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Hyperbilirubinemia as a Diagnostic Tool to Detect Perforated Appendicitis

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Abstract

Background: Acute appendicitis is one of the most common emergencies encountered in surgical practice. Diagnosis of acute appendicitis remains a challenge as other conditions like right iliac fossa pain show similar symptoms. The present study was aimed to determine the effectiveness of hyperbilirubinemia as a diagnostic tool to detect perforated appendicitis.

Methodology: A cross-sectional study was conducted from January 2019 to June 2020 in the Department of Surgery, XXX. The study included patients diagnosed with acute appendicitis or perforated appendicitis clinically and imaging. The serum bilirubin was estimated in all the patients. All statistical analyses were performed using SPSS software. *P*-value <0.05 was considered as statistically significant.

Results: A total of 85 (male: 52; female: 33) patients with a mean age of 28.7 ± 12.3 years were included in the study. Hyperbilirubinemia (>1.0 mg/dL) was observed in 37 (43.5%) while 48 (56.5%) had normal bilirubin levels (≤ 1.0 mg/dL) in overall patients. Total bilirubin levels >1.0 mg/dL was observed in 4 (5.3%) and 33 (73.4%) patients with acute appendicitis and perforated appendicitis, respectively. Sensitivity and Specificity of bilirubin in predicting acute appendicitis and appendiceal perforation was 90.0% and 73.3%, respectively. Positive and negative predictive values of bilirubin in predicting acute appendicitis and appendiciting acute appendicitis and appendiciting acute appendicities and appendicities appendicities and appendicities appendicities appendicities appendicities appendicities appendicities appendicities and appendicities ap

Conclusion: The present study confirms the use of hyperbilirubinemia as a marker in predicting acute appendicitis or perforated appendicitis especially appendiceal perforation.

Keywords: Acute Appendicitis; perforated appendicitis; hyperbilirubinemia; serum bilirubin diagnostic tool **INTRODUCTION**

Acute appendicitis is one of the most common emergency encountered in surgical practice with an incidence of around 233 cases in 100000 individuals.^[1] It is commonly observed in young adults (10-19 years) with 70% of the patients below 30 years.^[2] The incidence is slightly higher in male compared to females, with a lifetime incidence of 8.6% and 6.7% in male and female, respectively.^[1] Most of the patients are presented with various signs and symptoms.^[3] Diagnosis of acute appendicitis remains a challenge as similar symptoms are seen in right iliac fossa pain caused by lower right sided inflammatory disorders and other conditions that do not require surgery like inflammatory bowel disease in young adults, pelvic inflammatory disease or mittelschmerz in women, benign gynaecological disease such as ovarian cysts, mesenteric adenitis in children, urinary tract infections, ruptured ovarian, omental torsion, endometriosis, diverticulitis, ectopic pregnancy, and crohn's disease.^[2–4]

Diagnosis can be a combination of history, physical examination, blood tests, urine tests, scoring systems,

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and radiological imaging.^[5,6] Delay in diagnosis and surgery in acute appendicitis may lead to various complications like appendiceal perforation which in turn may cause peritonitis, small bowel obstruction, urinary retention, and abdominal abscess formation causing an increase in morbidity and mortality.^[7,8] In some patients, diagnostic difficulties may lead to missed appendicitis or negative appendicectomies.^[9] The incidence of perforated appendicitis is 13-37% with a mortality rate of 3-15% compared to nonperforated appendicitis (0.1-0.5%).^[2] Hence, proper diagnosis plays a vital in identifying the condition.

It is evident that clinical diagnosis is often biased and none of the methods stand alone in conforming the appendicitis accurately and preventing acute redundant surgical intervention. As on date, there is no confirmatory laboratory marker for the preoperative diagnosis of acute appendicitis and perforated appendicitis.^[10] Recently, studies have reported hyperbilirubinemia as a marker for acute appendicitis which may be due to high bacterial load in the flora of the inflamed appendix than normal appendix.^[2,7,11] Portal venous system that supplies around 80% of blood to liver, carries toxins and bacteria from intestine. Liver is the major site of body that clears bacteria and their toxic by-products. But in acute appendicitis the liver might fail to clear high bacterial load leading to hyperbilirubinemia due to damage of hepatocytes. Proinflammatory cytokines such as interleukin-6 and tumor necrosis factor causes decreased clearance of bilirubin leading to hyperbilirubinemia.^[12] Thus, elevated Serum bilirubin level may help in the early and accurate diagnosis of acute appendicitis and in predicting its serious complications, most importantly the perforation. The present study was aimed to determine the effectiveness of hyperbilirubinemia as a diagnostic tool to detect the perforated appendicitis.

Materials and methods

This is a cross-sectional study conducted at department of surgery, XXX, from 1st January 2019 to 30th June 2020. The Study was approved by Institute Human Ethics Committee (IEC) and was conducted in accordance with the Helsinki Declaration. Written informed consent was obtained from all patients. All patients admitted in surgery unit during the study period with right iliac fossa pain, fever, nausea, jaundice and signs of peritonitis, clinically or

radiologically diagnosed as acute appendicitis were studied. After detailed history, physical examination and routine laboratory investigation, patients diagnosed with acute appendicitis or perforated appendicitis clinically and imaging were included in the study.

Patients with past history of jaundice or liver disease, chronic alcoholism with known chronic alcoholic liver disease, hemolytic disease, acquired or congenital biliary disease, HBsAg positive, choledocholithiasis positive, hepato-biliary cancer, and multiple blood transfusions in the past and present were excluded from the study.

Study procedure

Demographics (age, gender, fever, jaundice) data, total leukocyte count (TLC), serum total bilirubin, direct bilirubin, imaging (ultrasonography) and clinical score were collected and recorded. The normal total bilirubin range considered was 0.3 to 1 mg/dL. Patients were diagnosed for acute and perforated appendicitis clinically, aided by ultrasonography imaging, and emergency appendicectomy was performed by either open or laparoscopic method. Acute or perforated appendicitis was diagnosed intraoperative and histopathologically also.

Statistical analysis

All statistical analyses were performed using SPSS software. All continuous variables were presented as mean and standard deviation, and categorical variables were presented as absolute numbers and percentage. Independent sample t-test was used to calculate *P*-value and values <0.05 was considered as statistically significant.

Results

A total of 85 cases of acute appendicitis diagnosed either clinically, radiologically, intra operatively or histopathologically were included in the study. Of which, 52 (61%) were male and 33 (39%) were female with a mean age 28.5 \pm 13.6 years and 29.03 \pm 10.2 years, respectively. On presentation, fever [30 (35.3%)] and jaundice [20 (23.5)] were observed to be the most common symptoms. The average duration between initial symptoms to hospital presentation was 5.99 days in acute appendicitis and 3.70 days in perforated appendicitis (*P*= 0.076). Table 1 represents

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diagnosis of acute and perforated appendicitis using different methods. Compared with clinical diagnosis, perforated appendicitis was diagnosed more with ultrasonography (13 Vs 30).

From blood tests, TLC was found to be $\leq 11.0 \times 10^{9}$ /L in 42 (49.4%) patients and $\geq 11.0 \times 10^{9}$ /L in 43 (50.6%) patients. The mean total bilirubin and mean direct bilirubin levels was found to be 1.39 ± 1.02 mg/dL and 0.44 ± 0.44 mg/dL, respectively. Intraoperative diagnosis showed acute appendicitis in 42 (49.4%) and perforated appendicitis in 43 (50.6%) patients (table 1). Perforated appendicitis was diagnosed in more number of patients intraoperatively compared to clinical diagnosis (43 Vs 13). The sensitivity and specificity of clinical and ultrasonography diagnosis was compared with intraoperative findings individually and the results showed a significant difference (*P*<0.001; table 2).

Of included all patients in the study, hyperbilirubinemia (>1.0 mg/dL) was observed in 37 patients (43.5%) while 48 patients (56.5%) had normal bilirubin levels (<1.0 mg/dL). Intra-operative total bilirubin levels >1.0 mg/dL was observed in 3 (7.1%) acute appendicitis patients and in 37 (86%) perforated appendicitis patients. Histopathologically, 4 (5.3%) and 33 (73.4%) patients with acute appendicitis and perforated appendicitis, respectively had total bilirubin levels >1.0 mg/dL (table 3). Intra-operative diagnosis showed a sensitivity of 92.85% and specificity of 86.04% in diagnosing acute appendicitis and perforated appendicitis while histopathological diagnosis showed a sensitivity of 90.0% and specificity of 73.3%.

The positive predictive value of bilirubin in predicting acute appendicitis and perforated appendicitis was and 75.0% with intra-operative and 86.66% histopathological diagnosis, respectively while negative predictive value was 92.5% and 89.1%, respectively. The odd ratio of intra-operative and histopathological diagnosis was 80.16 and 24.75, respectively. A significant difference in mean total bilirubin levels diagnosed both intra-operatively (P < 0.001) and histopathologically (P < 0.001) was observed on comparing acute appendicitis and perforated appendicitis. Direct bilirubin also differed significantly between acute appendicitis and perforated appendicitis in both intraoperative (P < 0.001) and histopathological diagnosis (P = 0.01):

table 4). Images during the surgery of acute and perforated appendicitis was presented in Figure 1.

Discussion

Acute appendicitis can be cured by surgery with a short recovery period while perforated appendicitis may cause life threating conditions. Perforation and abscess formation are rare in the beginning of appendicitis but can be as high as 80% post 48hrs of onset of symptoms. The incidence of appendicular perforation is 19.2% of acute appendicitis.^[13] Due to atypical presentations and diagnostic difficulties, unnecessary appendectomy rates vary widely from ~ 20 to 30 %, which may cause a small risk of wound sepsis, adhesive intestinal obstruction, and occurrence of incisional hernia.^[3]

Despite the advances in the diagnostic field, the diagnosis of acute appendicitis remains an enigma for the surgeon. However, in acute and perforated appendicitis, a high specificity was noted between disease state and bilirubin levels.^[10,14–19] As in acute appendicitis or perforated appendicitis, inflammation causes bacterial toxins to invade hepatic parenchyma impairing bilirubin excretion from canaliculi.^[8] The present study evaluated hyperbilirubinemia as a marker in patients presented with acute appendicitis and perforated appendicitis.

In the present study, the number of men were more than women, affirming higher prevalence in male.^[20] The mean age in our study population was 28.7±12.3 years consistent with literature.^[16] Elevated TLC were observed in 50.6% of our patients, which was in par with the study conducted by Jamaluddin et al., where 46.5% of their study patients have shown an increased TLC.^[18] Compared to clinical diagnosis. ultrasonography modalities were proven effective in predicting complicated appendicitis.^[3,21] In the present study also, ultrasonography showed high specificity (62.8%) over clinical diagnosis (30.2%).

Hyperbilirubinemia (> 1.0 mg/dL) was reported in 43.5% of patients. Our findings were comparable to the study by Estrada et al., that reported elevated total bilirubin levels in 38% of study patients.^[22] Eren et al., reported hyperbilirubinemia in 10% of patients with acute appendicitis while in 59% of patients with perforated appendicitis.^[7] In accordance with this, the present study reported hyperbilirubinemia in 7.1% and 86% of patients with acute appendicitis and perforated

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appendicitis, respectively. Mean duration of symptoms and time of presentation to hospital in nonperforated and perforated appendicitis was found to be 5.9 days and 3.7 days, respectively. Studies have shown that majority of the patients presented on 4^{th} or 5^{th} day and rarely on around on 7^{th} day.^[18,23,24]

Ramaswami et al., reported, sensitivity of 93.33% and specificity of 72.86%, of bilirubin in predicting acute appendicitis and perforated appendicitis while Saxena et al., reported 92.82% and 75% of sensitivity and specificity, respectively.^[9,25] In line with previous studies, the sensitivity and specificity of bilirubin in predicting acute appendicitis and perforated appendicitis was found to be 90% and 73.3%, respectively, in the present study. Positive and negative predicative values of bilirubin in predicting acute appendicitis and perforated appendicitis was found to be 75% and 89.1%, with an odds ratio of 24.75. Chaudhary et al., reported similar findings, where positive and negative predictive values was 72.7% and100%, respectively.^[26] The present study has certain limitations that include, geographical limitation, small study population, and inaccuracy in timing of onset of symptoms and of the blood tests performed.

Conclusion

The present study confirms the use of hyperbilirubinemia as a marker in predicting acute appendicitis or perforated appendicitis especially appendiceal perforation. Along with routine laboratory tests and clinical findings, elevated serum bilirubin levels may help in accurate and precise diagnosis of acute or perforated appendicitis.

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Type of diagnosis	Type of appendicitis	Number of patients	Percentage (%)
Clinically	Acute appendicitis	72	84.7
	Perforated appendicitis	13	15.3
Ultrasonography	Acute appendicitis	55	64.7
	Perforated appendicitis	30	35.3
Intra-operative	Acute appendicitis	42	49.4
	Perforated appendicitis	43	50.6

Table 1 - Diagnosis of acute and perforated appendicitis using different techniques.

Histopathological	Acute appendicitis	40	47.1
	Perforated appendicitis	38	44.7
	Acute necrotising appendicitis	7	8.2

Table 2 - Comparing sensitivity and specificity of clinical and ultrasonography diagnosis with intraoperative diagnosis.

	Sensitivity (%)	Specificity (%)	p-value
Clinical diagnosis	100	30.2	< 0.001
Ultrasonography diagnosis	92.9	62.8	< 0.001

Table 3 - Total bilirubin levels diagnosed by intra-operation and histopathology

Type of diagnosis	Type of appendicitis	Total bilirubin (mg/dL)	Number of patients	Percentage (%)
Intra-operative diagnosis	Acute appendicitis	≤ 1.0	39	92.9
		> 1.0	3	7.1
	Perforated appendicitis	≤ 1.0	6	14.0
		> 1.0	37	86.0
Histopathological diagnosis	Acute appendicitis	≤ 1.0	36	94.7
		> 1.0	4	5.3
	Perforated appendicitis	≤ 1.0	12	26.6
		> 1.0	33	73.4

Table 4 - Comparison of mean values of total bilirubin and direct bilirubin between acute appendicitis and perforated appendicitis

	Parameters	Acute	Perforated	Necrotising	p-value
		Appendicitis	Appendicitis	Appendicitis	
Intra-operative	Number of patients	42	43		
	Total bilirubin	0.74 (0.3)	2.02 (1.1)	-	< 0.001
	Direct bilirubin	0.28 (0.1)	0.60 (0.6)	-	< 0.001
Histopathological	Number of patients	40	38	7	
	Total bilirubin	0.76 (0.36)	1.98 (1.17)	1.77 (0.45)	< 0.001
	Direct bilirubin	0.29 (0.15)	0.57 (0.57)	0.61 (0.52)	0.01

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Figure legends:

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Figure 1 - Intra-operative images. A & B - Acute appendicitis, C & D - Appendiceal perforation