of hyperbilirubinemia and elevated C reactive protein as a predictive factor. IAIM. 2017;4(3):18-23.
- Hong YR, Chung CW, Kim JW, Kwon CI, Ahn DH, Kwon SW, et al. Hyperbilirubinemia is a significant indicator for the severity of acute appendicitis. J Korean Soci Coloproctol. 2012 Oct;28(5):247.
- Franke C, Böhner H, Yang Q, Ohmann C, Röher HD. Ultrasonography for diagnosis of acute appendicitis: results of a prospective multicenter trial. World J Surg. 1999 Feb 1;23(2):141.
- Cakirer S, Basak M, Colakoglu B, Bankaoglu M. Diagnosis of acute appendicitis with unenhanced helical CT: a study of 130 patients. Emerg Radiol. 2002 Sep 1;9(3):155-61.
- 9. Ramu TR, Kandhasamy SC, Andappan A. A Prospective Study on the Diagnostic Value of Hyperbilirubinemia as a Predictive Factor for Appendicular Perforation in Acute Appendicitis. Cureus. 2018 Aug;10(8).
- Khan S. Evaluation of hyperbilirubinemia in acute inflammation of appendix: a prospective study of 45 cases. Kathmandu Univ Med J. 2006 Jul;4(3):281-9.
- Estrada JJ, Petrosyan M, Barnhart J, Tao M, Sohn H, Towfigh S, et al. Hyperbilirubinemia in appendicitis: a new predictor of perforation. J Gastroint Surg. 2007 Jun 1;11(6):714-8.
- 12. Bali RS, Rajni, Watali Y, Gupta SK, Gupta G. Evaluating serum bilirubin levels in acute appendicitis and appendicular perforation. Int J Res Med Sci 2020;8:859-62.
- 13. Fike FB, Mortellaro VE, Juang D, Sharp SW, Ostlie DJ, St Peter SD: The impact of postoperative abscess formation in perforated appendicitis. J Surg Res. 2011, 170:24-26.
- 14. Orr RK, Porter D, Hartman D: Ultrasonography to evaluate adults for appendicitis: decision making based on metaanalysis and probabilistic reasoning. Acad Emerg Med. 1995, 2:644-650.

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- 15. Pritchett CV, Levinsky NC, Ha YP, Dembe AE, Steinberg SM: Management of acute appendicitis: the impact of CT scanning on the bottom line. J Am Coll Surg. 2017, 210:699-705.
- 16. Atahan K, Ureyen O, Aslan E et al,: Preoperative diagnostic role of hyperbilirubinemia as marker of appendix perforation J Int Med Res. 2011, 39:609-618.
- Chaudhary P, Kumar A, Saxena N, Biswal UC. Hyperbilirubinemia as a predictor of gangrenous/perforated appendicitis: a prospective study. Annal gastroenterol: Quarterly Pub Hellenic Soci Gastroenterol. 2013;26(4):325.
- 18. 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 Aug 1;198(2):193-8.
- Ramasamy Ramu T, Chinnakkulam Kandhasamy S, Andappan A, et al. (August 27, 2018) A Prospective Study on the Diagnostic Value of Hyperbilirubinemia as a Predictive Factor for Appendicular Perforation in Acute Appendicitis. Cureus 10(8): e3214. DOI 10.7759/cureus.3214
- 20. Whiting JF, Green RM, Rosenbluth AB, Gollan JL. Tumor necrosis factor-alpha decreases hepatocyte bile salt uptake and mediates endotoxin-induced cholestasis. Hepatology. 1995 Oct;22(4):1273-8.
- 21. Zimmerman HJ, Fang M, Utili R, Seeff LB, Hoofnagle J. Jaundice due to bacterial infection. Gastroenterology. 1979 Aug 1;77(2):362-74.
- 22. Franson TR, Hierholzer Jr WJ, LaBrecque DR. Frequency and characteristics of hyperbilirubinemia associated with bacteremia. Revi Infec Dis. 1985 Jan 1;7(1):1-9.

- 23. Miller DF, Irvine RW. Jaundice in acute appendicitis. Lancet. 1969 Feb 15;293(7590):321-3.
- 24. Atahan K, Üreyen O, Aslan E, Deniz M, Çökmez A, Gür S, et al. Preoperative diagnostic role of hyperbilirubinaemia as a marker of appendix perforation. J Inter Med Res. 2011 Apr;39(2):609-18.
- 25. Miller DJ, Keeton GR, Webber BL, Saunders SJ. Jaundice in severe bacterial infection. Gastroenterology. 1976 Jul 1;71(1):94-7.
- 26. Geier A, Fickert P, Trauner M. Mechanisms of disease: mechanisms and clinical implications of cholestasis in sepsis. Nature Clin Pract Gastroenterol Hepatol. 2006 Oct;3(10):574-85.
- Nishida T, Fujita N, Megawa T, Nakahara M, Nakao K. Postoperative hyperbilirubinemia after surgery for gastrointestinal perforation. Surg Today. 2002 Aug 1;32(8):679-84.
- 28. Mir Ma, Haq I, Manzoor F: Diagnostic value of total leucocyte count(TLC) C- reactive protein(CRP) and bilirubin in patients with suspected acute appendicitis. IJCMR 2016, 3:1249-1253
- 29. Sisson RG, Ahlvin RC, Harlow MC. Superficial mucosal ulceration and the pathogenesis of acute appendicitis. Am J Surg 1971;122:378-380.
- Bennion RS, Wilson SE, Serota AI, Williams RA. The role of gastrointestinal microflora in the pathogenesis of complications of mesenteric ischemia. Rev Infect Dis 1984;6:S132-S138.
- Bennion RS, Wilson SE, Williams RA. Early portal bacteremia in mesenteric ischemia. Arch Surg 1984;119:151-155.
- 32. Estrada JJ, Petrosyan M, Barnhart J, et al. Hyperbilirubinemia in appendicitis: a new predictor of perforation. 2007;11:714-718