

Role of Hyperbilirubinemia as a Diagnostic Predictor of Appendicular Perforation

Dr. A. Q. Khan¹, Dr. Anirudha Patil², Dr. Praful Pawar³

1. Introduction

Acute appendicitis is most common cause of acute abdomen in young adults¹. In recent years studies emerge that showed that elevated serum bilirubin levels could indicate a perforated case of acute appendicitis²⁻⁶. An elevated serum bilirubin that is not explained by liver disease or biliary obstruction can be present in many patients of acute appendicitis. Appendicular perforations though one of the most commonly faced problems, confirm diagnosis cannot be made with ultrasonography and TLC. The present study is aimed towards establishing relationship between appendicular perforation and elevated serum bilirubin levels; so as to diagnose the severity of acute appendicitis preoperatively.

2. Material and Method

A Two year prospective study. The present study was conducted in the Department of Surgery, Mahatma Gandhi Mission Medical College and Hospital, Aurangabad. Two years from October 2012 to October 2014. Patients admitted with clinical diagnosis of acute appendicitis or appendicular perforation under the Department of Surgery, MGM Hospital and Medical Research Centre, Aurangabad during the study period. A total of 100 patients with clinical diagnosis of acute appendicitis or appendicular perforation were studied.

Inclusion Criterion:

- All patients diagnosed as acute appendicitis clinically on admission.
- All patients diagnosed as appendicular perforation clinically on admission.
- For both these groups, only patients with histopathological report suggestive of acute appendicitis or appendicular perforation were included.

Exclusion Criterion:

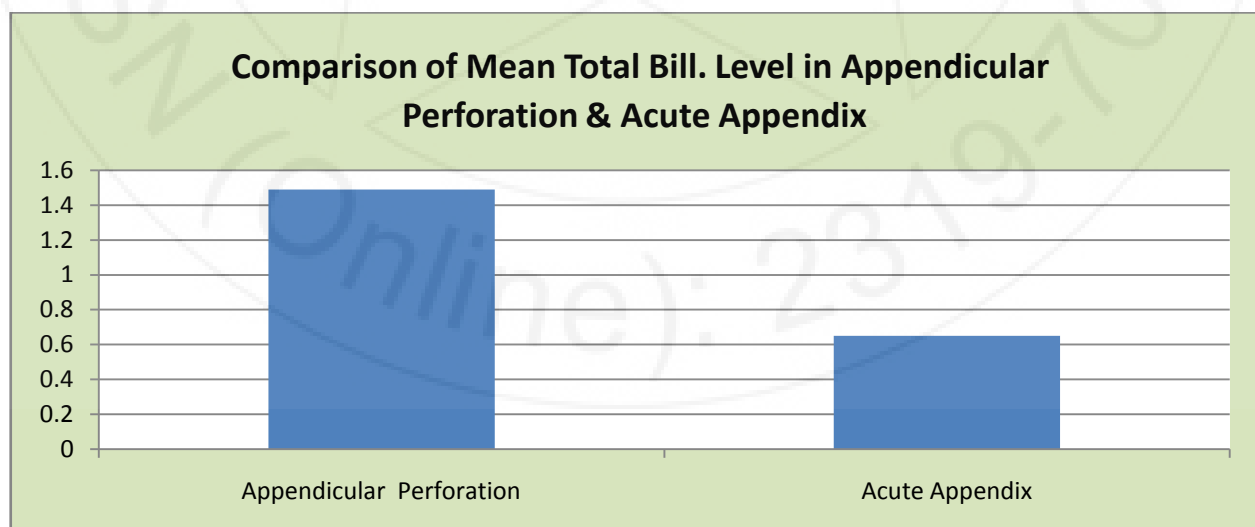
- All patients documented to have a past history of;
 - Jaundice or Liver disease.
 - Chronic alcoholism (that is intake of alcohol of > 40 g/day for Men and > 20 g/day in Women for 10 years).⁷²
 - Hemolytic disease.
 - Acquired or congenital biliary disease.
- All patients with positive HBsAg.
- All patients with cholelithiasis.
- All patients with cancer of hepato-biliary system.
- Viral hepatitis

3. Results

Table 1: Comparison of Mean Total Billirubin level

	Mean	SD	z-value	p-value
Appendicular Perforation	1.49	0.77	7.29	P=0.001 Significant
Acute Appendix	0.65	0.27		

Graph 1: Comparison between mean total bilirubin of acute appendicitis and appendicular perforation.



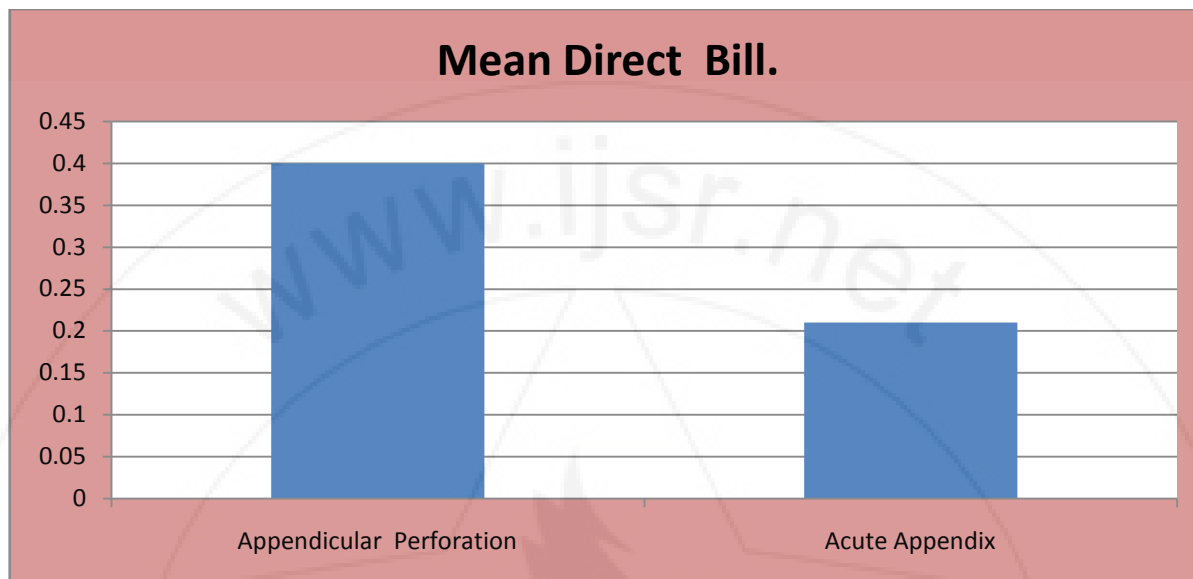
The mean Total Bilirubin for patients with Acute appendicitis was 0.77 and that for Appendicular Perforation was 1.49(p=0.001) which was a significant rise

in Total Bilirubin in Patients with Appendicular Perforation.

Table 2: Comparison of Mean Direct Billirubin level

Direct Billirubin level	Mean	SD	z-value	p-value
Appendicular Perforation	0.40	0.43	2.95	P=0.0032
Acute Appendix	0.21	0.15		Significant

Graph 2: Comparison of mean direct bilirubin in acute appendicitis and appendicular perforation.

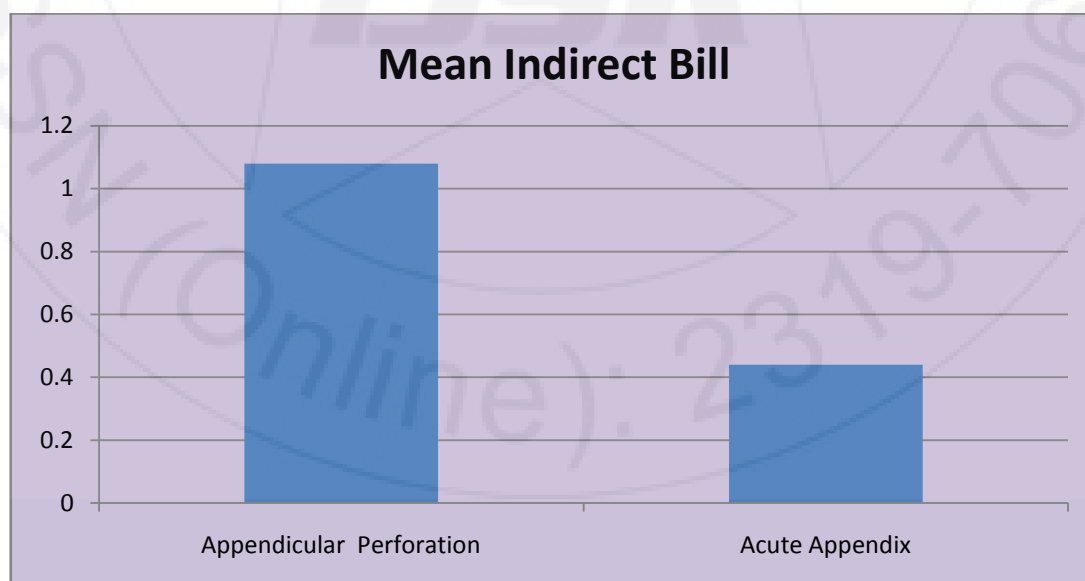


The mean value for Direct Bilirubin in Acute Appendicitis was 0.21 whereas in Appendicular Perforation was 0.40 (p=0.0032) which is significant.

Table 3: Comparison of Mean Indirect Billirubin level

Indirect Billirubin level	Mean	SD	z-value	p-value
Appendicular Perforation	1.08	0.64	6.78	P=0.0001
Acute Appendix	0.44	0.19		Significant

Graph 3: Comparison of mean indirect bilirubin level in acute appendicitis and appendicular perforation



The mean value for indirect Bilirubin level in Acute Appendicitis was 0.44 whereas for Appendicular Perforation was 1.08 (p=0.0001) which is significant. This means there is rise in both components of Total Bilirubin,

Direct as well as Indirect Bilirubin in patients with Appendicular Perforation which is significant.

Table 4: Sensitivity, Specificity, Negative Predictive Value & positive Predictive Value of Total Billirubin level outcome over final diagnosis

Total Billirubin level outcome	Final diagnosis		Total
	Perforation Present	Perforation Absent	
Positive [Raised]	44	10	54
Negative [Normal]	06	40	46
Total	50	50	100

Sensitivity	$\frac{a}{a + c}$	= 88.00 %	95% CI: 75.68 % to 95.44 %
Specificity	$\frac{d}{b + d}$	= 80.00 %	95% CI: 66.28 % to 89.95 %
Positive Predictive Value	$\frac{a}{a + b}$	= 81.48 %	95% CI: 68.57 % to 90.73 %
Negative Predictive Value	$\frac{d}{c + d}$	= 86.96 %	95% CI: 73.73 % to 95.03 %

Sensitivity: Therefore the sensitivity of Total Bilirubin in predicting Appendicular perforation is 88%.

Specificity: Therefore the specificity of Total Bilirubin in predicting Appendicular perforation is 80%.

Positive Predictive Value: Therefore the Positive predictive value of Total bilirubin in predicting Appendicular perforation is 81.48%.

Negative predictive value: Therefore the Negative predictive value of Total Bilirubin in predicting Appendicular perforation is 86.96%.

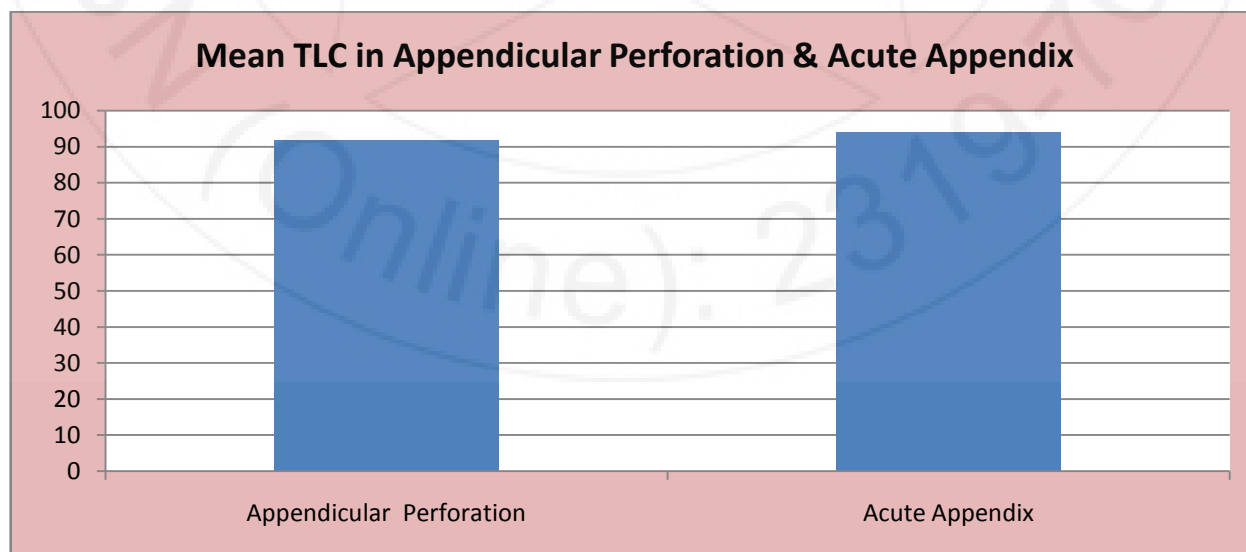
Analysing values for total serum bilirubin results in clear difference between acute appendicitis and appendicular perforation. There is significant difference between both

direct as well as indirect bilirubin levels so it is mixed type of hyperbilirubinemia in appendicular perforation. In similar fashion we compared SGOT, SGPT and ALP levels for acute appendicitis and appendicular perforation but the statistical difference was non significant for the liver enzymes.

Table 5: Comparison of Mean TLC:

	Mean	SD	z-value	p-value
Appendicular Perforation	91.86	42.15	0.263	P=0.782 Not significant
Acute Appendix	93.86	31.18		

Graph 4: Comparison of mean TLC in acute appendicitis and appendicular perforation



The mean value for TLC in Acute Appendicitis was 93.86 whereas for Appendicular Perforation it was 91.86 ($p=0.782$) the value which was not significant.

So we can conclude that though TLC count is raised in Acute Appendicitis and Appendicular Perforation it cannot differentiate between Acute Appendicitis and Appendicular Perforation.

4. Discussion

Several serum markers have been analysed so as to predict the severity of acute appendicitis including IL-6 and lipopolysaccharide binding protein⁷. The presence of jaundice in sepsis is well documented, specially associated with gram negative organisms^{8,9,10}. Several mechanisms have been described explaining elevated total bilirubin levels in systemic infections. Some bacteria including E.Coli have been associated with increased levels of total serum bilirubin levels^{9, 11}. Some endotoxins released in the peripheral blood stream interfere with the liver's mechanism for the bilirubin uptake and canalicular excretion¹². Endotoxins produce cholestasis by damaging biliary salt transport through cytokine mediated mechanisms¹³. E.Coli is the most frequently isolated bacteria from peritoneal fluid in acute appendicitis¹⁴. Elevated total bilirubin level in acute appendicitis can either appear as a result of bacteremia, or endotoxemia, both possible in catarrhal and phlegmonous forms as well as in the perforated appendicitis³.

Several studies done reporting elevated levels of serum bilirubin in acute appendicitis^{15,16}. Sand et al derived hypothesis that elevated total bilirubin levels can be associated with appendicular perforation². Estrada et al also found out same results⁴. They explain the raised serum bilirubin levels by the invasion of gram negative bacteria through muscularis propria of the appendix, leading to the direct invasion or translocation of germs through portal system and liver, interfering with bilirubin excretion through bile ducts by endotoxin action. In our study Sensitivity and specificity of bilirubin in predicting appendicular perforation 88% and 80% respectively; similarly positive predictive value and negative predictive value of bilirubin in predicting appendicular perforation 81.48% and 86.96% respectively. The sensitivity in predicting appendicular perforation in our study was found to be more than that by Sand et al² which was 70% ; but specificity of predicting appendicular perforation was 80% in our study which was 86% in the study done by Sand et al. Emmanuel³ found out that specificity of hyperbilirubinemia for appendicular perforation was found to be 70% which was less than our study but he also found that TLC was not specific in predicting appendicular perforation which is same as our study. Khan S et al¹⁷ found out the specificity and sensitivity of the hyperbilirubinemia in predicting appendicular perforation was 100% and 82.07%.

The positive predictive value of hyperbilirubinemia in appendicular perforation was found to be 91% in the study done by Emmanuel A et al³ which was found to be 81.48% in our study. The study done by Khan S had

positive predictive value of 100% and negative predictive value of 17.3% which were 81.48% and 86.96% respectively in our study.

5. Conclusion

Finding of present study suggest;

- Total serum bilirubin appears to be a new promising laboratory marker for diagnosing appendicular perforation.
- The patients with clinical signs and symptoms of appendicitis and with hyperbilirubinemia should be identified as having a higher probability of appendicular perforation suggesting, total serum bilirubin levels have a predictive potential for the diagnosis of appendicular perforation.

References

- [1] O' Connel PR. The Vermiform Appendix. In: Williams NS, Bulstrode CJK, O'Connell PR (Ed.). Bailey and Love's - Short practice of surgery. 25 ed. London: Arnold: 2008; p. 1204-8.
- [2] Sand M, Bechara GF, 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; 198(2): 193-8
- [3] Emmanuel A, Murchan P, Wilson I, Balfe P. The value of hyperbilirubinaemia in the diagnosis of acute appendicitis. *Ann R Coll Surg Engl* 2011; 93(3): 213-7.
- [4] Estrada JJ, Petrosyan M, Krumenacker J Jr, Huang S, Moh P. Hyperbilirubinemia in Appendicitis: A New Predictor of Perforation. *Journal of Gastrointestinal Surgery* 2007; 11: 714-5.
- [5] B. Socea, A Carap
- [6] *Chirurgia* (2013) 108: 829 – 834 No.6, November – December. Doi : 10.1016/j.ijisu.2013.05.029 Epub 2013 May 31.
- [7] Branescu C, Serben D, Dascalu A MIL-6 and lipopolysaccharide binding protein markers of inflammation in acute appendicitis. *Chirurgia* 2013; 108(2):206-14.
- [8] Whitehead M W, Hainsworth I, Kinghan J G. The causes of obvious jaundice in south west wales: perception vs reality.
- [9] Chand N, Sanyal A J. Sepsis induced cholestasis *hepatology* 2007;45(1): 230-41.
- [10] Orban C. Diagnostic criteria for sepsis in burn patients. *Chirurgia* 2012;107(6):697-700.
- [11] Shander A. Anemia in the critically ill. *Crit care chin.* 2004;20(2):159-78
- [12] Roelofsen H Vander veere CN. Decreased bilirubin transport in the perfused liver of endotoxemic rats. *Gastroenterology* 1994; 107(4):1075-84.
- [13] Whiting JF, Green RM. TNF-alfa decrease hepatocyte bile salt uptake and mediated endotoxin induced cholestasis. *Hepatology.*1995;22(pt 1):1273-78.
- [14] Brook I. Bacterial studies of peritoneal cavity and post operative surgical wound drainage following perforated appendix in children, *Ann Surg*1980;192(2):208-212.
- [15] Agrej MV, House AK. Jaundice may herald an appendiceal abscess. *Aust NZJ Surg.*1986; 56(6):511-13.
- [16] Ogilvie T A. Acholuric jaundice and appendicitis. *BJS* 1951;38(152):529-30.
- [17] Khan S. Elevated serum Bilirubin in Acute Appendicitis: a new Diagnostic tool. *Kathmandu University Medical Journal* 2008; 6 (2): 161-5