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Evaluation of Hyperbilirubinemia as a New Diagnostic Marker for Acute Appendicitis and it's Role in the Prediction of Appendicular Perforation

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Abstract: ***Background: Hyperbilirubinemiain acute approach, serological markers for appendicitis and it's perforation, additives and strengthening the existing scoring systems, decrease rate of negative appendicectomy, early & non invasive diagnosis of appendicular perforation. Materials and methods: A prospective non - randomized study conducted in Department of General Surgery, Government Siddhartha Medical College, Vijayawada during the period of October 2021 to November 2022. Results: Of the the fifty patients studied 42 were diagnosed to have acute appendicitis and 8 were diagnosed to have appendicular perforation.36 patients (85.7%) of the total patients diagnosed with Acute appendicitis (n=42) were found to have elevated bilirubin levels (> 1.0 mg/dL) while 6 patients (14.2%) had normal bilirubin levels (≤ 1.0 mg/dL). Similarly, 7 patients (87.5%) of the total patients diagnosed with Appendicular perforation (n=8) were found to have elevated bilirubin levels (> 1.0 mg/dL) while 1 patient (12.5%) had normal bilirubin levels (≤ 1.0 mg/dL). The mean bilirubin levels in patients diagnosed with Acute appendicitis was 1.45 ±0.65 mg/dL (range, 0.75 – 2.05 mg/dL) while in patients diagnosed with Appendicular perforation was 1.92±1.16 mg/dL (range, 0.74 – 3.06 mg/dL). The Sensitivity and Specificity of serum bilirubin as a marker in predicting acute appendicitis and Appendicular perforation was 83.7% and 12.5% respectively. Similarly the Positive predicative value and Negative predicative value for the same is 78.7% and 14.2% respectively. The Odds ratio was calculated to be 0.85. 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. Patients with clinical signs and symptoms of appendicitis and with hyper bilirubinemia higherthe normal range should be identified as having a higher probability of Appendicular perforation suggesting, serum bilirubin levels have an adequate predictivepotential for the diagnosis of Appendicular perforation.***

Keywords: Hyperbilirubinemia, acute appendicitis, appendicular perforation.

1. Introduction

Appendicitis or acute inflammation of vermiform appendix, is most common abdominal surgical emergency; lifetime risk approaches about 8.6% in males and 6.7% in females. Although acute appendicitis is the most common surgically correctable cause of abdominal pain, its diagnosis remains challenging in many instances. It is difficult to diagnose in cases of retrocaecal or retro - ileal appendix. Laboratory studies contribute to the diagnosis of appendicitis, like white blood cell count, C - reactive protein, etc. Ultra - sonogram abdomen has been widely accepted as the diagnostic tool for appendicitis, but no single test is definitive.

In order to decrease the number of unnecessary appendicectomy, various diagnostic scoring systems have been developed in an attempt to improve the diagnostic accuracy of acute appendicitis. These scoring systems are based on clinical features, laboratory investigations. Some of them are Alvarado, Modified Alvarado, Ripasa. Still there is no definitive marker for acute appendicitis and appendicular perforations. Recent studies show that serum bilirubin is raised in acute appendicitis and appendicular perforations. But the significance of the same is not stressed.

In view of 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, to see whether elevated serum bilirubin levels have a predictive potential for the diagnosis of appendicular perforation.

2. Objectives of the Study

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

3. Materials and Methods

The study was conducted in the Department of General Surgery, Government Siddhartha Medical College, Vijayawada during the period of November 2021 to November 2022 Study design: A prospective non randomizedstudy. A total of 50 patients with clinical

diagnosis of acute appendicitis or appendicular perforation were studied.

Selection criteria:

Inclusion:

- All patients diagnosed as acute appendicitis clinically on admission.
- All patients diagnosed as appendicular perforation clinically on admission.

In 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 - o 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
- Hemolytic disease.
- Acquired or congenital biliary disease.
- All patients with positive HBsAg. All patients with cholelithiasis.
- All patients with cancer of hepato - biliary system.

4. Results

A total of 50 patients with clinical diagnosis of acute appendicitis or appendicular perforation admitted in the Department of General surgery, GOVERNMENTSIDDHARTHA MEDICAL COLLEGE, Vijayawada, were studied.

As per the study, the age group 11 - 20years is most commonly affected (48%) followed by age group 21 - 30 (36%). The youngest patients of this study were of 8 years old while the oldest patient was a 60 year lady.

Table 1: Liver Function Tests

Parameters	Mean	SD
Total bilirubin (mg/dl)	1.54	0.83
Direct bilirubin (mg/dl)	1	0.7
Indirect bilirubin (mg/dl)	0.5	0.2
SGOT (U/L)	27.9	12.2
SGPT (U/L)	25.9	11
ALP (U/L)	80.8	21.6

The mean Total bilirubin of all 50 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, 15.740.1U/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 2: Total bilirubin levels

Total Bilirubin (mg/dl)	Number	Percentage
<1.0	14	28
>1.0	36	72
Total	50	100

14 patients (28%) of all 50 patients were found to have normal bilirubin levels (≤ 1.0 mg/dL), while 36 patients (72%) had raised bilirubin levels (>1.0 mg/dL).

Table 3: Bilirubin levels in patients with uncomplicated acute appendicitisas diagnosis

Total bilirubin (mg/dl)	No. of patients	percentage
>1.0	31	73.8
<1.0	11	26.1
Total	42	100

Of 42 patients diagnosed as uncomplicated acute appendicitis, 31 patients (73.8%) had raised bilirubin levels (> 1.0 mg/dL), while the remaining 11 patients (26.1%) had normal levels (≤ 1.0 mg/dL).

Table 4: Bilirubin levels in patients with Appendicular perforation diagnosis

Total bilirubin (mg/dl)	Number	
>1.0	7	87.5
<1.0	1	12.5
Total	8	100

8 patients diagnosed as Appendicular perforation, 7patients (87.5%) had raised bilirubin levels (> 1.0 mg/dL), while the remaining 01 patients (12.5%) had normal levels (≤ 1.0 mg/dL).

Table 5: Total leukocyte count (TLC)

TLC count /mm^3	Number	Percentage
</=11000	27	54
>/=1100	23	46
Total	50	100

27 patients (54%) had Total Leukocyte count less than 11, 000/mm3 while
23 patients (46%) counts above 11, 000/mm3.

Table 6: Differential Leukocyte Count (DLC)

Differential count (DLC)	Mean	SD
Neutrophils	71.7	11.5
Lymphocyte	23.7	10.7
Monocyte	3.6	2.6
Eosinophils	1	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.

Table 7: Pre- Operative Diagnosis

Pre - op diagnosis	Number	percentage
Acute appendicitis	45	90
Appendicular perforation	5	10
Total	50	100

In the study population of 50 patients, 45 patients (90%) were diagnosed as acute appendicitis while 5 patients (10%) were diagnosed with Appendicular perforation.

Table 8: Ultrasonographic findings

Findings	Number	Percentage
Normal	9	18
Acute Appendicitis	36	72
Appendicular Perforation	5	10
Total	50	100

On Ultrasonography, 36 patients (72%) were diagnosed as Acute appendicitis, 5 patients (10%) as Appendicular perforation and 9 patients (18%) were reported as normal ultrasonographic findings.

Table 9: Histopathological diagnosis

Diagnosis	Number	Percentage
Acute Appendicitis	42	84
Appendicular perforation	8	16
Total	50	100

Histopathologically, 42 patients (84%) were confirmed as Acute appendicitis while 8 patients (16%) were diagnosed with Appendicular perforation.

Table 10: Comparison of mean serum bilirubin levels in patients with acute appendicitis and Appendicular perforation

Bilirubin levels (mg/dl)	Acute Appendicitis (mean)	Appendicular Perforation (mean)
Total Bilirubin	1.45	1.92
Direct Bilirubin	0.95	1.22
Indirect Bilirubin	0.5	0.68

The mean bilirubin levels in patients diagnosed with Acute appendicitis was 1.45 ±0.65 mg/dL (range, 0.75 – 2.05 mg/dL) while in patients diagnosed with Appendicular perforation was 1.92±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.

Mean Bilirubin values of Acute Appendicitis and Appendicular perforation

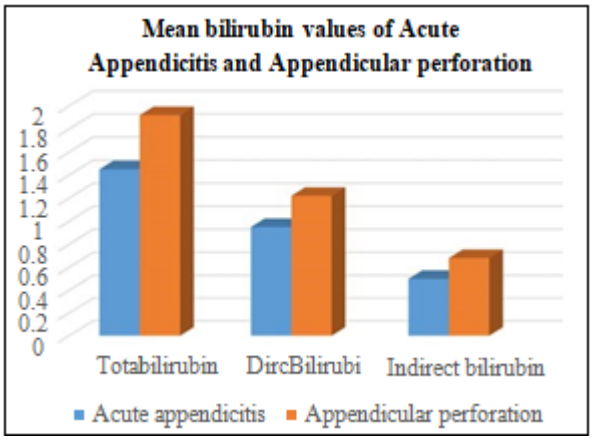

Table 11: Correlation of acute appendicitis and Appendicular perforation with total serum bilirubin levels

Serum bilirubin (mg/dl)	Final diagnosis (n=50)			
	Acute Appendicitis (n=42)		Appendicular Perforation	
	No.	%	No.	%
>1.0	36	85.7	7	87.5
<1.0	6	14.2	1	12.5
Total	42	100	8	100

36 patients (85.7%) of the total patients diagnosed with Acute appendicitis (n=42) were found to have elevated bilirubin levels (> 1.0 mg/dL) while 6 patients (14.2%) had normal bilirubin levels (≤ 1.0 mg/dL). Similarly, 7 patients (87.5%) of the total patients diagnosed with Appendicular perforation (n=8) were found to have elevated bilirubin levels (> 1.0 mg/dL) while 1 patient (12.5%) had normal bilirubin levels (≤ 1.0 mg/dL).

	Accuracy
Sensitivity	83.70%
Specificity	12.50%
Positive predictive value	78.70%
Negative predictive value	14.20%
Odds ratio	0.85

The Sensitivity and Specificity of serum bilirubin as a marker in predicting acute appendicitis and Appendicular perforation was 83.7% and 12.5% respectively. Similarly the Positive predicative value and Negative predicative value for the same is 78.7% and 14.2% respectively. The Odds ratio was calculated to be 0.85.

5. Discussion

The diagnosis of acute appendicitis is mostly 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.4 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 interventional procedures are associated with complications in as high as 50% of cases.5 Hence, it is to be noted that, the diagnosis of Appendicitis still remains a dilemma in spite of many advances in various laboratory and also radiological investigations. A new tool to help in the diagnostic evaluation of acute appendicitis would thus be welcome.

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

Thus, 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 S. bilirubin have the credibility to help us foresee an impending complication of an acute appendicitis.

Importance of hyper bilirubinemia and its association in acute appendicitis has being postulated lately. There are only a few case reports in the available literature that describe the finding of hyperbilirubinemia in patients of acute appendicitis.54 It is hypothesized that an association exists

between hyperbilirubinemia and acute appendicitis and its complications.5

The present study was undertaken to study the relationship between hyper bilirubinemia and acute appendicitis and to evaluate its credibility as a diagnostic marker for acute appendicitis and also, to evaluate whether elevated bilirubin levels have the potential to predict appendicular perforation.

In the present study of the 50 patients enrolled for the study, 27 patients (54%) were males while the remaining 23 patients (46%) were females. The mean age in our study population (50 patients) was 23.18 ± 11.98 years (range, 11.11–35.00 years) and, this is consistent with the quoted incidence of Acute Appendicitis in the literature where it is most frequently seen in patients in their second through fourth decades of life.33, 34 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). Hyper bilirubinemia (> 1.0 mg/dL) in our study was found in 36 patients (72%) of all the 50 patients (n=50) who were enrolled in the study, while 14 patients (28%) had normal bilirubin levels (≤ 1.0 mg/dL). Estrada et al[6] had found hyperbilirubinemia in 59 (38%) of 157 patients studied with acute appendicitis. According to Sibabratakar et al[11] 54% had elevated TSB, while it was within normal limits in 46.4% of patients. From the patients with hyperbilirubinemia, 97.01% had positive histology for acute appendicitis, while the remaining 2.99% had normal histology.

The mean total serum bilirubin of all 50 patients was 1.5 ± 0.7 mg/dL (range, 0.7 – 2.3 mg/dL), which was above the normal range of ≤ 1.0 mg/dL considered for the study, hence indicating the occurrence of hyperbilirubinemia. The mean of Direct bilirubin was 1.0 ± 0.73 mg/dL (range, 0.32 - 1.74 mg/dL) while that of Indirect bilirubin was 0.5±0.22 mg/dL (range, 0.34 – 0.77 mg/dL). This finding was consistent with hyper bilirubinemia found in a study conducted by Khan S[7], who found average level of serum bilirubin in his study population to be 2.38 mg/dL. According to R Syed Raj and et al[10] Mean bilirubin different categories as per histopathological reports showed maximum value in gangrenous appendicitis 2.133mg/dl, followed by appendicitis with perforation which was 2.026 mg/d1, mean bilirubin was 1.312 mg/dl in category of acute appendicitis and meanbilirubin was 0.579 mg/dl and 0.604 mg/dl respectively in histologically unremarkable and lymphoid hyperplasia. In the raised categories both direct and indirect bilirubin were raised.

All patients who were included in the study, were found to have SGOT and SGPT within the normal range, thus excluding any associated liver pathology (Exclusion criteria). The mean SGOT and SGPT of the studied patients 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 around 80.8 ± 21.6 U/L (range, 59.2 - 102.4 U/L).

In our study population of 50 patients, 46 patients (92%) were diagnosed as acute appendicitis pre - operatively while 04 patients (8%) were diagnosed with Appendicular perforation. The diagnosis was confirmed post - operatively by histopathological examination reports (HPE) and those differing from the pre - operative diagnosis were excluded from the study.

Amongst the patients diagnosed with Acute appendicitis without perforation (46 patients), 35 patients (70%) were found to have an elevated bilirubin (>1.0 mg/dL) while only 11 patients (30%) had normal bilirubin levels (≤1.0 mg/dL). In patients diagnosed with Appendicular perforation (n=4), 3 patients (75%) had bilirubin elevated (>1.0 mg/dL), while only 1 patient (25%) had normal levels (>1.0 mg/dL). Thus, Hyper bilirubinemia was found in most of the patients diagnosed with acute appendicitis (70%) or Appendicular perforation (75%).

The total leukocyte count was found to be elevated in just 20 patients (40%) of the total 50 patients. The mean of TLC count in all patients was 10070±3512/mm^3 (range, 6418 - 13788/mm3), in which the highest percentage constituted Neutrophils with 71.7% followed by 23.7% by Lymphocytes.

On Ultrasonography abdomen, 36 patients (72%) were diagnosed as Acute appendicitis, 3 patients (6%) were diagnosed as Appendicular perforation and 11 patients (22%) 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.

In the present study, 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[8] in his study found the mean bilirubin levels in patients with Appendicular perforation to be significantly higher than those with a non - perforated appendicitis. According to Thangadurai Ramaswamy et al[9] out of 378 of the study population, 18% of themhad appendicular perforation and 82% had acute appendicitis. Out of 67 perforations, 60 patients have hyperbilirubinemia (90%) whereas out of 311 patients with appendicitis, only 89 (29%) of them had elevated bilirubin. Hyperbilirubinemia with a cutoff point of 0.9 mg% for appendicitis patients has a sensitivity of 89.6%, specificity of 71.4%, a positive predictive value of 27%, and a negative predictive value of 96.9%. Hyperbilirubinemia with a cutoff point of >1.3 mg% for appendicular perforation has a sensitivity of 80%, specificity of 89%, a positive predictive value of 93%, and a negative predictive value of 96%.

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 83.7% and 12.79% respectively. Similarly Positive predictive value and Negative predicative value of bilirubin in predicting acute appendicitis and Appendicular perforation diagnosis was 83.7% and 14.2% respectively. The Odd's ratio was calculated to be 0.85.

The sensitivity in our study was more than that by Sand et al[8] in which, he found the sensitivity and specificity in his study of hyperbilirubinemia for predicting Appendicular perforation to be 70% and 86.0% respectively.

6. 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 an adequate predictivepotential for the diagnosis of Appendicular perforation.

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