Original Research Article

A study on evaluation of hyperbilirubinemia as a new diagnostic marker for acute appendicitis and its role in prediction of appendicular perforation

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Abstract

Background: The most common cause of acute abdomen is Appendicitis. The diagnosis of acute appendicitis is based on the clinical history and physical examination. It is difficult to diagnose in cases of the retro caecal or retro ileal appendix. Studies show that serum bilirubin is raised in acute appendicitis and appendicular perforations. But the significance of which is not stressed. On the bacterial invasion of the appendix, there is a transmigration of bacteria and the release of proinflammatory cytokines like TNF α, IL6. The cytokines reach the liver through the superior mesenteric vein and may lead to inflammation, abscess and liver dysfunction.

Aim and objectives: To study the association between hyperbilirubinemia and acute appendicitis, and to evaluate its trustworthiness as a diagnostic marker for acute appendicitis.

Materials and methods: The study was conducted in the Department of General Surgery, Govt. Kilpauk Medical College, Chennai during the period of April 2019 to October 2019. A total of 170 patients with the clinical diagnosis of acute appendicitis or appendicular perforation were studied. 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 reports suggestive of acute appendicitis or appendicular perforation were included.

Results: The mean TLC was 10186.43 ±4728.32 in the study population, ranged between 13 (/Mm^3) to 22540 (95% CI 9470.53 to 10902.33). In acute appendicitis positive group, 18 (15.93%) had of

hyper bilirubin, this proportion was 35 (61.4%) among acute appendicitis negative group. The difference in the proportion of hyper bilirubin between acute appendicitis was statistically significant (P-value <0.001).

Conclusion: Patients with clinical signs and symptoms of appendicitis and with hyperbilirubinemia higher than the normal range should be identified as having a higher probability of Appendicular perforation suggesting, serum bilirubin levels have a predictive potential for the diagnosis of Appendicular perforation.

Key words

Uncontrolled Hyperbilirubinemia, Acute Appendicits, Appendicular Profileration.

Introduction

Appendicitis is the most common surgical emergency worldwide. The most commonly performed abdominal surgery is appendicectomy. Diagnosis can be made clinically. Up to 25% of appendicectomy turns into negative appendicectomies in clinically diagnosed appendicitis [1]. In order to reduce the negative appendicectomy various Diagnosing modalities used like white blood cell count, C Reactive protein, ultrasonogram, and CT scan [2]. Various scoring systems are developed like Alvarado, Appendicitis inflammatory response score and RIPASA. But the negative appendicectomy rate remains constant [3]. It is observed that elevated bilirubin values in appendicitis and complicated appendicitis. Various studies also prove the same [4]. The Vermiform Appendix is considered by most to be a vestigial organ. Its importance in surgery is due only to its propensity for inflammation, which results in the clinical syndrome known as Acute Appendicitis [5]. Acute appendicitis is the most common cause of acute surgical abdomen leading to emergency laparotomy [6]. Acute appendicitis presents as acute abdominal pain in the emergency care unit, the surgeon must realize that the reliance is based entirely on the clinical features rather than the lab or radiological findings [7]. It is a very good aphorism that, in the diagnosis of acute abdominal conditions special investigation can be used only to reinforce the clinical diagnosis, seldom if ever can they establish or refute it. This is particularly appropriate in the case of acute appendicitis [8]. Diagnostic difficulties may lead to negative appendicectomies or cases of missed appendicitis resulting in complications such as appendiceal perforation (AP) or abscess formation [9]. In uncomplicated acute appendicitis and complicated appendicitis there is the transmigration of bacterial endotoxins and cytokines into the bloodstream. They reach the liver through the portal vein and cause hepatic dysfunction which leads to elevated bilirubin levels [10].

Materials and methods

The study was conducted in the Department of General Surgery, Govt. Kilpauk Medical College, Chennai during the period of April 2019 to October 2019. A total of 170 patients with the clinical diagnosis of acute appendicitis or appendicular perforation were studied. 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 reports suggestive of acute appendicitis or appendicular perforation were included.

Exclusion criteria: All patients documented to have a past history of Jaundice or Liver disease, Hemolytic disease, Chronic alcoholism (that is the intake of alcohol of > 40 g/day for, All patients with positive HBsAg, All patients with cholelithiasis, All patients with cancer of the hepato-biliary system.

The nature of the study was explained to the patients. And the patients were included in this study after getting written informed consent.

History and clinical examination were done for all and recorded in the proforma.

Statistical methods

Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency, and proportion for categorical variables. Data was also represented using appropriate diagrams like a bar diagram, pie diagram, and box plots. The association between categorical explanatory variables and the quantitative outcome was assessed by comparing the mean values. The mean differences along with their 95% CI were presented. The association between explanatory variables and categorical outcomes was assessed by cross-tabulation and comparison of percentages. A chi-square test was used to test statistical significance. P value < 0.05 was considered statistically significant. IBM SPSS version 22 was used for statistical analysis.

Table - 1: Descriptive analysis of age in study population (n=170).

Parameter	Mean ± SD	Median	Minimum	Maximum	95% C. I	
					Lower	Upper
Age	31.38 ± 15	28.00	4.00	72.00	29.11	33.65

Table - 2: Descriptive analysis of gender in the study population (n=170).

Gender	Frequency	Percentages
Male	122	71.8%
Female	48	28.2%

Table - 3: Descriptive analysis of liver function test in study population (n=170).

Parameter	Mean ± SD	Median	Minimum	Maximum	95% C.I	
					Lower	Upper
Total Bilirubin	0.87 ± 0.36	0.80	0.30	2.70	0.81	0.92
Direct Bilirubin	0.36 ± 0.15	0.30	0.10	0.90	0.34	0.38
Indirect Ct	0.51 ± 0.25	0.50	0.20	1.90	0.47	0.55
SGOT	27.74 ± 11.52	28.50	0.00	91.00	26.00	29.49
SGPT	27.17 ± 10.03	28.00	0.30	55.00	25.65	28.69
Alp	74.31 ± 23.91	76.00	22.00	120.00	70.69	77.93

Table - 4: Descriptive analysis of TLC (/mm3) in study population (n=170).

Parameter	Mean ± SD	Median	Minimum	Maximum	95% C.I	
					Lower	Upper
TLC (/Mm3)	10186.43 ± 4728.32	9800.00	13.00	22540.00	9470.53	10902.33

Table - 5: Descriptive analysis of DLC parameters in study population (n=170).

DLC Parameter	Mean ± SD	Median	Minimum	Maximum	95% C.I	
					Lower	Upper
Neutrophils	71.65 ± 11.5	75.00	45.00	90.00	69.91	73.39
Lymphocytes	24.09 ± 10.72	21.00	7.00	50.00	22.47	25.72
Eosinophils	3.21 ± 2.41	3.00	0.00	9.00	2.85	3.58
Monocytes	0.86 ± 0.98	1.00	0.00	4.00	0.71	1.01

Table - 6: Descriptive analysis of clinical diagnosis on in the study population (n=170).

Clinical Diagnosis On	Frequency	Percentages
AA	157	92.4%
AP	13	7.6%

Table - 7: Comparison of acute appendicitis with hyper bilirubin (n=170).

Hyper Bilirubin	Acute Appendicitis		Chi-square	P-value
	Positive (N=113)	Negative (N=57)		
Yes	18 (15.93%)	35 (61.4%)	36.515	**<0.001**
No	95 (84.07%)	22 (38.6%)		

Table – 8: Predictive validity of hyper bilirubin in predicting acute appendicitis (n=170).

Parameter	Value	95% CI	
		Lower	Upper
Sensitivity	15.93%	9.72%	24.00%
Specificity	38.60%	26.00%	52.43%
False positive rate	61.40%	47.57%	74.00%
False negative rate	84.07%	76.00%	90.28%
Positive predictive value	33.96%	21.52%	48.27%
Negative predictive value	18.80%	12.18%	27.07%
Diagnostic accuracy	23.53%	17.37%	30.63%

Table - 9: Comparison of appendicular perforation with hyper bilirubin (n=170).

Hyper Bilirubin	Appendicular Perforation		Chi-square	P-value
	Positive (N=57)	Negative (N=113)		
Yes	35 (61.4%)	18 (15.93%)	36.515	**<0.001**
No	22 (38.6%)	95 (84.07%)		

Table - 10: Predictive validity of hyper bilirubin in predicting appendicular perforation (n=170).

Parameter	Value	95% CI	
		Lower	Upper
Sensitivity	61.40%	47.57%	74.00%
Specificity	84.07%	76.00%	90.28%
False positive rate	15.93%	9.72%	24.00%
False negative rate	38.60%	26.00%	52.43%
Positive predictive value	66.04%	51.73%	78.48%
Negative predictive value	81.20%	72.93%	87.82%
Diagnostic accuracy	76.47%	69.37%	82.63%

Results

The mean age was 31.38 ± 15 in the study population, ranged between 4 years to 72 years (95% CI 29.11 to 33.65) as per **Table – 1**.

Among the study population, 122 (71.8%) were participants male and the remaining 48 (28.2%) participants were female (**Table – 2**).

The mean total bilirubin was 0.87 ± 0.36 in the study population, the minimum level was 0.30

mg/dl and the maximum level was 2.70 mg/dl in the study population (95% CI 0.81 to 0.92). The mean direct bilirubin was 0.36 ± 0.15 in the study population, the minimum level was 0.10 mg/dl and the maximum level was 0.90 mg/dl in the study population (95% CI 0.34 to 0.38). The mean direct bilirubin was 0.51 ± 0.25 in the study population, the minimum level was 0.20 mg/dl and the maximum level was 1.90 mg/dl in the study population (95% CI 0.47 to 0.55). The mean SGOT was 27.74 ± 11.52 in the study population, the minimum level was 0 IU/L and the maximum level was 91 IU/L in the study population (95% CI 26 to 29.49). The mean SGPT was 27.17 ± 10.03 in the study population, the minimum level was 0.30 IU/L and the maximum level was 55 IU/L in the study population (95% CI 26 to 29.49). The mean ALP was 74.31 ± 23.91 in the study population. The minimum level was 22 and the maximum level was 120 in the study population (95% CI 70.69 to 77.93) as per **Table - 3**.

The mean TLC was 10186.43 ± 4728.32 in the study population, ranged between 13 (/Mm3) to 22540 (95% CI 9470.53 to 10902.33) as per **Table – 4**.

The mean Neutrophils were 71.65 ± 11.5 in the study population, ranged between 45 to 90% (95% CI 69.91 to 73.39). The mean Lymphocytes were 24.09 ± 10.72 in the study population, ranged between 7 to 50% (95% CI 22.47 to 25.72). The mean Eosinophils were 3.21 ± 2.41 in the study population, ranged between 0 to 9% (95% CI 2.85 to 3.58). The mean Monocytes were 0.86 ± 0.98 in the study population, ranged between 0 to 4% (95% CI 0.71 to 1.01) as per **Table - 5**.

Among the study population, 157 (92.4%) participants had Acute Appendicitis and 13 (7.6%) participants had appendicular perforation (**Table – 6**).

In acute appendicitis positive group, 18 (15.93%) had of hyper bilirubin, this proportion was 35 (61.4%) among acute appendicitis negative group. The difference in the proportion of hyper bilirubin between acute appendicitis was statistically significant (P-value <0.001) as per **Table - 7**.

When compared to acute appendicitis, hyper bilirubin had sensitivity of 15.93% (95% CI 9.72% to 24%), Specificity was 38.60% (95 CI 26% to 52.43%), False positive rate was 61.40% (95 CI 47.57% to 74%), False negative rate was 84.07% (95 CI 76 % to 90.28%), Positive predictive value was 33.96% (95 CI 21.52% to 48.27%), Negative predictive value was 18.80% (95 CI 12.18% to 27.07%), and the total diagnostic accuracy was 23.53% (95 CI 17.37% to 30.63%) as per **Table - 8**.

In Appendicular Perforation positive group, 35 (61.4%) had of hyper bilirubin, this proportion was 18 (15.93%) among Appendicular Perforation negative group. The difference in the proportion of hyper bilirubin between Appendicular Perforation was statistically significant (P-value <0.001) as per **Table - 9**.

When compared to appendicular perforation, hyper bilirubin had sensitivity of 61.40% (95% CI 47.57% to 74.00%), Specificity was 84.07% (95 CI 76.00% to90.28%), False positive rate was 15.93% (95 CI 9.72% to 24.00%), False negative rate was 38.60% (95 CI 26.00% to 52.43%), Positive predictive value was 66.04% (95CI 51.73% to 78.48%), Negative predictive value was 81.20% (95 CI 72.93% to87.82%), and the total diagnostic accuracy was 76.47% (95 CI 69.37% to 82.63%) as per **Table - 10**.

Discussion

The study was conducted in the Department of General Surgery, Govt. Kilpauk Medical College, Chennai during the period of April 2019 to October 2019. A total of 170 patients with the clinical diagnosis of acute appendicitis or appendicular perforation were studied. All patients diagnosed as acute appendicitis clinically on admission. The study done by Khan

S, 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 [11]. In a study by Beg RB, et al., bilirubin showed the highest specificity in diagnosing complicated cases at 75% compared to WBC (19%) and CRP (35%) [12]. Juric I, et al. have reported a sensitivity of 65.33% for hyperbilirubinemia in acute uncomplicated cases and 92% for complicated appendicitis [13]. The study was done by Koito Scathen, et al. in which there was hyperbilirubinemia in 86.6% of the patient of acute appendicitis bilirubin ranged from 1.2 mg/dl - 8.4 mg/dl. In my study, a total of 170 patients were taken for study.113 patients have Acute appendicitis and 57 patients have appendicular Perforation. In Acute appendicitis 18 patients (16%) have hyperbilirubinemia and in appendicular perforation 35 patients (61.4%). In my study the mean age is 31.38+15 years, 71.8% males and 28.2% females, total bilirubin ranges from 0.3 to 2.70. In acute appendicitis positive group, 18 (15.93%) had of hyper bilirubin, this proportion was 35 (61.4%) among acute appendicitis negative group [14]. The difference in the proportion of hyper bilirubin between acute appendicitis was statistically significant (P-value <0.001). In the Appendicular Perforation positive group, 35 (61.4%) had of hyper bilirubin, this proportion was 18 (15.93%) among Appendicular Perforation negative group. The difference in the proportion of hyper bilirubin between Appendicular Perforation was statistically significant (P-value <0.001) [15]. Some bacterias including E. Coli have been associated with increased levels of total serum bilirubin levels [16]. Some endotoxins released in the peripheral bloodstream interfere with the liver's mechanism for the bilirubin uptake and canalicular excretion [17]. Endotoxins produce cholestasis by damaging biliary salt transport through cytokine-mediated mechanisms. E. Coli is the most frequently isolated bacteria from peritoneal fluid in acute appendicitis. Elevated total bilirubin levels in acute appendicitis can either appear as a result of bacteremia or endotoxemia, both possible in catarrhal and phlegmonous forms as well as in perforated appendicitis [18]. Several studies had reported elevated levels of serum bilirubin in acute appendicitis. Rao PM, et al. derived hypothesis that elevated total bilirubin levels can be associated with appendicular perforation [19, 20].

Conclusion

Patients with clinical signs and symptoms of acute appendicitis and with hyperbilirubinemia having a higher probability of Appendicular perforation suggesting that serum bilirubin levels have a predictive potential for the diagnosis of Appendicular perforation. But to diagnose acute appendicitis with serum bilirubin values needs further study**.**

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