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Hyperbilirubinemia an Early Predictor of perforation in acute appendicitis

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I. Introduction

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. Different clinical signs and symptoms always mimic the diagnosis of acute appendicitis, as 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. These might delay laparotomy and lead to appendiceal perforation with increased morbidity and hospital stay [1-3]. A safe alternative seems to be appendectomy as soon as the condition is suspected, a strategy that increases the number of unnecessary appendectomies [4,5]. A timelier and more accurate diagnosis has been attempted by the employment of additional laboratory tests [6-11], scoring systems [12-15], ultrasound imaging [16,17], computed tomography (CT) scan [18,19], scintigraphy [20], MRI [21], and laparoscopy [22-24]. None of these methods stands alone as they all come in support of, and are secondary to a primary clinical assessment. Hyperbilirubinemia is a new diagnostic tool for perforation of appendix. 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 Kupffer cell function, it may cause dysfunction or damage to hepatocytes (liver parenchyma). It reflects a rise in serum bilirubin (SB) 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 SB levels without a rise in liver enzymes.

The association between the elevated SB levels and the variety of infectious diseases has been noted in few studies [25-27]. This finding most commonly occurs in neonates with gram negative bacterial infection. It has also been described in patients with severe intra-abdominal infection. The pathogenesis is thought to be because of bacteremia or endotoxinemia causing impaired excretion of bilirubin from the bile canaliculi. There are only a few reports in the literature that describe the finding of hyperbilirubinemia in patients with either severe post-operative infection after appendectomy or with complicated appendicitis. The present study has been designed to evaluate the association between hyperbilirubinemia in cases of acute appendicitis and its complications. The significance of other parameters such as age, duration of symptoms, total leucocyte count (TLC), ultrasonography, Alvarado score and C-reactive protein (CRP) has also been evaluated in these cases. The establishment of a possible role of hyperbilirubinemia as a predictor of gangrenous/perforated appendicitis has been stressed so that SB levels upon admission can be used in conjunction with other diagnostic tests such as ultrasonography and CT to help determine the presence of perforation and aid in proper clinical Assessment.

II. Materials and methods

This was a single-center cohort, prospective study conducted by the department of Surgery from October 2019 to September 2020. 50 consecutive cases of acute appendicitis admitted in surgical unit 3 were recruited in the study. These were subjected to investigation to support the diagnosis. Investigation included total leukocytes count, differential leukocytes count, ultrasound, liver function tests (LFT) and CRP.

The patients were selected from those attending the emergency department at the hospital. The age of patients varied from 15 to 64 years with most of the patients falling within the age range from 15-24 years. Inclusion criteria were: patients of 15 years of age and above scheduled for appendectomy for acute appendicitis

at the emergency unit of our hospital. Exclusion criteria were: appendectomy performed incidentally or for other indications; age below 15 years; patients with appendicular lump; history of alcoholic liver disease; hemolytic or liver diseases associated with hyperbilirubinemia; history of gastrointestinal or hepatopancreatobiliary malignancy in the past. 64 patients were enrolled, 14 excluded. Out of these 14 patients, 3 had presence of liver abscesses, 4 had multiple large mesenteric lymph nodes, 2 had the presence of peritoneal tubercles suggestive of tuberculosis and 5 patients had multiple liver nodules suggestive of cirrhosis. Patients were clinically evaluated by detailed history, routine examination on initial contact with patients and the following investigations were done; complete hemogram, liver function test (LFT) (Table 1), kidney function test (KFT), blood sugar, CRP, serum proteins, X-ray chest posteroanterior (PA) view these investigations blood samples were drawn within half an hour of presentation in the emergency department and radiological investigations were done within 2 h of admission. Determination of SB was done with photometric testing using 2,4-dicholoroaniline. This method is based on the principle that in acidic solution, direct bilirubin forms a red colored azocompound with diazotized 2,4-dicholoroaniline. A specific mixture of detergents enables a safe determination of the total bilirubin.

Table 1: Reference range of serum bilirubin and liver enzymes Routine LFT results were compared with laboratory reference values given in Table 1. Alvarado scoring criteria

Test	Normal range
Serum Bilirubin	
Total	1.2 mg/dL
Direct	0.2 mg/dL
Liver Enzymes	
ALT	≤50 U/L
AST	≤50 U/L
ALP	50-300 U/L

ALT, alanine aminotransferase; AST, aspartate aminotransferase ALP, alkaline phosphatase

Table 2: Alvarado scoring system

Features	Score
Symptoms	
Migratory right iliac fossa pain	1
Nausea / Vomiting	1
Anorexia	1
Signs	
Right iliac fossa tenderness	2
Fever >37.30 °C	1
Rebound tenderness in right iliac fossa	1
Laboratory tests	
Leukocytosis (>10000/μL)	2
Neutrophilic shift to the left >75%	1
Total score	10

Table 3: Distribution of cases in different age groups (n = 50)

Age group	No. (%)
15-24	24 (48%)
25-34	17 (34%)
35-44	7 (14%)
45- 54	1 (2%)
55- 64	1 (2%)
Total	50 (100%)

Table 4: Distribution of the cases according to level of total serum bilirubin (SB) (n= 50) and histological examination

Histopathology	Total SB		Total
	<1.2 mg/dL	>1.2 mg/dL	
	No. (%)	No. (%)	
Acute Appendicitis	12 (24%)	30 (60%)	42 (84%)
Gangrenous Appendix	Nil	3 (6%)	3 (6%)
Perforated Appendix	Nil	5 (10%)	5 (10%)
Normal Appendix	Nil	Nil	Nil
Total	12 (24%)	38 (76%)	50 (100%)

Histopathology	Frequency	%
Negative (acute appendicitis with no perforation or gangrene)	42	84%
Positive (acute appendicitis with perforation and/or gangrene)	8	16%
Total	50	100%

Table 5: Distribution of liver function test according to alanine aminotransferase (ALT) (n= 50), aspartate aminotransferase (AST) and alkaline phosphatase

	Acute appendicitis	Gangrenous appendix	Perforated appendix	Normal appendix	Total
Alaline aminotransferase (Normal range 15-50 U/L)					
Normal	35 (70%)	3 (6%)	2 (4%)	Nil	40 (80%)
Minimally elevated (<1 times - <2 times)	7 (14%)	Nil	3 (6%)	Nil	10 (20%)
Moderately elevated (>2 times)	Nil	Nil	Nil	Nil	Nil
Total	42 (84%)	3 (6%)	5 (10%)	Nil	50 (100%)
Aspartate aminotransferase (Normal range 15-50 U/L)					
Normal	39 (78%)	3 (6%)	3 (6%)	Nil	45 (90%)
Minimally elevated (<1 times - <2 times)	3 (6%)	Nil	1 (2%)	Nil	4 (8%)
Moderately elevated (>2 times)	Nil	Nil	1 (2%)	Nil	1 (2%)
Total	42 (84%)	3 (6%)	5 (10%)	Nil	50 (100%)
Alkaline phosphatase (Normal range 50-300 U/L)					
Normal	39 (78%)	5 (10%)	2 (4%)	Nil	46 (92%)
Minimally elevated (<1 times - <2 times)	2 (4%)	Nil	1 (2%)	Nil	3 (6%)
Moderately elevated (>2 times)	1 (2%)	Nil	Nil	Nil	1 (2%)
Total	42	03	05	Nil	50

Table 6: Distribution of Alvarado score

Alvarado score	No of cases
10	1 (2%)
9	5 (10%)
8	10 (20%)
7	18 (36%)
6	7 (14%)
5	1 (2%)
4	2 (4%)
3	2 (4%)
2	4 (8%)

Table 7: P-value chart of different parameters

	Negative		Positive		P value
	Mean±SD	Min-Max	Mean±SD	Min-max	
Age	26.93±9.33	15-60	28.63±8.83	15-40	0.466
Hb	13.85±1.11	12-17	13.88±0.99	13-15	0.958
TLC	11690.48±4132.49	6200-24000	12162.50±4624.45	8100-22000	0.822
Serum billirubin	1.52±0.59	0.6-3.0	3.62±0.70	3.0-5.0	<0.001
AST	28.02±15.88	10-90	37.13±28.83	16-102	0.551
ALT	33.83±17.21	14-83	46.38±18.90	25-72	0.047
ALP	178.52±137.97	50-847	189.13±164.58	48-584	0.0947
CRP	107.19±28.86	60-179	168.25±12.24	156-186	<0.001
Alvarado score	6.48±1.78	2-9	8.25±1.49	6-10	0.01
Duration	2.26±1.21	1-5	2.00±0.92	1-4	0.71

Hb, hemoglobin; TLC, total leukocyte count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; CRP, C-reactive protein

Table 8: Sensitivity, specificity, positive and negative predictive value of different parameters, AUC-area under curve

	AUC	Cut off	Sensitivity	Specificity	PPV	NPV	P value
Serum bilirubin	0.997 (0.0-1.00)	2.1	100%	92.9%	72.7%	100%	<0.001
TLC	0.525 (0.307-0.704)	13500	37.5%	78.6%	25%	86.8%	0.379
CRP	0.973 (0.0-1.000)	149	100%	95.2%	80%	100%	<0.001
AST	0.567 (0.336-0.798)	28	50%	69%	23.5%	87.9%	0.419
ALT	0.723 (0.556-0.890)	35	75%	64.3%	28.6%	93.1%	0.056
ALP	0.507 (0.297-0.718)	172.5	87.5%	40.5%	21.9%	94.4%	0.231
Alvardo score	0.781 (0.556-1.000)	9.0	62.5%	95.2%	71.4%	93%	<0.001

AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value; TLC, total leukocyte count; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase

III. Discussion

In this study of 50 patients, hyperbilirubinemia was found in 30 of 42 patients with acute suppurative appendicitis and in all 8 patients with gangrenous/perforated appendicitis. This hyperbilirubinemia was mixed in type (both conjugated and unconjugated) in most of the patients and at the same time there was no elevation or minimal elevation (<100 U/L) in ALT and AST in most of the cases. Similarly, ALP was either within the normal range or was minimal to moderately elevated. For gangrenous/perforated appendicitis, the P-value of SB was <0.001, specificity 92.9%, sensitivity 100%, positive predictive value 72.7% and negative predictive value was 100%.

The level of SB was higher than 3 mg/dL in cases of gangrenous/perforated appendicitis while in cases with acute appendicitis it was lower than 3 mg/dL (P<0.05). Broadly, we can say that it was predominantly isolated hyperbilirubinemia in the majority of cases. These findings are almost similar to another reported study [28]. Since these findings were documented at the time of admission, it is unlikely that liver injury because of anesthetic agents, blood transfusion, or medication was the cause of elevated bilirubin levels. Moreover, as per our exclusion criteria patients with alcoholic liver disease, viral hepatitis, hemolytic or congenital liver diseases were excluded from the study.

The most likely explanation of the rise in SB is therefore circulating endotoxinemia as a result of appendiceal infection. Utili *et al* [29-31] has shown with *in vitro* infusion of endotoxin into the isolated rat liver that there is a dose-dependent decrease in bile salt excretion from the liver and that it is possible that *Escherichia coli* endotoxin exerts direct damage at the cholangiolar level.

It was demonstrated by Sisson *et al* in 1971 [32] 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 [33,34]. 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* [35] 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.

Indirect evidence of bacterial translocation from inflamed gastrointestinal tract or peritonitis to the liver via the portal vein and the development of hepatitis and pyogenic liver abscess was observed by Dieulafoy [36]. Two classical findings were described: firstly, simultaneous inflammation of the intestine (e.g. appendix), peritoneum and development of pyogenic liver abscesses, and secondly, bacteriological similarities of the gastrointestinal tract and pyogenic liver abscesses. These bacteria commonly reach liver from intra-abdominal organs, commonly from the appendix. Direct evidence of bacterial translocation from inflamed organs was observed in clinical and experimental studies. Recently, in one study, blood samples from the superior mesenteric vein in acute appendicitis showed bacteria in 38% of patients. These findings suggest that bacteria may transmigrate and produce portal bacteremia, hepatocellular dysfunction or pyogenic liver abscess. This low percentage of positive blood cultures cannot explain hepatocellular dysfunction in the majority of cases. Thus, there must be other substances involved. It has been shown that liver dysfunction is caused by cytokines released from the gut due to injury/inflammation. In a study [29,30], rats were subjected to intra-abdominal sepsis from cecal ligation and puncture and the following observations were made: 1) the small intestine is an important source of adrenomedullin release during poly microbial sepsis; 2) norepinephrine induced hepatocellular dysfunction in early sepsis, mediated by activation of a-2 adreno-receptors; and 3) TNF produces hepatocellular dysfunction despite normal cardiac output and hepatic microcirculation [37]. 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, hyper-dynamic 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 hyper-dynamic stage of sepsis.

Our study shows that isolated hyperbilirubinemia without much elevation in the liver enzymes is a significant predictor of appendiceal perforation. This was demonstrated by a study by Estrada *et al* [35] and other studies [38,39] showing nearly a threefold risk of perforated appendicitis in patients with total bilirubin levels greater than 1 mg/dL. The other factors which we studied in this series were age, duration of symptoms, Alvarado score, total leukocyte count, ultrasonography, and CRP. P value was not significant in any of these criteria except CRP ($P<0.001$).

The positive predictive value of SB and CRP was 72.7% and 80%, comparable to other published studies [40,41]. The negative predictive value of SB was 100% in our study as compared to 16% in the study by Khan *et al*. The negative predictive value of CRP was also 100% in our study. Therefore, in suspected cases of appendicitis elevation of SB/CRP can be used as a criterion to diagnose and manage acute appendicitis. Both sensitivity and specificity of elevated total SB level and CRP in acute appendicitis with perforation and/or gangrene is higher as compared to TLC and liver enzyme. This finding is similar to other reported studies [35,42,43]. This study also shows that the Alvarado scoring system is also of great value with a significant P value and comparable sensitivity and specificity. Therefore, SB estimation, a simple cheap and easily available test in every laboratory, can be added to the routine investigation list of clinically suspected case of acute appendicitis for the confirmation of diagnosis. Since the rise in SB level was significantly higher in patients with appendiceal perforation, it has a definite predictive potential in these cases. Therefore, obtaining SB values upon admission can be used in conjunction with more modern diagnostic tests such as CT scan, ultrasonography to help determine the presence of perforation and thus aid in prompt clinical management.

References

[1]. Harrison MW, Lindner DJ, Campbell JR, Campbell TJ. Acute Appendicitis in children: factors affecting morbidity. Am J Surg. 1984;147:605–610. [PubMed]
[2]. Savrin RA, Clatworthy HW., Jr Appendiceal rupture: a continuing diagnostic problem. Paediatrics. 1979;63:36–43. [PubMed]
[3]. Scher KS, Coil JA. The continuing challenge of perforating appendicitis. Surg Gynecol Obstet. 1980;150:535–538. [PubMed]
[4]. Karakas SP, Guelfguat M, Leonidas JC, Springer S, Singh SP. Acute appendicitis in children: comparison of clinical diagnosis with ultrasound and CT imaging. Pediatr Radiol. 2000;30:94–98. [PubMed]
[5]. Hoffmann J, Rasmussen OO. Aids in the diagnosis of acute appendicitis. Br J Surg. 1989;76:774–779. [PubMed]
[6]. Oruc MT, Kulah B, Ozozan O, et al. The value of 5-hydroxyl indole acetic acid measurement in spot urine in diagnosis of acute appendicitis. East African Med J. 2004;81:40–41. [PubMed]
[7]. Taha AS, Grant V, Kelly RW. Urine analysis for interleukin-8 in the non-invasive diagnosis of acute and chronic inflammatory diseases. Postgrad Med J. 2003;79:159–163. [PMC free article] [PubMed]
[8]. Hallan S, Asberg A. The accuracy of C-reactive protein in diagnosing acute appendicitis – a meta analysis. Scan J Clin Lab Invest. 1997;57:373–80. [PubMed]
[9]. Goodwin AT, Swift RI, Bartlett MJ, Fernando BS, Chadwick SJ. Can serum interleukin-6 levels predict the outcome of patients with right iliac fossa pain? Ann R Coll Surg Engl. 1997;79:130–133. [PMC free article] [PubMed]
[10]. Vermeulen B, Morabia A, Unger PF. Influence of white cell count on surgical decision making in patients with abdominal pain in the right lower quadrant. Eur J Surg. 1995;161:483–486. [PubMed]
[11]. Albu E, Miller BM, Choi Y, Lakhanpal S, Murthy RN, Gerst PH. Diagnostic value of C-reactive protein in acute appendicitis. Dis Colon Rectum. 1994;37:49–51. [PubMed]
[12]. Christian F, Christian GP. A simple scoring system to reduce the negative appendicectomy rate. Ann R Coll Surg Engl. 1992;74:281–285. [PMC free article] [PubMed]
[13]. Alvarado A. A practical score for the early diagnosis of acute appendicitis. Ann Emerg Med. 1986;15:557–564. [PubMed]
[14]. Ohmann C, Franke C, Yang Q. Clinical benefit of a diagnostic score for appendicitis: results of a prospective interventional study. German Study Group of Acute Abdominal Pain. Arch Surg. 1999;134:993–996. [PubMed]
[15]. Zielke A, Sitter H, Rampp T, et al. Can diagnostic scoring systems help decision making in primary care of patients with suspected acute appendicitis? Zielke Dtsch Med Wochenschr. 1999;124:545–550. [PubMed]
[16]. Douglas CD, Macpherson NE, Davidson PM, Gani JS. Randomised controlled trial of ultrasonography in diagnosis of acute appendicitis, incorporating the Alvarado score. BMJ. 2000;321:919–922. [PMC free article] [PubMed]
[17]. Rettenbacher T, Hollerweger A, Gritzmann N, et al. Appendicitis: should diagnostic imaging be performed if the clinical presentation is highly suggestive of the disease? Gastroenterology. 2002;123:992–998. [PubMed]
[18]. Walker S, Haun W, Clark J, McMillin K, Zeren F, Gilliland T. The value of limited computed tomography with rectal contrast in

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