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RESEARCH ARTICLE

ASSOCIATION BETWEEN SERUM BILIRUBIN LEVELS AND ACUTE INFLAMMATION OF APPENDIX

¹Lalrammuana, R., ¹Vignesh, V., ¹Lalthatluanga, S.R., ¹Nejobala Chanu, A., ¹Vikramaditya,
¹Lalruatlina Pachuau, ²*Gojen Singh Kh and ³Lekhachandra Sharma, K.

¹Junior Residents, Department of Surgery, Regional Institute of Medical Sciences, Imphal

²Associate Professor, Department of General Surgery, Regional Institute of Medical Sciences, Imphal, India

³Professor, Department of Surgery, Regional Institute of Medical Sciences, Imphal, India

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ABSTRACT

Background: The aim of the study was to establish the association between serum bilirubin levels and acute inflammation of appendix. **Methods:** A Cross sectional study was conducted among 215 patients of acute appendicitis with or without complication in the Department of General Surgery, Regional Institute of Medical Sciences, Imphal. These were subjected to investigations to support the diagnosis. These cases were also subjected to liver function tests and clinical diagnosis was confirmed perioperatively and post-operatively by histopathological examination. Their clinical and investigative data were compiled and analyzed. Statistical analysis was performed using chi square test and t test. The level of significance was set at $P < 0.05$. **Results:** Total serum bilirubin was high in 74% of cases and so the remaining 26% was normal. There was a good positive correlation ($r_s = 0.606$) between duration of appendicitis and serum bilirubin levels and this finding was statistically significant ($p < 0.000$). Mean serum bilirubin level in appendicular perforation was more than acute appendicitis but the finding was statistically insignificant ($p > 0.05$). **Conclusion:** With increase in the duration of appendicitis there was rise in the level of bilirubin in this study.

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INTRODUCTION

Acute appendicitis is one of the commonest causes of "Acute Surgical abdomen." Appendectomy is the most frequently performed emergency abdominal operation and is often the first major procedure performed by a surgeon in training. The diagnosis of appendicitis still remains a dilemma in spite of advances in the radiological and laboratory investigations. Experienced clinicians accurately diagnose appendicitis based on a combination of history, physical examination and laboratory studies about 80% of the time. Recently, elevation in serum bilirubin was reported, but the importance of the raised total bilirubin has not been stressed in acute appendicitis and appendicular perforation. It is well established that when microbes invade the body, leukocytes defend it. This leads to increase in the leukocyte count. Bacterial invasion in the appendix is followed by transmigration of bacteria and the release of pro-inflammatory cytokines such as TNF-alpha, IL6 and cytokines and reach the liver via superior mesenteric vein (SMV) and may produce inflammation, abscess or dysfunction of liver either directly or indirectly by altering the hepatic blood flow.

*Corresponding author: Gojen Singh Kh

Associate Professor, Department of General Surgery, Regional Institute of Medical Sciences, Imphal, India.

In view of the above context, the present study was undertaken to assess association between serum bilirubin level and acute inflammation of appendix (acute appendicitis and its complications). A retrospective review by Estrada JJ et al. studied the relationship between hyperbilirubinemia and appendicitis. Patients with liver function tests done 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 assessing factors predicting the presence or absence of appendicular gangrene/perforation. Elevated total bilirubin levels ($>1\text{mg/dl}$) were found in 59(38%) of 157 patients. Patients with gangrene/perforation were significantly more likely to have hyperbilirubinemia than those with acute suppurative appendicitis. No statistical differences were observed for any of the other variables. 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. Another study conducted by Khan S to determine the role and predictive value of elevated total serum bilirubin in the diagnosis of acute appendicitis. Out of 110 patients

studied, 71 (64.54%) were males and 39(35.45%) were females. Age distribution was between 6 years to 73 years with a mean of 29.5 years. Out of 110 cases, 106 cases had acute appendicitis out of which total serum bilirubin was elevated in 87 (82.07%) cases. The mean elevated total serum bilirubin was 2.26 mg/dL, ranged 1.2 to 11.5 mg/dL. An interesting finding observed was that patients in whom the appendix was gangrenous or perforated; elevation of total serum bilirubin was found to be higher as compared to simple suppurative acute appendicitis. The specificity and sensitivity was 100% and 82.07% respectively with predictive value of positive test 100% and predictive value of negative test 17.3%. The Study concluded that elevated total serum bilirubin (without severe abnormalities in the value of liver enzymes) is good indicator of acute appendicitis. The specificity and sensitivity of elevated total serum bilirubin was 100% and 82.07% respectively with a predictive value for positive test 100%. If total serum bilirubin is added to already existing laboratory tests, then the diagnosis of acute appendicitis in clinically suspected cases can be made with fair degree of accuracy and delay in appendicectomy can be avoided. A retrospective cohort study was conducted by Chambers AC et al among 1347 patients who underwent appendicectomy. Mean serum bilirubin levels; perforated/ gangrenous appendicitis 20.5 mg/L (SD 12.6), inflamed appendicitis mean 17.5mg/L (SD 11.1), normal appendicitis mean 12.6 mg/L (7.0). Kruskal Wallis indicated bilirubin levels were significantly different ($H = 128.87$, $df = 4$, $p < .001$) between histological groups, and a post hoc analysis with Bonferroni adjustment showed perforated/gangrenous to be significantly higher than all other groups ($p < .001$). Binary logistic regression combining White Cell Count (WCC) level, C-Reactive Protein (CRP) and Bilirubin levels gave a sensitivity and specificity of .69 with AUROC 0.766(std error.015) for gangrenous/ perforated. Assessment according to clinical relevance showed only 30.4% of patients with an abnormally raised bilirubin had gangrenous/perforated appendicitis. Serum bilirubin does not independently predict perforation/gangrenous appendicitis. Statistical analysis showed differences in mean bilirubin between histological groups however this did not relate to clinical significance as bilirubin levels were still within normal clinical limits. Diagnosis of complicated appendicitis should be made on clinical grounds, with utilization of biochemical/haematological investigations, but there should not be independent reliance on investigations such as bilirubin.

MATERIAL AND METHODS

Study design: Cross sectional study.

Study setting: The study was conducted in the Department of General Surgery, Regional Institute of Medical Sciences, Imphal, Manipur.

Study duration: The study was carried out from September 2014 to August 2016.

Study population: Clinically and ultrasonographically diagnosed patients with acute appendicitis admitted and operated between September 2014 to August 2016, in the Department of Surgery, RIMS Hospital, were taken for study during the study period.

Inclusion criteria

- All patient diagnosed and admitted as acute appendicitis with or without complication.

- Patients who were willing to participate in this study.

Exclusion Criteria

- All patients documented to have a past history of
 - Jaundice or Liver disease
 - Chronic alcoholism (i.e. intake of alcohol of >40g/day for Men and >20g/day in Women for 10 years)
 - Haemolytic disease
 - Acquired or Congenital biliary disease.
- Patients with seropositive HBsAg or HCV
- Patients with primary biliary tract disease.

Sample size: As per previous information the prevalence of appendicitis is 16%.

Formula for single proportion

$$n = \frac{4PQ}{L^2}$$

n= sample size

P= prevalence

L=5(Absolute allowable error) Q=100-P

$$= \frac{4 \times 16 \times (100 - 16)}{5^2}$$

$$= \frac{4 \times 16 \times 84}{5^2}$$

Sampling: Convenient sampling.

Study variable:

- Age
- Sex
- Duration of symptoms
- Diagnosis: Clinical/operative
- Serum bilirubin: Total/Direct(mg/dl)
- Liver enzymes: SGOT/SGPT/ALP
- Histopathology

Working definition: Acute appendicitis is the acute inflammation of appendix Routine serum bilirubin test results was compared with laboratory reference values given in Table-1.

Table 1. Reference Range of Serum Bilirubin and Liver Enzymes

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 - 35 U/L
ALP	30 - 120 U/L

Study tools: A preformed proforma was used to gather information about the subjects of study. Tools and materials used are as follows:

- Sterile surgical gloves

- Disposable sterile 2 cc syringe
- Serum vial
- Spirit swabs
- Tourniquet
- Ultrasonography machine.
- Randox RX Imola Autoanalyser machine.

Procedure

A total of 215 patients admitted with clinical diagnosis of "Acute Appendicitis" or "Appendicular Perforation" fulfilling the inclusion criteria were included in this study. After taking the proposed Informed Consent, data were collected using the questionnaire / proforma. The primary data for this study was the blood investigations of the patients. Routine blood investigations (i.e. complete hemogram, platelet count, reticulocyte count etc.)

- Serum Bilirubin (Total & Direct bilirubin)
- Liver Enzymes, which include -
- SGPT (Alanine transaminase)
- SGOT (Aspartate transaminase)
- ALP (Alkaline phosphatase)
- Seropositive for HbsAg/HCV
- Urine examination (routine & microscopy)

Serum bilirubin were measured by photometric method using Randox RX Imola Autoanalyser. Photometry is the most common analytical technique used in clinical biochemistry. Data collected included age, sex, duration of symptoms, clinical diagnosis/ operative finding and liver function test. Clinical diagnosis was confirmed by histopathology. Clinical and investigative data was compiled and analyzed, and observed.

Statistical Analysis: Datas were first entered in Microsoft excel 7. Then using SPSS software 16 data were analysed. Descriptive statistics used were mean, percentages & proportions. Chi square test and t-test were used for test of significance. Probability value of less than 0.05 was taken as significant.

Ethical Issue: The study was carried out only after obtaining approval from the Institutional Ethics Committee (IEC), Regional Institute of Medical Sciences, Imphal. Confidentiality. Informed consent was taken from all the participants.

Conflict of interest: None.

RESULTS AND OBSERVATIONS

A Cross sectional study was conducted among 215 patients of acute appendicitis with or without complication in the Department of General Surgery, Regional Institute of Medical Sciences, Imphal, Manipur from September 2014 to August 2016 to determine any association between serum bilirubin level and acute inflammation of appendix. Table 1 and Figure 1 showed that acute appendicitis was common in the age group ≤ 20 years (48.8%) followed by 21-30 years (33.0%) and so on. Mean age was 23.7 years with a standard deviation of 11.7 years. Minimum age for acute appendicitis in this study was 9 years and maximum was 60 years.

Table 1. Age distribution of the patients with acute appendicitis

Age in years	Frequency	Percentage
≤ 20	105	48.8
21-30	71	33.0
31-40	21	9.8
41-50	6	2.8
51-60	12	5.6
Total	215	100.0
Mean \pm SD	23.7 \pm 11.7	
Median (minimum-maximum)	21.0 (9-60)	

Table 2. Sex distribution of the patients with acute appendicitis

Sex	Frequency	Percentage
Female	115	53.5
Male	100	46.5
Total	215	100.0

Female constituted 53.5% of the patients which was more than males which constituted 46.5% of the patients as shown in Table 2.

Table 3. Age distribution of the patients stratified by sex

Age in years	Female (%)	Male (%)	Total (%)	Mann whitney U test p-value
≤ 20	71 (67.6)	34 (32.4)	105 (100.0)	
21-30	32 (45.1)	39 (54.9)	71 (100.0)	
31-40	6 (28.6)	15 (71.4)	21 (100.0)	NA
41-50	3 (50.0)	3 (50.0)	6 (100.0)	
51-60	3 (25.0)	9 (75.0)	12 (100.0)	
Total	115 (53.5)	100 (46.5)	215 (100.0)	
Mean \pm SD	20.4 \pm 9.9	27.4 \pm 12.5	23.7 \pm 11.7	NA
Mean (Range)	18 (10-60)	26 (9-60)	21 (9-60)	p-0.009

Table 3 shows that in the age group ≤ 20 year's acute appendicitis was common in females but in later years males were more common. Average age (median) among females (18 years) was significantly (p-0.009) less than males (26 years).

Table 4. Distribution of the patients by serum bilirubin level

Serum bilirubin	Frequency	Percentage
Total bilirubin		
Normal	56	26.0
High	159	74.0
Mean \pm SD	1.54 \pm 0.7	
Direct bilirubin		
Normal	40	18.6
High	175	81.4
Mean \pm SD	0.79 \pm 0.7	

Total bilirubin was high in 74% of cases and so the remaining 26% was normal. Direct bilirubin was high in 81.4% of cases as shown in Table 6.

Table 7. Distribution of the patients by liver enzymes

Liver enzymes	Frequency	Percentage
SGOT		
Normal (0-35U/L)	178	82.8
High (>35U/L)	37	17.2
Mean \pm SD	29.0 \pm 11.3	
SGPT		
Normal(0-35U/L)	194	90.2
High (>35U/L)	21	9.8
Mean \pm SD	26.2 \pm 12.7	
Alkaline phosphatase		
Normal(30-120U/L)	212	98.6
High (>120U/L)	3	1.4
Mean \pm SD	77.3 \pm 24.0	

SGOT level was increased in only 17.2% of cases and SGPT in 9.8% of cases. Alkaline phosphatase was raised in only 1.4% of cases.

Table 7. Distribution of the patients by other related investigations

Others related investigations	Frequency	Percentage
TLC		
Normal(4000-11000/cumm)	107	49.8
High(>11000/cumm)	108	50.2
Mean ± SD	11470 ± 4186	
Neutrophil		
Normal (40-75%)	104	48.4
High(>75%)	111	51.6
Mean ± SD	71.1 ± 12.3	
Lymphocyte		
Low (0-23)	111	51.6
Normal (24-45)	91	42.4
High (>45)	13	6.0
Mean ± SD	24.5 ± 11.7	

High TLC was found in half of the cases and also neutrophilia in half of the cases.

Table 8. Distribution of the patients by clinical diagnosis

Clinical diagnosis on admission	Frequency	Percentage
Acute appendicitis	191	88.8
Appendicular perforation	24	11.2
Total	215	100.0

Clinically 191 cases (88.8%) had acute appendicitis and the remaining 11.2% had appendicular perforation as shown in Table 8.

Table 10. Distribution of the patients by post operative finding

Post operative finding	Frequency	Percentage
Acute appendicitis	164	76.3
Appendicular perforation	51	23.7
Total	215	100.0

Table 10 and 9 show that after operation acute appendicitis was present in 76.3% of cases and appendicular perforation in 23.7% of cases.

Table 11. Relation between clinical diagnosis and post operative finding

Clinical diagnosis	Post operative finding			Chi-square test p-value
	AA (%)	AP (%)	Total (%)	
Acute appendicitis (AA)	158 (82.7)	33 (17.3)	191 (100.0)	Chi-square value=39.2 p<0.000
Appendicular perforation (AP)	6 (25.0)	18 (75.0)	24 (100.0)	
Total	164 (76.3)	51 (23.7)	215 (100.0)	

In Table 11, 82.7% of patients diagnosed as acute appendicitis clinically had acute appendicitis and for appendicular perforation it was 75% as shown in table 11. This finding is found to be statistically significant (p<0.05).

Table 13. Distribution of patients by duration of appendicitis

Duration of acute abdomen	Frequency	Percentage
One day	150	69.8
Two days	46	21.4
Three days	19	8.8
Total	215	100.0

Most of the patients were admitted within 24 hours of onset of symptoms (69.8%) followed by after 24 hours (21.4%) and after 72 hours (8.8%).

Table 14. Relation between duration of appendicitis and bilirubin level

Spearman's correlation	Total Bilirubin
Duration of appendicitis	r _s = 0.606
Significance	p=0.000

There was good positive correlation (r_s= 0.606) between duration of appendicitis and serum bilirubin level and this finding was statistically significant (p=0.000).

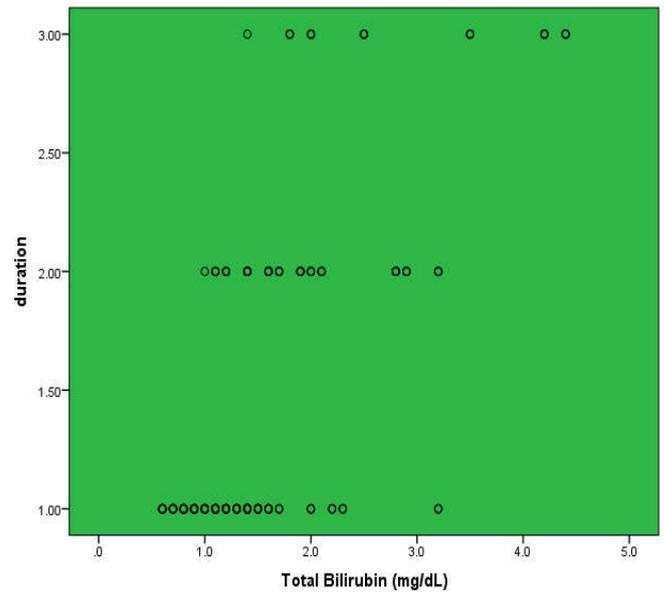


Figure 11. Scattered diagram showing relation between duration of appendicitis and bilirubin level

Table 15. Relation between duration of appendicitis and bilirubin level

Post operative finding	Total bilirubin Mean ± SD	Mann-Whitney U test p-value
Acute appendicitis	1.46 ± 0.6	p=0.566
Appendicular perforation	1.56 ± 0.8	

Mean serum bilirubin level in appendicular perforation was more than acute appendicitis but the finding was statistically insignificant (p>0.05).

Serum Bilirubin Autoanalyser



Photograph 1. Randox RX Imola for serum bilirubin analysis using photometric method



Photograph 2. Randox RX Imola for serum bilirubin analysis using photometric method

DISCUSSION

In this study 215 patients were enrolled for the study of which 115 patients (53.5%) were females while the remaining 100 patients (46.5%) were males. The mean age in this study population was 23.7 ± 11.7 years, minimum age was 9 years and maximum age was 60 years. Of the 215 patients, 191 (88%) were diagnosed as acute appendicitis clinically while 11.2% were diagnosed with Appendicular perforation. On Ultrasonography, 78.1% patients were diagnosed with acute appendicitis or appendicular perforation while 21.9 % had normal findings. Intra-operatively 76.3% were confirmed as acute appendicitis while 23.7% were diagnosed with Appendicular perforation. Patients with normal bilirubin level were seen in 26% while 74% had raised bilirubin levels. Out of 164 patients with acute appendicitis, 75.0% had raised bilirubin levels, while 25.0% had normal levels. 51 patients were diagnosed as appendicular perforation, 36 patients (70.6 %) had raised bilirubin levels, while the remaining 15 patients (29.4%) had normal levels. The mean bilirubin levels in patients diagnosed with acute appendicitis was 1.46 ± 0.6 mg/dL while in patients diagnosed with Appendicular perforation was 1.56 ± 0.8 mg/dL.

The Direct bilirubin in patients diagnosed with acute appendicitis was 0.9 ± 0.57 mg/dL. The Direct bilirubin in patients diagnosed with Appendicular perforation was 1.2 ± 1.06 mg/dL. In the study by Khan *et al.* 87.7% of acute appendicitis patients had raised bilirubin which is even higher than this study (75.0%). The mean level of bilirubin was also higher in that study (2.38 mg/dl vs 1.46 mg/dl). Other studies also had similar finding (raised serum bilirubin) like in the study by Agrawal *et al*, Emmanuel *et al*, Wasnik *et al* etc. Almost similar finding was observed in another Khan study where serum bilirubin was raised in 77% of cases. Even higher proportion with raised bilirubin was observed (99.4%) in a prospective study was carried out by Saxena *et al.* at rural tertiary healthcare center which included 213 patients. Patients with Appendicular perforation had a mean bilirubin level of 1.5mg/dl, which was significantly higher than those with a non perforated appendicitis in a study by Sand *et al.* Other studies that had increased serum bilirubin level in perforation than acute appendicitis were Estrada *et al*, Emmanuel *et al.*, Atahan *et al.*, Jamaluddin *et al.* and Giordano *et al.* In this study majority of the patients presented 24 hours (69.8%) followed

by 48 hours (21.5%) and 72 hours (8.8%) after the onset of symptoms. There was a significant positive correlation ($r_s = 0.606$) between duration of appendicitis and level of bilirubin. With the increase in duration of appendicitis there was raised in the level of bilirubin in this study.

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