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HYPERBILIRUBINEMIA AS AN INDICATOR IN PERFORATED APPENDICITIS

General Surgery

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ABSTRACT

Introduction: Acute appendicitis is one of the most common causes of urgent admission to the hospital.In appendicitis, elevated intra-luminal pressure and ischemic necrosis of mucosa causes tissue gangrene or perforation. This leads to cytotoxin facilitated progressive bacterial invasion or translocation into the hepatic parenchyma through portal system. This phenomenon interferes with the bilirubin excretion into the bile canaliculi. The rate of misdiagnosis of appendicitis and the rate of appendicular perforation has remained constant, inspite of increased use of ultrasonography, computed tomography scanning and laparoscopy. Among commonly used inflammation markers of Acute appendicitis, bilirubin concentration is not well studied and thus is rarely applied. Every investigation that can contribute towards a diagnosis of appendicitis is valuable to the emergency general surgeon

Aim:

1. To study the relationship between hyperbilirubinemia and acute appendicitis; and to evaluate its credibility as a diagnostic marker for acute appendicitis.
2. To evaluate whether elevated bilirubin levels have a predictive potential for the diagnosis of Appendicular perforation.

Material and methods: The study was conducted in the Department of General Surgery, Navodaya Medical College & Research centre, Raichur during the period of January 2020 to December 2020.Patients admitted with clinical diagnosis of acute appendicitis or appendicular perforation under the Department of Surgery, Navodaya Medical College & Research centre, Raichur during the study period. A total of 100 patients with clinical diagnosis of acute appendicitis or appendicular perforation were studied.

Results: .Normal bilirubin values were seen in 26% patients while, 74% had raised bilirubin levels (Hyperbilirubinemia). Of 81 patients with acute appendicitis, 71.6% had raised bilirubin levels, while 28.4% had normal levels. 19 patients were diagnosed as Appendicular perforation, 16 patients (84.21%) had raised bilirubin levels, while the remaining 03 patients (15.79%) had normal levels.Amongst the patients diagnosed with Acute appendicitis without perforation (n=81), 58 patients (71.6%) were found to have elevated bilirubin (>1.0 mg/dL) while only 23 patients (28.4%) had normal bilirubin levels (≤1.0 mg/dL). In patients diagnosed with Appendicular perforation (n=19), 16 patients (84.21%) had bilirubin elevated (>1.0 mg/dL), while only 3 patients (15.79%) had normal levels (>1.0 mg/dL). Thus, Hyperbilirubinemia was found in most of the patients diagnosed with acute appendicitis (71.6%) or Appendicular perforation (84.21%).

Conclusion: The present study suggests- Serum bilirubin levels appears to be a promising new laboratory marker for diagnosing acute appendicitis, however diagnosis of appendicitis remains essentially still - clinical. Its level come out to be a credible aid in diagnosis of acute appendicitis and would be helpful investigation in decision making.

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

KEYWORDS

INTRODUCTION

The most common cause of acute abdomen is Appendicitis. The diagnosis of acute appendicitis is based on clinical history and physical examination. It is difficult to diagnose in cases of retrocaecal or retro ileal appendix. Appendectomy is the most commonly performed abdominal surgery. 15-30% of Appendectomy specimen found to be normal. In order to decrease the number of unnecessary Appendectomy, significance of laboratory investigations like White Blood Cells, C- Reactive Protein, etc have been emphasized. Ultrasonagram of theabdomen has been widely accepted as the diagnostic tool for appendicitis. Many number of scoring system were developed to arrive the diagnosis. These scoring systems are based on clinical features, laboratory investigations. Some examples are Alvarado,Modified alvarado, RIPASA.

Still there is no definitive laboratory marker for acute appendicitis and appendicular perforations. Studies show that serum bilirubin is raised in acute appendicitis and appendicular perforations. But the significance of which is not stressed. On bacterial invasion of the appendix, there is transmigration of bacteria and release of pro-inflammatory cytokines like TNF α, Il6 .

The cytokines reach the liver through the superior mesentric vein and may lead to inflammation, abscess and liver dysfunction.

In view of the above context, the present study was undertaken to assess the relationship between HYPERBILIRUBINEMIA and acute appendicitis and to evaluate its credibility as a diagnostic marker for acute appendicitis and also, to see whether elevated bilirubin levels have a predictive potential for the diagnosis of appendicular perforation.

OBJECTIVES

The objectives of the study were-

1. To study the relationship between hyperbilirubinemia and acute appendicitis; and to evaluate its credibility as a diagnostic marker for acute appendicitis.
2. To evaluate whether elevated bilirubin levels have a predictive potential for the diagnosis of Appendicular perforation.

Investigations

The diagnosis is usually clinical; however, a decision to operate based on clinical suspicion alone can lead to the removal of a normal appendix in 15 to 30% of cases. The premise that it is better to remove a normal appendix than to delay diagnosis does not stand up to close scrutiny, particularly in the elderly.[1]

A number of Laboratory and Imaging studies have been devised to assist diagnosis.

Laboratory Tests

There is no gold standard test for appendicitis but it may be helpful in arriving the diagnosis.

WBC

A White Blood Cell count (WBC) may have significant role with leucocytosis, with more than 75% neutrophils.

A completely normal leukocyte count and differential count is found in about 10% of patients with acute appendicitis. A high white blood cell count (>20,000/mL) suggests complicated appendicitis with either gangrene or perforation.[2]

In early cases WBC count may be normal. There may be raise in WBC count over the time.

C-reactive protein

C-reactive protein (CRP) is an acute-phase reactant synthesized by the liver in response to infection or inflammation and rapidly increaseswithinthe first12hours.CRP has been reported to be useful in the diagnosis of appendicitis; however, it lacks specificity and cannot be used to distinguish between sites of infection. CRP levels of greater than 1 mg/dl are commonly reported in patients with appendicitis, but very highlevelsofCRPinpatients with appendicitis indicate gangrenous evolution of the disease, especially if it is associated with leukocytosis and neutrophilia.

However, CRP normalization is known tooccur12hoursafter onset of symptoms. Several prospective studies have shown that in adults who have had symptoms for longer than 24 hours, a normal CRP level has a negative predictive value of 97-100% for appendicitis.[3-5]

Multiple studies have been done evaluating the sensitivity of CRP level alone for the diagnosis of appendicitis in patients selected to undergo Appendectomy. Gurleyik et al noted a CRP sensitivity of 96.6% in 87 of 90 patients with histologically proven disease.[6]

Imaging Studies

Sonographic criterias for appendicitis (85% Specificity)

Noncompressible appendix of size > 6 mm AP diameter,
hyperechoic thickened appendix wall > 2 mm—*target sign*.
Appendicolith.
Interruption of submucosal continuity.
Periappendicular fluid.[7]

Computed tomography

Computed tomography (CT) is commonly used in theevaluation of adult patients with suspected acute appendicitis, especially so in the elderly.[2] CT has a high sensitivity and specificity in the diagnosis of appendicitis,[8] and rule out other causes of abdominal pain that mimic appendicitis.

In general, CT findings of appendicitis increase with the severity of the disease. Classic findings include a distended appendix greater than seven mm in diameter and circumferential wall thickening, which may give the appearance of a halo or target. As inflammation progresses, one may see Periappendicular fat stranding, edema, peritoneal fluid, phlegmon, or a periappendicular abscess.

Liver Function Tests

Importance of hyperbilirubinemia or elevated Serum Bilirubin (serum bilirubin) and its association in acute appendicitis has being postulated recently. It is hypothesized that an association exists between hyperbilirubinemia and acute appendicitis and its complications such as appendicular perforation.[9]

BILIRUBIN METABOLISM

Destruction of senescent RBC in the RE system 80-85%
Marrow destruction of matured RBC (15-20%)
Heme containing protein (liver turnover)- minimal

Hemoglobin

↓ **Heme oxygenase**

Biliverdin

↓ **Biliverdin reductase**

Bilirubin

↓

binds with albumin
Bilirubin albumin complex transported to the liver

↓

Liver takes up bilirubin

↓

UDP Glucuronyl transferase

Conjugate with glucuronic acid and forms monoglucuronide and diglucuronide

↓

After deconjugation, bilirubin is absorbed at terminal ilium, ileocecal junction

↓

Free bilirubin

↓

Reduction

Urobilinogen 20% (gives urine color) and Stercobilinogen 80% (gives stool color)

↓

Oxidized and re-entered into enterohepatic circulation (13%) Excreted through urine (4-7%)

Bilirubin is produced from the destruction of senescent RBCs by the removal of the iron by the action of the enzyme heme oxygenase; the reaction liberates carbon monoxide, the only reaction in the body releasing carbon monoxide. The intermediate product being biliverdin. Bilirubin a water insoluble compound is transported to the liver bound to albumin.

In the liver the bilirubin is taken up activity by two mechanisms. The first being a membrane bound carrier protein and the second being by two cytoplasmic proteins namely protein Y and Z. These proteins pick up the bilirubin diffusing into the cytoplasm.

Once in the hepatocyte the bilirubin is bound to glucuronic acid thus forming bilirubin mono and diglucuronide by the enzyme UDP glucuronyl transferase. The enzyme reduced products get excreted as stercobilinogen.

The kidneys excrete a part of the absorbed bilirubin as urobilinogen and the rest enters the enterohepatic circulation.

Hyperbilirubinemia and appendicitis

Hyperbilirubinemia, has not been considered as a potential marker for preoperative diagnosis of acute appendicitis and appendicular perforation until now. Increased secretion and decreased bilirubin clearance has a role in the hyperbilirubinemia of patientswith appendicular perforation.

Bacterial infections cause hepatic dysfunction leading to abnormalities in bile acid production and bile flow. This results in hyperbilirubinemia.

Extrahepatic bacterial infection, as in perforated appendicitis, have a proinflammatory cytokine and nitric oxide – triggered cholestasis by affecting hepatocellular and bile duct function.[10]

Most common bacterial species causing acuteappendicitisare *Escherichia coli* and Bacteroides fragilis. These organisms interfere with hepatocyte microcirculation and cause sinusoidal damage .

*E. Coli*endotoxin leads to impaired bile production. And also,

E. Coli infection causes hemolysis of erythrocytes. This leads to hyperbilirubinemia.

Acute Appendicitis/Appendicular perforation
(Inflammatory response causes appendix to become more oedematous and ischmeic)

↓

Causes transmigration/translocation of bacteria/toxins/cytokines

↓

Leading to endotoxemia / bacteremia

↓

Invasion of Bacteria into the hepatic parenchyma interferes with the physiology of excretion of bile

↓

Hyperbilirubinemia

Cholestasis in severe bacterial infection, particularly in childhood or post operatively, is presumably hepatocellular in nature. It can also be related to cholestatic effect of endotoxin on sodium- potassium-ATPase.[11]

All the constituents of bile show an increased level in serum. Conjugation of biliarysubstanceisintactbutexcretionis defective. Serum alkaline phosphatase is raised. The rise is due to increased synthesis or release of enzymes from liver or biliary plasma membrane.The minimal hepatocellular damage may be suspected by noting minimal elevated transaminase value and sometimes serum bilirubin.

There are no sufficient number of studies involving large number of patients to ascertain relationship between hyperbilirubinemia and acute appendicitis.

Literature review

It is postulated that there is relationship between hyperbilirubinemia and acute appendicitis and its complications.

A retrospective analysis by Sand M et al, done at The Department of General and Visceral Surgery, AugustaKrankenanstalt, Academic Teaching Hospital of the Ruhr University, Bochum, Germany involving 538 patients (306 females: 232 males, mean age, 35.6 years) with histologically confirmedacute appendicitis who underwent conventional or laparoscopic Appendectomy between January 2004 to December 2007 found the mean bilirubin level of all patients was 0.9mg/dl (±0.6 SD mg/dl; range 0.1 to 4.3mg/dl; median 0.7mg/dl).Patients with Appendicular perforation, however had a mean bilirubin level of 1.5mg/dl (±0.9 SD mg/dl; range 0.4 to 4.3 mg/dl; median 1.4mg/dl), which was significantly higher than those with a non perforated appendicitis *(p<0.05)*. The Specificity of hyperbilirubinemiaforappendicularperforationwas0.86compared with 0.55 for white blood count and 0.96 for C-reactive protein.[12] The study concluded that the Patients with hyperbilirubinemia and clinical symptoms of appendicitis should be identified as having probability of appendicular perforation than those with normal bilirubin levels.[13]

A retrospective analysis done at Department of Surgery, St. Luke's Hospital, Kilkenny, Ireland by Emmanuel A et al, whereby retrospective analysis of appendectomies performed in two hospitals (n=472) was done. Data collected included laboratory and histological results.Patients were grouped according to histology findings and comparisons were madebetweenthe groups.[12]They found that the mean bilirubin levels were higher for patients with simple appendicitis compared to those with a non- inflamed appendix (p<0.001). More patients with simple appendicitis had hyperbilirubinemia on admission (30% vs 12%) and the odds of these patients having appendicitis were over three times higher (odds ratio:3.25, p<0.001). Hyperbilirubinemia had a specificity of 88% and apositive predictive value of 91% for acute appendicitis. Patients with appendicitis who had a perforated or gangrenous appendix had higher mean bilirubin levels (p=0.01) and were more likely to have hyperbilirubinemia (p<0.001).The specificity of hyperbilirubinemia for perforation or gangrene was70%. The specificities of white cell count andC-reactiveprotein were less than hyperbilirubinemia for simple appendicitis (60% and 72%) and perforated or gangrenous appendicitis (19% and 36%). The authors concluded that hyperbilirubinemia is a valuable marker for acute appendicitis. Patients with hyperbilirubinemia are also more likely to have appendicular perforation or gangrene. Bilirubin should be included in the assessment of patients with suspected appendicitis.[12]

A retrospective review done at the Department of Surgery,Keck School of Medicine of the University of Southern California and LosAngelesCounty, USCMedicalCenter, Los Angeles, CA, USA betweenJanuary 2005 to December 2005 by Estrada J et al studied the relationship between hyperbilirubinemia and appendicitis. Patients with liver function tests on admission and pathologically confirmed appendicitis were included in the study.Age, duration of symptoms, temperature, white blood cell counts, systemic inflammatory response score, and bilirubin levels were independent variables in a logistic regression analysis assessingfactors predicting the presence or absence of appendicular gangrene/perforation.[14] Elevated total bilirubin levels(>1mg/dl)were found in 59 (38%) of 157 patients. Patients with gangrene/perforation were significantly *(p=0.004)* morelikelyto have hyperbilirubinemia than those with acute suppurative appendicitis. No statistical differences were observed for any of the other variables. On logistic regression theonlysignificant relationship between the presence or absence of appendicalgangrene and perforation was the presence of hyperbilirubinemia (p=0.031, 95% confidence interval 1.11–7.6). The odds of appendicular perforation are three times higher (odds ratio 2.96) for patients with hyperbilirubinemia compared to those with normal bilirubin levels. Hyperbilirubinemia is frequently associated with appendicitis. Elevated bilirubin levels have a predictive potential for the diagnosis of appendicular perforation.[15]

MATERIALS AND METHODS

The study was conducted in the Department ofGeneral Surgery, Navodaya Medical College & Research centre, Raichur during the periodofJanuary 2020 to December 2020.

Source of data

Patients admitted with clinical diagnosis of acute appendicitis or appendicular perforation under the Department of Surgery, Navodaya Medical College & Research centre, Raichur during the study period.

Sample size

A total of 100 patients with clinical diagnosis of acute appendicitis or appendicular perforation were studied.

Sampling method

The sample size was calculated based on the following formula.

$$n = \frac{Z^2 x p x}{q d^2}$$

Where,

n = Sample size

Z = 1.96 ≈ 2 (considering confidence as 95%)

p = prevalence (prevalence is taken as 50% as exact prevalence is not known)

q = 100 – p that is, 50%

d = Absolute error which was 10%

Selection criteria

Inclusion

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

Exclusion

- 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).16
- Hemolytic disease.
- Acquired or congenital biliary disease.

- All patients with positive HBsAg.
- All patients with cholelithiasis.
- All patients with cancer of hepato-biliary system.

Procedure

Ethical clearance has been obtained from "Ethical Clearance Committee" of the institution for the study. Based on the selection criteria patients admitted with clinical diagnosis of acute appendicitis or appendicular perforation under Department of Surgery, Navodaya Medical College & Research centre during the study period were screened. 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 was done for all and recorded in the profoma

The following tests were carried out on admission.
- Routine blood investigations (Complete blood count, platelet count, reticulocyte count).
- Peripheral smear to rule out hemolytic anemia.
- Serum haptoglobulin if peripheral smear and blood tests indicate features of hemolytic anemia.
- Serum Bilirubin (Total and Direct bilirubin).
- Liver Function Tests (LFTs) which include;

- SGPT (Alanine transaminase).
- SGOT (Aspartate transaminase).
- ALP (Alkaline phosphatase).

- Seropositivity for HbsAg
- Urine analysis (routine and microscopy).

The serum bilirubin and LFTs were carried out using the Auto Analyser machine available in the hospital and HbsAg was tested by ELISA / Spot technique using HEPALISA© or HEPACARD© kit.

Reference Range of Serum Bilirubin and Liver Enzymes[17]

Test	Normal Range
Serum Bilirubin	
Total	0.3 - 1.0 mg/dl
Direct	0.1 – 0.3 mg/dl
Liver Enzymes	
SGPT	0 – 35 U/L
SGOT	0 – 35U/L
ALP	30 – 120U/L

The results were grouped as Normal or Raised (hyperbilirubinemia) as per the above reference values.

STATISTICALANALYSIS

The data obtained was tabulated on Microsoft excel spreadsheet and analysed as below.

- Patients with clinical diagnosis of acute appendicitis having hyperbilirubinemia were expressed in percentage as

$$= \frac{\text{Patients with clinical diagnosis of acute appendicitis with elevated Serum bilirubin level}}{\text{All patients with clinical diagnosis of acute appendicitis}}$$

- Mean of the level of elevation of Serum bilirubin was calculated for patients with clinical diagnosis of acute appendicitis.
- Patients with clinical diagnosis of appendicular perforation having hyperbilirubinemia were expressed in percentage as;

$$= \frac{\text{Patients with clinical diagnosis of appendicular perforation with elevated Serum bilirubin}}{\text{All patients with clinical diagnosis of appendicular perforation}}$$

- Mean of the level of elevation of serum bilirubin were calculated for patients with clinical diagnosis of appendicular perforation.
- A hypothesis was made based on the observation of the level of the two means.
- Also, sensitivity, specificity, positive predictive value, negative predictive value and Odds ratio was determined by 2 x 2 table as below.

	Acute appendicitis	Appendicular perforation
Raised Sr. Bilirubin	A	B
Normal Sr. Bilirubin	C	D
	a + c	b + d

$$\text{Sensitivity:} \frac{a}{a+c} \times 100$$

$$\text{Specificity:} \frac{b}{b+d} \times 100$$

$$\text{Positive predictive value:} \frac{a}{a+b} \times 100$$

$$\text{Negative predictive value:} \frac{d}{c+d} \times 100$$

$$\text{Odds ratio:} \frac{ad}{bc}$$

RESULTS

A total of 100 patients with clinical diagnosis of acute appendicitis or appendicular perforation admitted in the Department of General surgery, Navodaya Medical College & Research centre were studied. As per the study, the age group 11-20years is most commonly affected (44%) followed by age group 21-30 (32%). The youngest patients of this study were of 8 years old while the oldest patient was a 70 year lady

Table 3: Distribution of patients by age

Age Group (years)						
≤10	11-20	21-30	31-40	41-50	51-60	61-70
8	44	32	8	3	4	1

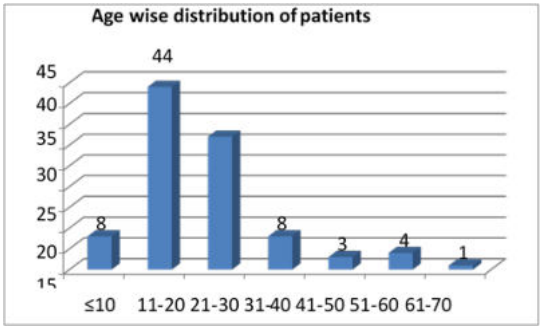


Table 4: Sex distribution

Sex	Number	Percentage
Male	56	56
Female	44	44
Total	**100**	**100.00**

Out of 100 patients enrolled for the study, 56 patients (56%) were males while the remaining 44 patients (44%) were females.

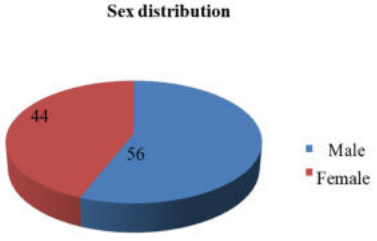


Table 5: Mean Age distribution among sex

Sex	Age (yrs)	SD
Male	24	11.93
Female	21.9	11.93
Overall	**23.1**	**11.99**

The overall mean age of all 100 patients was 23.1 ± 11.99 years (range, 11.11–35.09 years). The average age in males and females was 24 ± 11.93 years (range, 12.07 –35.93 years) and 23.1 ± 11.93 years (range, 11.17 –35.03 years) respectively.

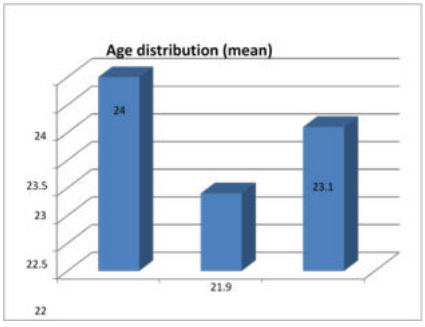


Table 6: Liver Function Tests

Parameters	Mean	SD
Total bilirubin (mg/dL)	1.5	0.8
Direct bilirubin (mg/dL)	1.0	0.7
Indirect bilirubin (mg/dL)	0.5	0.2
SGOT (U/L)	27.9	12.2
SGPT (U/L)	25.9	11.0
ALP (U/L)	80.8	21.6

The mean Total bilirubin of all 100 patients was 1.5 ± 0.8 mg/dL (range,

0.7 – 2.3 mg/dL) while the Direct bilirubin was 1.0 ± 0.7 mg/dL (range, 0.3-1.7 mg/dL). The mean SGOT and SGPT were 27.9 ± 12.2 U/L (range, 15.7-40.1

U/L) and 25.9 ± 11.0 U/L (range, 14.9 – 35.9 U/L). The mean ALP values were 80.8 ± 21.6 U/L (range, 59.2 -102.4 U/L).

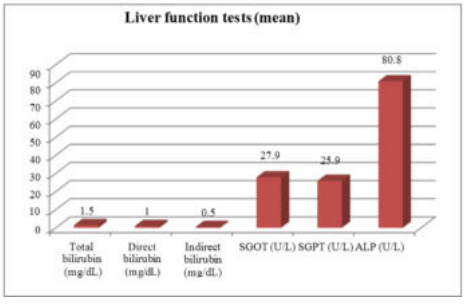


Table 7: Total bilirubin levels

Total bilirubin (mg/dL)	Number	Percentage
< 1.0	26	26.0
≥ 1.0	74	74.0
Total	**100**	**100.00**

26 patients (26%) of all 100 patients were found to have normal bilirubin levels (≤ 1.0 mg/dL), while 74 patients (74%) had raised bilirubin levels (> 1.0 mg/dL).

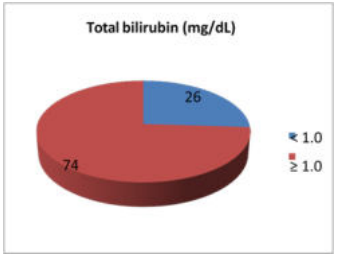


Table 8: Bilirubin levels in patients with uncomplicated acute appendicitis as diagnosis

Total bilirubin (mg/dL)	Distribution in Patients with uncomplicated Acute Appendicitis	
	Number	Percentage
> 1.0	58	71.60
≤ 1.0	23	28.40
Total	**81**	**100.00**

Of 81 patients diagnosed as uncomplicated acute appendicitis, 58 patients (71.6%) had raised bilirubin levels (> 1.0 mg/dL), while the remaining 23 patients (28.4%) had normal levels (≤ 1.0 mg/dL).

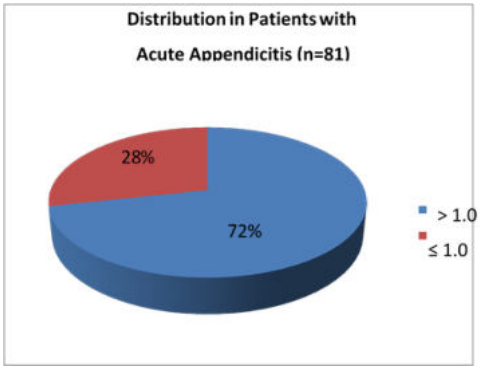


Table 9. Bilirubin levels in patients with Appendicular perforation diagnosis

Total bilirubin (mg/dL)	Distribution in Patients with Appendicular perforation	
	Number	Percentage
> 1.0	16	84.21
< 1.0	03	15.79
Total	**19**	**100.00**

19 patients diagnosed as Appendicular perforation, 16 patients (84.21%) had raised bilirubin levels (> 1.0 mg/dL), while the remaining 03 patients (15.79%) had normal levels (≤ 1.0 mg/dL).

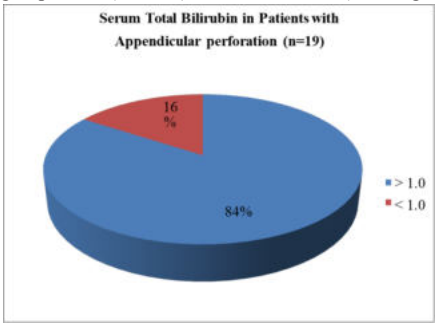


Table 10. Total leukocyte count (TLC)

TLC count/mm^3	Distribution (n=100)	
	Number	Percentage
≤ 11,000	65	65
> 11,000	35	35
Total	**100**	**100.00**

65 patients (65%) had Total Leukocyte count less than 11,000/mm^3 while 35 patients (35%) counts above 11,000/mm^3.

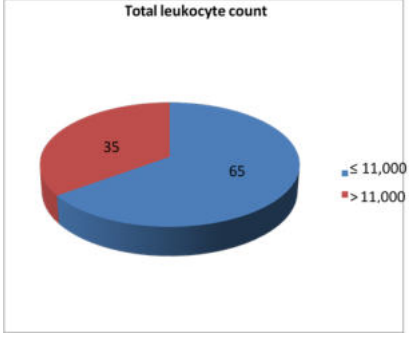
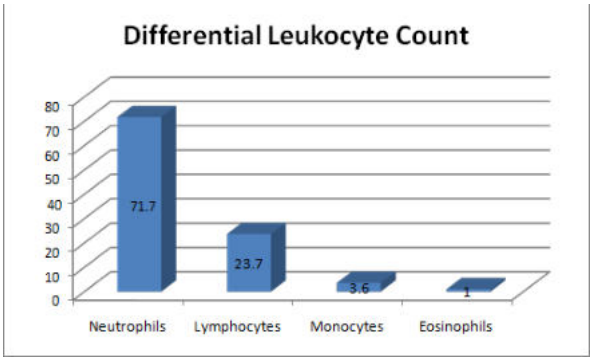


Table 11. Differential Leukocyte Count (DLC)

Differential Leukocyte Count (DLC		Mean value	
		Mean	SD
Total count (/mm^3)		10030	3712
Differential count	Neutrophils	71.7	11.5
	Lymphocyte s	23.7	10.7
	Monocytes	3.6	2.6
	Eosinophils	1.0	1.4

The mean of TLC count in all patients was 10030±3712/mm3 (range, 6318 - 13742/mm3), in which the highest percentage constituted neutrophils with 71.7% followed by 23.7% by Lymphocytes.



Differential Leukocyte Count

Table 12. Pre-Operative Diagnosis

Pre – Operative Diagnosis	Distribution (n=100)	
	Number	Percentage
Acute appendicitis	91	91
Appendicular perforation	09	09
Total	**100**	**100**

In the study population of 100 patients, 91 patients (91%) were diagnosed as acute appendicitis while 9 patients (9%) were diagnosed with Appendicular perforation.

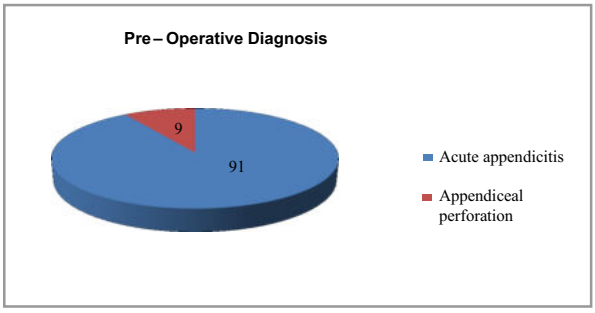


Table 13. Ultrasonographic findings

Findings	Distribution (n=100)	
	Number	Percentage
Normal	18	18
Acute Appendicitis	69	69
Appendicular perforation	13	13
Total	**100**	**100**

On Ultrasonography, 69 patients (69%) were diagnosed as Acute appendicitis, 13 patients (13%) as Appendicular perforation and 18 patients (18%) were reported as normal ultrasonographic findings.

Ultrasonographic findings

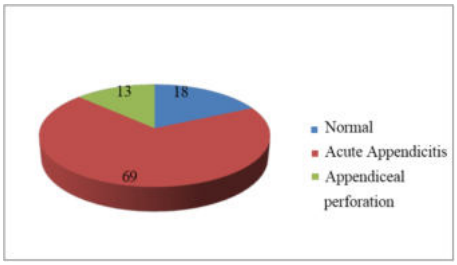


Table 14. Histopathological diagnosis

Diagnosis	Distribution (n=100)	
	Number	Percentage
Acute appendicitis	81	81
Appendicular perforation	19	19
Total	**100**	**100**

Histopathologically, 81 patients (81%) were confirmed as Acute appendicitis while 19 patients (19%) were diagnosed with Appendicular perforation.

Histopathological diagnosis

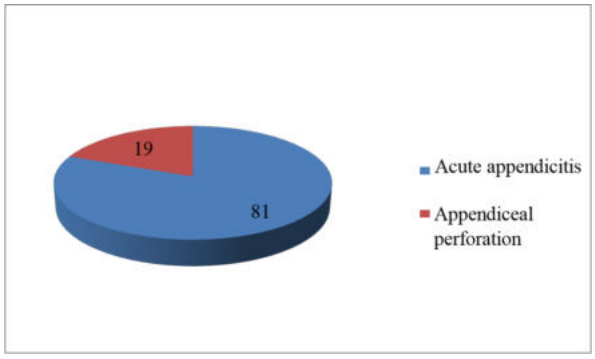


Table 15. Comparison of mean serum bilirubin levels in patients with acute appendicitis and Appendicular perforation

Bilirubin levels (mg/dL)	Diagnosis			
	Acute appendicitis		Appendicular perforation	
	Mean	SD	Mean	SD
Total bilirubin	1.4	0.65	1.9	1.16
Direct bilirubin	0.9	0.57	1.2	1.06
Indirect bilirubin	0.5	0.21	0.70	0.33

The mean bilirubin levels in patients diagnosed with Acute appendicitis was 1.4 ±0.65 mg/dL (range, 0.75 – 2.05 mg/dL) while in patients diagnosed with Appendicular perforation was 1.9±1.16 mg/dL (range, 0.74 – 3.06 mg/dL). The Direct bilirubin and Indirect bilirubin in patients diagnosed with Acute appendicitis were 0.9±0.57 mg/dL and 0.5±0.21 respectively. The Direct bilirubin and Indirect bilirubin in patients diagnosed with Appendicular perforation were 1.2±1.06 mg/dL and 0.70±0.33 mg/dL respectively.

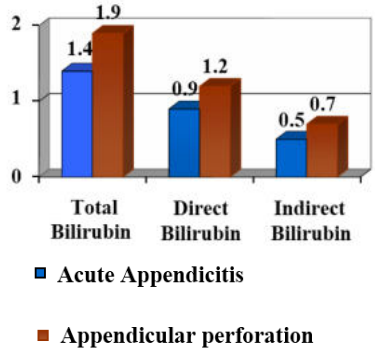


Figure 21: Mean Bilirubin values of Acute Appendicitis and Appendicular perforation

Table 16. Correlation of acute appendicitis and Appendicular perforation with total serum bilirubin levels

Serum bilirubin (mg/dL)	Final diagnosis (n=100)			
	Acute appendicitis (n=81		Appendicular perforation (n=19)	
	Number	%	Number	%
> 1.0	58	71.6	16	84.21
≤ 1.0	23	28.4	03	15.79
Total	**81**	**100.00**	**19**	**100.00**

58 patients (71.6%) of the total patients diagnosed with Acute appendicitis (n=81) were found to have elevated bilirubin levels (> 1.0 mg/dL) while 23 patients (28.4%) had normal bilirubin levels (≤ 1.0 mg/dL). Similarly,

16 patients (84.21%) of the total patients diagnosed with Appendicular perforation (n=19) were found to have elevated bilirubin levels (> 1.0 mg/dL)

while 03 patients (15.79%) had normal bilirubin levels (≤ 1.0 mg/dL).

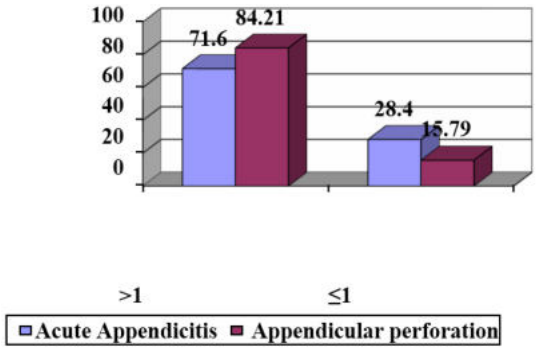


Figure 22: Bilirubin values among patients with Acute Appendicitis and Appendicular perforation

From Table, following values were calculated as -

Sensitivity

$$= \frac{a}{a+c} = \frac{58}{58+16} = 71.6\%$$

Therefore, sensitivity of bilirubin in predicting acute appendicitis and Appendicular perforation diagnosis was 71.6%.

Specificity

$$= \frac{d}{b+d} = \frac{3}{16+3} = 15.79\%$$

Therefore, specificity of bilirubin in predicting acute appendicitis and Appendicular perforation diagnosis was 15.79%

Positive predictive value

$$= \frac{a}{a+b} = \frac{58}{58+16} = 78.38\%$$

Therefore, Positive predictive value of bilirubin in predicting acute appendicitis and Appendicular perforation diagnosis was 78.38%.

Negative predictive value

$$= \frac{d}{c+d} = \frac{3}{23+3} = 11.54\%$$

Therefore, Negative predictive value of bilirubin in predicting acute appendicitis and Appendicular perforation diagnosis was 11.54%.

Odds ratio:

$$= \frac{ad}{bc} = \frac{58 \times 3}{23 \times 16} = 0.472$$

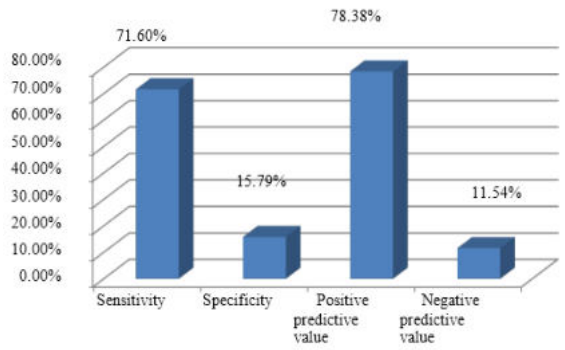
Therefore, Odds ratio is 0.472.

Table 17. Accuracy of serum bilirubin as a marker in predicting Appendicular perforation

	Accuracy
Sensitivity	71.6%
Specificity	15.79%
Positive predictive value	78.38%
Negative predictive value	11.54%
Odds ratio	0.472

The Sensitivity and Specificity of serum bilirubin as a marker in predicting acute appendicitis and Appendicular perforation was 71.6% and 15.79% respectively. Similarly the Positive predicative value and Negative predicative value for the same is 78.38% and 11.54% respectively. The Odds ratio was calculated to be 0.472.

Accuracy of serum bilirubin as a marker in predicting Appendicular perforation



DISCUSSION

Acute appendicitis is the most common cause of " acute abdomen" in young adults. Appendectomy is the most frequently performed emergency abdominal operation and is often the first major procedure performed by a surgeon in training.[1] About 8% of people in Western countries have appendicitis at some time in their lifetime.[2]

The peak incidence of acute appendicitis is in the second and third decade of life. It is relatively rare in infants, and becomes increasingly common in childhood and early adult life. The incidence of appendicitis is equal in males and females before puberty. In teenagers and young adults, the male – female ratio increases to 3:2 at age 25.[1] The lifetime rate of Appendectomy is 12% for men and 25% for women, with approximately 7% of all people undergoing appendectomy for acute appendicitis during their lifetime.[18,19]

Obstruction of the lumen is believed to be the major cause of acute appendicitis.[2] Faecoliths are the usual cause of obstruction. Less-common causes are hypertrophy of lymphoid tissue, tumors, intestinal parasites.[17] The bacteriology of normal appendix is similar to that of normal colon.

The principal organism seen in normal appendix, in acute appendicitis, and in perforated appendicitis are *Escherichia Coli* and *Bacteroids fragilis.* However a wide variety of both facultative and anaerobic bacteria may be present.[17]

The diagnosis of acute appendicitis is essentially clinical; however, a decision to operate based on clinical suspicion alone can lead to the removal of a normal appendix in 15 to 50% of cases.[20] The premise that it is better to remove a normal appendix than to delay diagnosis does not stand up to close scrutiny, particularly in the elderly1 as such procedures are associated with complications in 50% cases.[21] Hence, the diagnosis of Appendicitis still remains a dilemma in spite of the advances in various laboratory and radiological investigations.

A new tool to help in the diagnosis of acute appendicitis would thus be welcome.

Serum Bilirubin level elevation will help in the accuracy of clinical diagnosis of acute appendicitis and more importantly help in foreseeing and preventing impeding complications of acute appendicitis.

This study was taken up with this thought – that is it possible to add serum bilirubin as a new laboratory marker to aid in the diagnosis of acute appendicitis and if so, does it have the credibility to help us foresee an impending complication of acute appendicitis?

Importance of hyperbilirubinemia and its association in acute appendicitis has being postulated recently. There are only a few case reports in the available literature that describe the finding of hyperbilirubinemia in patients of acute appendicitis.[15] It is hypothesized that an association exists between hyperbilirubinemia and acute appendicitis and its complications.[15]

The present study was undertaken to study the relationship between hyperbilirubinemia and acute appendicitis and to evaluate its credibility as a diagnostic marker for acute appendicitis and also, to evaluate whether elevated bilirubin levels have a predictive potential for the diagnosis of Appendicular perforation.

This study was conducted in the Department of General Surgery, Navodaya Medical College & Research centre over a period of one year from January 2020 to December 2020 on 100 patients with clinical diagnosis of Acute appendicitis and Appendicular perforation.

In the present study of the 100 patients enrolled for the study, 56 patients (56%) were males while the remaining 44 patients (44%) were females. The mean age in our study population (100 patients) was 23.1 ± 11.99 years (range, 11.11–35.09 years). This is consistent with the quoted incidence of Appendicitis in the literature where it is most frequently seen in patients in their second through fourth decades of life.[18,19] The average age group in males 24 ± 11.93 years (range, 12.07 –35.93 years) was slightly higher than females 23.1 ± 11.93 years (range, 11.17 –35.03 years).

Hyperbilirubinemia (> 1.0 mg/dL) in our study was found in 74 patients (74%) of all the 100 patients (n=100) enrolled in the study, while 26 patients (26%) had normal bilirubin levels (≤ 1.0 mg/dL). Estrada et al[15] had found hyperbilirubinemia in 59 (38%) of 157 patients studied with acute appendicitis.

The mean total serum bilirubin of all 100 patients was 1.5 ± 0.8 mg/dL (range, 0.7 – 2.3 mg/dL), which was above the normal range (≤ 1.0 mg/dL) considered for the study, hence indicating the occurrence of hyperbilirubinemia. The mean of Direct bilirubin was 1.0 ± 0.7 mg/dL (range, 0.3-1.7 mg/dL) while that of Indirect bilirubin was 0.5±0.2 mg/dL (range, 0.3 – 0.7 mg/dL). Our finding was consistent with hyperbilirubinemia found in a study conducted by Khan S,[22] who found average level of serum bilirubin in his study population to be 2.38 mg/dL.

All patients were found to have SGOT and SGPT within the normal range, thus excluding any associated liver pathology (Exclusion criteria). The mean SGOT and SGPT were 27.9 ± 12.2 U/L (range, 15.7-40.1 U/L) and 25.9 ± 11.0 U/L (range, 14.9 – 35.9 U/L). The mean ALP values were 80.8 ± 21.6 U/L (range, 59.2 -102.4 U/L).

In our study population of 100 patients, 91 patients (91%) were diagnosed as acute appendicitis pre-operatively while 09 patients (9%) were diagnosed with Appendicular perforation.

The diagnosis was confirmed post-operatively by histopathological reports (HPR) and those differing from the pre- operative diagnosis were excluded from the study.

Amongst the patients diagnosed with Acute appendicitis without perforation (n=81), 58 patients (71.6%) were found to have elevated bilirubin (>1.0 mg/dL) while only 23 patients (28.4%) had normal bilirubin levels (≤1.0 mg/dL). In patients diagnosed with Appendicular perforation (n=19), 16 patients (84.21%) had bilirubin elevated (>1.0 mg/dL), while only 3 patients (15.79%) had normal levels (>1.0 mg/dL). Thus, Hyperbilirubinemia was found in most of the patients diagnosed with acute appendicitis (71.6%) or Appendicular perforation (84.21%).

The total leukocyte count was found elevated in just 35 patients (35%) of the total 100 patients. The mean of TLC count in all patients was 10030±3712/mm3 (range, 6318 - 13742/mm3), in which the highest percentage constituted Neutrophils with 71.7% followed by 23.7% by Lymphocytes.

On Ultrasonography, 69 patients (69%) were diagnosed as Acute appendicitis, 13 patients (13%) as Appendicular perforation and 18 patients (18%) were reported as normal ultrasonographic findings. Ultrasonography per- se was 82% sensitive for appendicitis and/or Appendicular perforation, hence Ultrasonography is a helpful tool in diagnosing appendicitis or perforation.

The mean bilirubin levels in patients diagnosed with Acute appendicitis was 1.4 ±0.65 mg/dL (range, 0.75 – 2.05 mg/dL) while in patients diagnosed with Appendicular perforation was 1.9±1.16 mg/dL (range, 0.74 – 3.06 mg/dL). Hence, we see that patients with Appendicular perforation had higher levels of bilirubin as compared to that of acute appendicitis. So we infer that, patients with features suggestive of appendicitis with higher values of bilirubin, are more susceptible of having Appendicular perforation than those with normal or slightly elevated total serum bilirubin.

Sand et al[13] in his study found the mean bilirubin levels in patients with Appendicular perforation to be significantly higher than those with a non- perforated appendicitis.

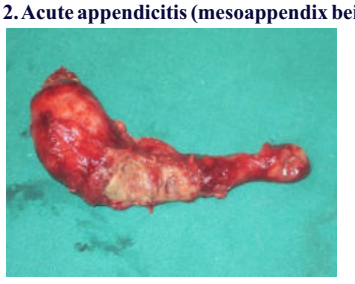
The Direct bilirubin and indirect bilirubin in patients diagnosed with acute appendicitis were 0.9±0.57 mg/dL and 0.5±0.21 respectively. Similarly, direct bilirubin and indirect bilirubin in patients diagnosed with Appendicular perforation were 1.2±1.06 mg/dL and 0.70±0.33 mg/dL respectively.

The Sensitivity, Specificity, Positive predictive value, Negative predictive value and Odds ratio was calculated from a 2x2 table. Sensitivity and Specificity of bilirubin in predicting acute appendicitis and Appendicular perforation diagnosis was 71.6% and 15.79% respectively. Similarly Positive predictive value and Negative predicative value of bilirubin in predicting acute appendicitis and Appendicular perforation diagnosis was 78.38% and 11.54% respectively. The Odd□ s ratio was calculated to be 0.472.

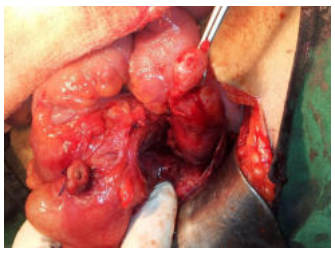
The sensitivity in our study was more than that by Sand et al[13] in which, he found the sensitivity and specificity in his study of hyperbilirubinemia for predicting Appendicular perforation to be 70% and 86.0% respectively.

Photograph 1: Acute Appendicitis

Photograph 2. Acute appendicitis (mesoappendix being ligated)



Photograph 3: Inflamed Appendix with Faecalith



Photograph 4: Appendicular perforation (ligated and cut at base)

CONCLUSION

The present study suggests-

- Serum bilirubin levels appears to be a promising new laboratory marker for diagnosing acute appendicitis, however diagnosis of appendicitis remains essentially still - clinical. Its level come out to be a credible aid in diagnosis of acute appendicitis and would be helpful investigation in decision making.
- 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.

SUMMARY

Acute appendicitis is the most common cause of "acute abdomen" in young adults. Diagnosis of Appendicitis still remains a dilemma in spite of the advances in various laboratory and radiological investigations. Importance of hyperbilirubinemia or elevated Serum Bilirubin and its association in acute appendicitis has been postulated recently. It is hypothesized that an association exists between hyperbilirubinemia and acute appendicitis and its complications.

The present study was undertaken to assess relationship between hyperbilirubinemia and acute appendicitis and to evaluate its credibility as a diagnostic marker for acute appendicitis and also, to see whether elevated bilirubin levels have a predictive potential for the diagnosis of Appendicular perforation.

The present study was conducted in the Department of Surgery, Navodaya Medical College & Research centre during the period of January 2020 to December 2020. A total of 100 patients with clinical diagnosis of acute appendicitis or Appendicular perforation were studied. The serum bilirubin and LFTs were carried out in all the patients.

In this study, males (56%) outnumbered females (44%) and overall the mean age was 23.1 ± 11.99 years. Mean total bilirubin was noted as 1.5 ± 0.8 mg/dL (range, 0.7 – 2.3 mg/dL) while direct bilirubin was 1.0 ± 0.7 mg/dL (0.2-1.7 mg/dL). The mean SGOT and SGPT were 27.9 ± 12.2 U/L (range, 15.7-40.1U/L) and 25.9 ± 11.0 U/L (range, 14.9 35.9U/L). The mean ALP values were 80.8 ± 21.6 U/L (range, 59.2 - 102.4 U/L).

Normal bilirubin values were seen in 26% patients while, 74% had raised bilirubin levels (Hyperbilirubinemia). Of 81 patients with acute appendicitis, 71.6% had raised bilirubin levels, while 28.4% had normal levels. 19 patients were diagnosed as Appendicular perforation, 16 patients (84.21%) had raised bilirubin levels, while the remaining 03 patients (15.79%) had normal levels. The total leukocyte count was less than 11,000/mm^3 in 65% patients while, 35% patients had counts above 11,000/mm^3.

Of the 100 patients, 91% were diagnosed as acute appendicitis clinically while 9% were diagnosed with Appendicular perforation. On Ultrasonography, 82% patients were diagnosed with acute appendicitis or appendicular perforation while 18% had normal findings. Post-operatively 81% were confirmed as acute appendicitis while 19% were diagnosed with Appendicular perforation.

The mean bilirubin levels in patients diagnosed with acute appendicitis was 1.4 ±0.65 mg/dL (range, 0.75 – 2.05 mg/dL) while in patients diagnosed with Appendicular perforation was 1.9±1.16 mg/dL (range, 0.74 – 3.06 mg/dL). The Direct bilirubin and Indirect bilirubin in patients diagnosed with acute appendicitis was 0.9±0.57 mg/dL and 0.5±0.21 respectively. The Direct bilirubin and Indirect bilirubin in patients diagnosed with Appendicular perforation was 1.2±1.06 mg/dL and 0.70±0.33 mg/dL respectively. 58 patients (71.6%) of the total patients diagnosed with acute appendicitis (n=81) were found to have elevated bilirubin levels while 23 patients (28.4%) had normal bilirubin levels. Similarly, 16 patients (84.21%) of the total patients diagnosed with Appendicular perforation (n=19) were found to have elevated bilirubin levels while 03 patients (15.79%) had normal bilirubin levels.

The Sensitivity and Specificity of serum bilirubin as a marker in predicting acute appendicitis and Appendicular perforation was 71.6% and 15.79% respectively. Similarly the Positive predicative value and Negative predicative value for the same was 78.38% and 11.54% respectively with odds ratio 0.472.

Serum bilirubin levels appears to be a promising new laboratory marker for diagnosing acute appendicitis, however diagnosis of appendicitis is essentially still - clinical. Patients with clinical signs and symptoms of appendicitis and with hyperbilirubinemia double the normal range (Raise in Direct Bilirubin being still higher) 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.

LIST OF ABBREVIATIONS USED

ALP - Alkaline phosphatase
ALT - Alanine transaminase
AST - Aspartate transaminase
ATP - Adenosine triphosphate
cm - Centimeter(s)
CRP - C-reactive protein
CT - Computed tomography
dL - Deciliter(s)
DLC - Differential leukocyte count
E. Coli - Escherichia coli
ELISA - Enzyme linked immunosorbent assay
g - Gram(s)
HbsAg - Hepatitis B surface antigen
IL-6 - Interleukin-6
LFT - Liver function tests
mg - Milligram(s)
mL - Milliliter(s)
mm - Millimeter(s)
n - Total number
NPV - Negative predictive value
OR - Odds ratio
PPV - Positive predictive value
SB - Serum bilirubin
SGOT - Serum glutamic oxaloacetic transaminase
SGPT - Serum glutamic pyruvic transaminase
SMV - Superior mesenteric vein
Sr. - Serum
TLC - Total leukocyte count
TNF - Tumor necrosis factor
TSB - Total serum bilirubin
USG - Ultrasonography
WBC - White blood cells

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. *John Maa. "The Appendix". In Townsend CM,* Beauchamp RD, Evers BM, Mattox KL, eds. *Sabiston Textbook of Surgery. 18th ed.* Philadelphia, Pa: Saunders Elsevier; 2008. p: 1333- 1347.
3. Thimsen DA, Tong GK, Gruenberg JC. Prospective evaluation of C- reactive protein in patients suspected to have acute appendicitis. *Am Surg* 1989; 55(7): 466-8.
4. de Carvalho BR, Diogo-Filho A, Fernandes C, Barra CB. Leukocyte count, C reactive protein, alpha-1 acid glycoprotein and erythrocyte sedimentation rate in acute appendicitis. *Arq Gastroenterol* 2003; 40(1): 25-30.
5. Albu E, Miller BM, Choi Y, et al. Diagnostic value of C- reactive protein in acute appendicitis. *Dis Colon Rectum.* 1994; 37(1): 49-51.
6. Gurleyik E, Gurleyik G, Unalmiser S. Accuracy of serum C-reactive protein measurements in diagnosis of acute appendicitis compared with surgeon's clinical impression. *Dis Colon Rectum* 1995; 38(12): 1270-4.
7. Bhajekar M.V.: Surgical Appendix. In Indian journal of Medical Sciences, Bombay: 1963.
8. Rao PM, Rhea JT, Novelline RA, Mostafavi AA, McCabe CJ. Effect of computed tomography of the appendix on treatment of patients and use of hospital resources. N Engl J Med 1998; 338: 141-6.
9. Berk PD, Wolkoff AW. Bilirubin Metabolism and Hyperbilirubinemia. In: Kasper DL, Braunwald Braunwald E, *Fauci* AS, Hauser SL, Longo DL, Jameson JL, et al. Harrison□s Textbook of Internal Medicine. 16th ed. Vol. II. New York: McGraw Hill Medical Publishing Division; 2001. p. 919
10. Geier A, Fickert P, Trauner M. Mechanisms of disease: mechanismand clinical implications of cholestasis in sepsis. Nat Clin Pract Gastroenterol Hepatol 2006; 3: 574-85.
11. Sherlock S, Dooley J. Assessment of Liver Function. In: Liver and hepatobiliary Diseases. 11thEd. Oxford: Black Well Publishing Company; 2002. p 20.
12. 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.
13. 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
14. William C, Mayers, MD., Rocco Ricciardi, MD. Liver Function. In: *Townsend CM,* Beauchamp RD, Evers BM, Mattox KL, eds. Sabiston Text Book of Surgery. The biological basis of modern surgical practice, Book-I. 11th ed. A Heart Court Asia PTE LTD; 2001. p.1010.
15. Estrada JJ, PetrosyanM, Krumenacker J Jr, Huang S, Moh P. Hyperbilirubinemia in Appendicitis: A New Predicator of Perforation. Journal of Gastrointestinal Surgery 2007;11: 14–5.
16. Kasper DL, Braunwald Braunwald E, *Fauci* AS, Hauser SL, Longo DL, Jameson JL, et al. Harrison□s Principles of Internal Medicine. 16th ed. McGraw Hill; 2005.
17. Bernard M. Jaffe and David H. Berger. "The Appendix". In Brunicardi F, Andersen D, Billiar T, Dunn D, Hunter J, Matthews J, et al. Schwartz's Principles of Surgery. 9th ed. New York: McGraw Hill; 2009. p.1073- 1092.
18. Addiss DG, Shaffer N, Fowler BS, Tauxe RV. The epidemiology of appendicitis and appendectomy in the United States. Am J Epidemiol 1990; 132 (5): 910-25.
19. Flum DR, Morris A, Koepsell T, Dellinger EP. Has misdiagnosis of appendicitis decreased over time? A population-based analysis. JAMA 2001; 286 (14): 1748-53.
20. Deutsch A, Shani N, Reiss R. Are some appendectomies unnecessary: an analysis of 319 white appendices. J R Coll Surg Edinb 1983; 28: 35-40.
21. Piper R, Kager E, Nasman P. Acute appendicitis a clinical study of 1018 cases of emergency appendicectomy. Acta Chir Scand. 1982; 148:51-62.
22. Khan S. Evaluation of hyperbilirubinemia in acute inflammation of appendix: A prospective study of 45 cases. KUMJ 2006; 4(3) 15: 281-9.