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A Comparative Study of Diagnostic Value of Hyperbilirubnemia in Predicting Appendicitis and Its Complications

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Abstract
Background: *Appendiceal perforation in patients with acute appendicitis may cause a variety of potentially life-threatening complications. Escherichia coli endotoxin has been shown to impact physiological bile flow in vivo. This had led to the theory that hyperbilirubinemia in patients with appendicitis may have a predictive potential for the preoperative diagnosis of appendiceal perforation. The aim of this retrospective study was to investigate the diagnostic value of hyperbilirubinemia as a preoperative laboratory marker for appendiceal perforation in patients with acute appendicitis*
Methods: *We identified 100patients with histologically proved acute appendicitis who underwent laparoscopic or conventional appendectomy between august 2017 and august 2018 in a surgical department in govt rajaji hospital. A retrospective multiple chart review of the medical records including laboratory values and histologic results was conducted.*
Results: *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.*
Conclusion: *Patients with hyperbilirubinemia and clinical symptoms of appendicitis should be identified as having a higher probability of appendiceal perforation than those with normal bilirubin level*

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I. 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. Appendicectomy is the most commonly performed abdominal surgery. 15-30% of appendicectomy specimen found to be normal.In order to decrease the number of unnecessary appendicectomy, significance of labarotory investigations like White Blood Cells,,C- Reactive Protein, etc have been emphasised.Ultrasonagram abdomen 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 siginificance of which is not stressed.On bacterial invasion of the appendix, there is transmigration of bacteria and release of proinflammatory 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.

II. 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 for patients with acute abdominal pain and suspected acute appendicitis

III. Materials And Methods

The study was conducted in the Department of General Surgery, Govt.Rajaji Hospital and Medical College, Madurai during the period of August 2017 to August 2018.

Study design

A prospective non randomised study.

Source

The present study was conducted in the Department of Surgery, Govt.Rajaji Hospital and Medical College, Madurai

Study period

One year from August 2017 to August 2018..

Source of data

Patients admitted with clinical diagnosis of acute appendicitis or appendicular perforation under the Department of Surgery, Govt.Rajaji Hospital and Medical College, Madurai 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.

$$n = \frac{Z2 \times p \times q}{d2}$$

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.

For 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). 71 o 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, Govt.Rajaji Hospital and medical college,Madurai during the study period werescreened. The nature of the study was explained to the patients. 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

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 HEPALISAor HEPACARDkit.

Statistical analysis

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

Patients with clinical diagnosis of acute appendicitis with

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

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 mean. 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

IV. Results

A total of 100 patients with clinical diagnosis of acute appendicitis or appendicular perforation admitted in the Department of General surgery, Govt.Rajaji Hospital and medical college,Madurai 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

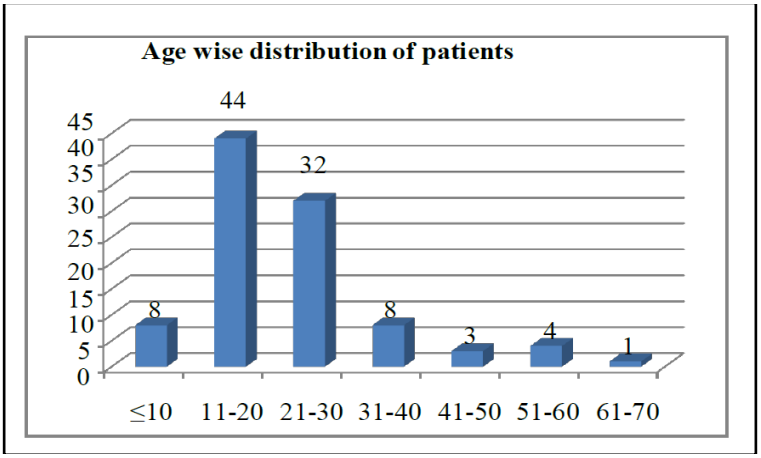


Table 4: Liver Function Tests

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 /L).

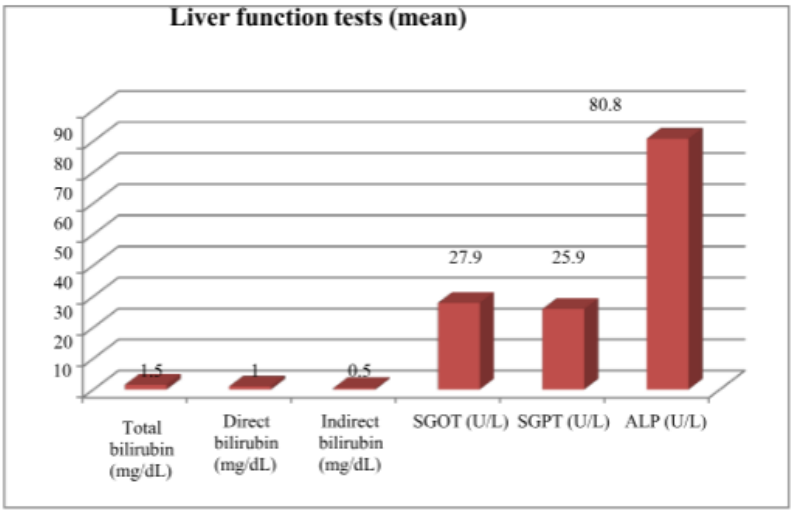


Table 5: Total bilirubin level

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 6: 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 7. 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).

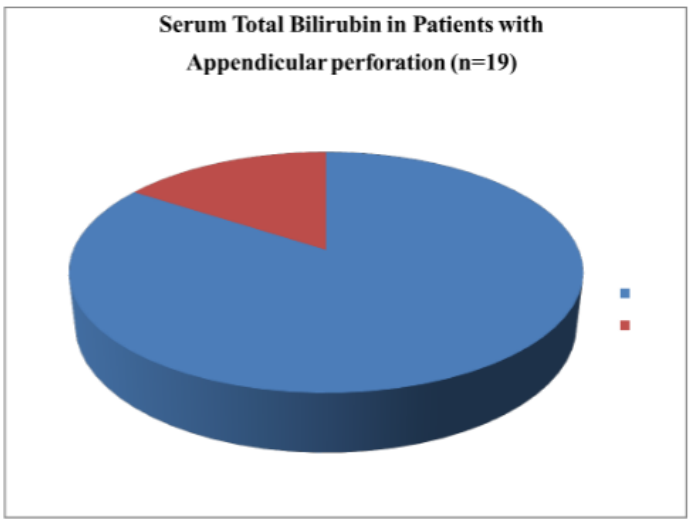


Table 8. Histopathological diagnosis

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.

Histopathologicaldiagnosis

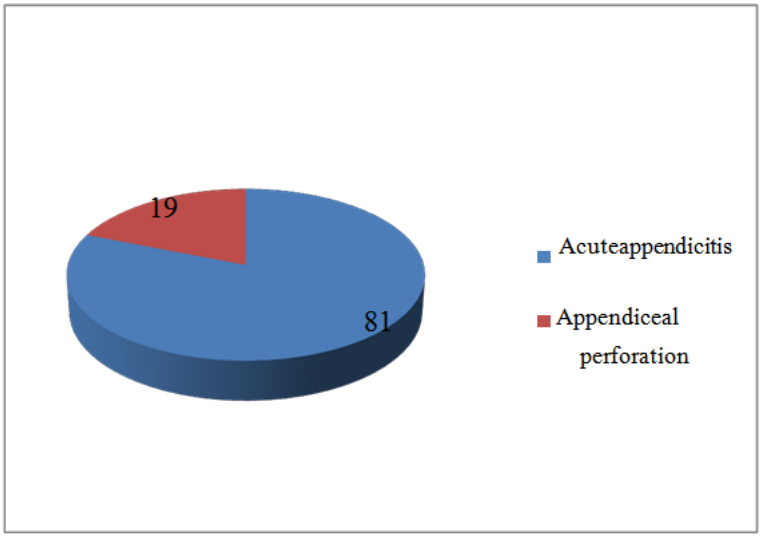


Table 9. Comparison of mean serum bilirubin levels in patients with acute appendicitis and Appendicular perforation

Bilirubin levels (mg/dL)	Diagnosis			
	Acute appendicitis		Appendicular perforation	
	Mean	SD	Mean	SD
T. bilirubin	1.4	0.65	1.9	1.16
Direct	0.9	0.57	1.2	1.06
Indirect	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 was1.9±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.

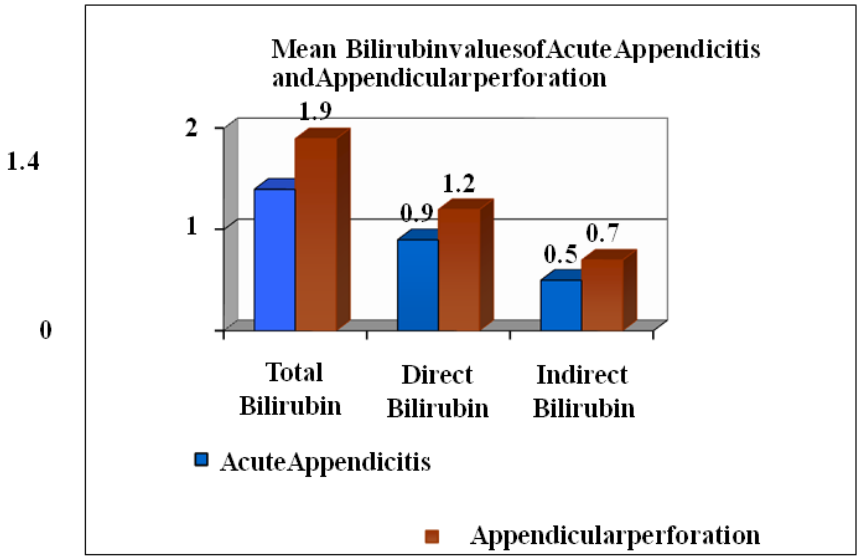
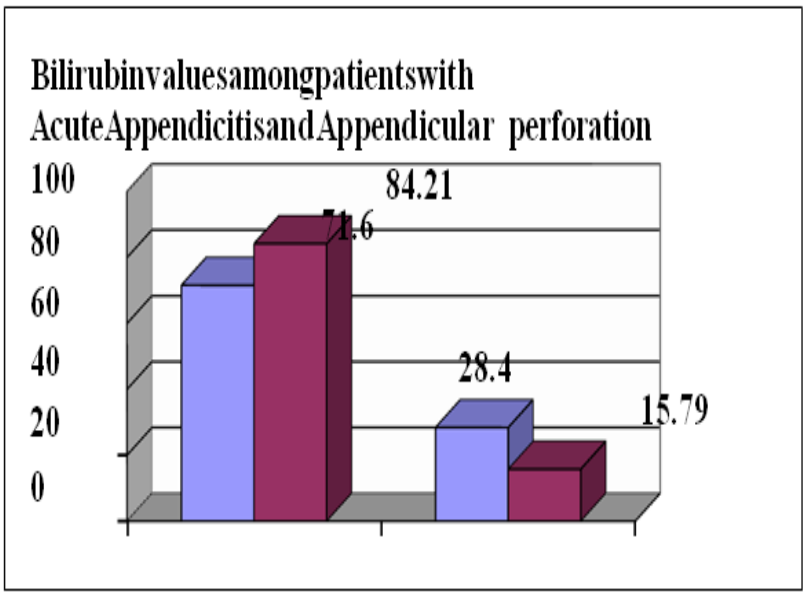


Table 10. Correlation of acute appendicitis and Appendicular perforationwith total serum bilirubin levels

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, 16patients (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).



From Table, following values were calculated as –

Sensitivity
Sensitivity of bilirubin in predicting acute appendicitis & appendicular perforation diagnosis was 71.6%

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

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

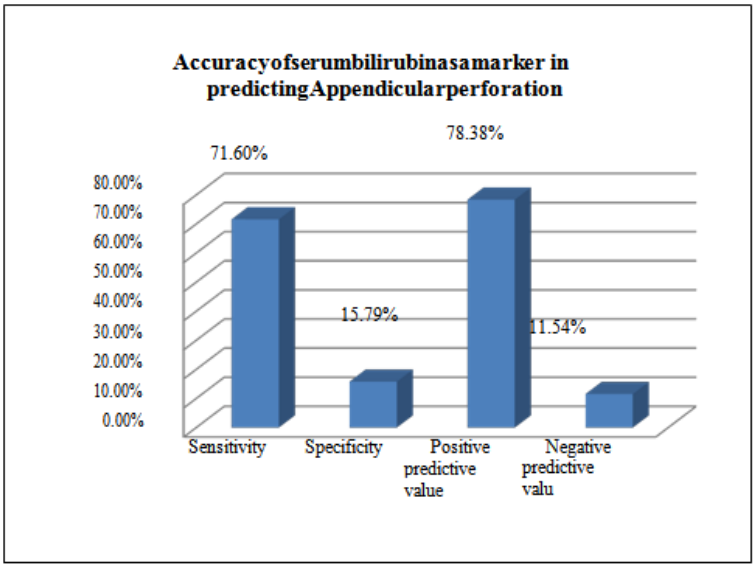
Negative predictive value
Negative predictive value of bilirubin in predicting acute appendicitis and Appendicular perforation diagnosis was 11.54%.

Odds ratio: Odds ratio is 0.472.

Table 11. Accuracy of serum bilirubin as a marker in predicting Appendicular perforation

	Accuracy
Sensitivity	71.6%
Specificity	15.79%
Positivepredictivevalue	78.38%
Negativepredictivevalue	11.54%
Oddsratio	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 r atio was calculated to be 0.472



V. Discussion

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.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 alhad 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)..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).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 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.

VI. Conclusion

The present study suggests-

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

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.

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.

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