VALIDITY OF SERUM TOTAL BILIRUBIN AS A DIAGNOSTIC TOOL FOR ACUTE APPENDICITIS

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ABSTRACT

Background: Acute appendicitis occurs through bacterial invasion in appendix leads to transmigration of bacteria and release of tumour necrosis factor (TNF)-alpha, Interleukin-6 (IL6) and cytokines. These reach the liver through a superior mesenteric vein and may produce inflammation or dysfunction of liver either directly or indirectly by altering hepatic blood flow with rising of total serum bilirubin. Objective: To evaluate the validity of elevated serum total bilirubin as a diagnostic marker for acute appendicitis and if elevated serum total bilirubin levels have a predictive potential for the diagnosis of complicated appendicitis. Methods: This is a prospective cross-section study including ninety-four (94) of adult patients have right iliac fossa pain attending to the Emergency Department (ED) at Suez Canal University Hospital. All 94 patients undergo total serum bilirubin measuring and postoperative histopathological examination of the removed appendix. Results: Amongst the patients diagnosed with acute appendicitis post-operatively, 57 patients (70.4%) were found to have elevated serum total bilirubin (>1.2mg/dL) while 24 patients (29.6%) had normal serum total bilirubin levels (≤1.2 mg/dL). Conclusion: Serum total bilirubin level appears to be a promising new laboratory marker for diagnosing acute appendicitis and have a predictive potential for the diagnosis of complicated appendicitis.

KEYWORDS: acute appendicitis, total serum bilirubin

Introduction

Acute appendicitis (AA) is defined as an inflammation of the inner lining of the vermiform appendix that spreads to its other parts. Despite diagnostic and therapeutic advancement in medicine, appendicitis remains a clinical emergency and is one of the more common causes of acute abdominal pain [1].

Appendicitis is one of the more common surgical emergencies, and it is one of the most common causes of abdominal pain. In Asian and African countries, the incidence of acute appendicitis is probably lower (5-6.5% of populations) because of the dietary habits of the inhabitants of these geographic areas. The incidence of appendicitis is lower in cultures with a higher intake of dietary fibre. Dietary fibre is thought to decrease the viscosity of faeces, decrease bowel transit time, and discourage the formation of fecaliths, which predispose individuals to obstructions of the appendicular lumen [2].

Although AA is not a life-threatening disease, mortality is still reported as high as 1%; diagnosis of AA is often a clinical challenge because it can mimic several abdominal pain condi-
All adult patients who will attend to Emergency Department in pain and have symptoms and signs suspect that he has acute appendicitis leads to transmigration of bacteria and release of TNF-perforated appendicitis [5].

For a long time, the preoperative diagnosis of acute appendicitis (AA) largely relies on the clinical assessment, previous experience, total white blood cell (WBC) counts, neutrophils percentage or a combination of several examinations. These traditional methods are rather non-specific. Recently ultrasonography and computed tomography (CT) were applied in the diagnosis of AA, CT has 92-98% sensitivity, and up to 100% specificity, pathognomonic features are thickened wall > 2 mm, the diameter of appendix > 6 mm, fecaliths, thickened adipose tissue, abscess.[4] Ultrasonography applications have resulted in significantly reduced cases of negative appendectomy and perforated appendicitis [5].

Acute appendicitis occurs through bacterial invasion in appendix leads to transmigration of bacteria and release of TNF-alpha, IL6 and cytokines. These reach the liver through a superrior mesenteric vein and may produce inflammation or dysfunc-tion of liver either directly or indirectly by altering hepatic blood flow with rising of total serum bilirubin. [6]

Our study aimed to evaluate the validity of elevated serum total bilirubin as a diagnostic marker for acute appendicitis, and elevated serum total bilirubin levels have a predictive potential for the diagnosis of complicated appendicitis during periods six months in Suez Canal University Hospital.

Material and methods:

Study Design: This is a prospective cross-section study

Study Population: Ninety-four (94) of adult patients have right iliac fossa pain attending to the Emergency Department (ED) at Suez Canal University Hospital.

Inclusion criteria: All adult patients with acute right iliac fossa pain associated with one or more of the following:

- Tenderness;
- Rebound tenderness;
- Migratory pain;
- Anorexia;
- Nausea and vomiting;
- Fever;
- Elevated leucocyte count

Exclusion criteria: patients have one or more of the following criteria will be excluded from the study:

- Patients with any history of the hepatic disorder and abnormal liver function tests (LFTs);
- Patient with any hemolytic disorders;
- Patient with obstructive jaundice;
- Patient below the age of 18 years;
- Pregnancy

Methodology:

All adult patients who will attend to Emergency Department in Suez Canal University Hospital complaining of right iliac fossa pain and have symptoms and signs suspect that he has acute appendicitis.

Investigations:

Laboratory: - Complete Blood Count (CBC) for WBCs count and Neutrophils Left Shift, Serum bilirubin will be added.

Radiological: - Abdomen X-ray, Pelvi-abdominal sonography.

Histopathology: Histopathological examination of removed appendix.

Sample size:

\[
 n = \left[ \frac{Z_{\alpha/2}}{E} \right]^2 \times \frac{S_n(1-S_n)}{P} 
\]

\[
 n = (1.96/0.08)^2 \times 0.8(1-0.8)/0.9762
\]

\[
 n = 600.25 \times 0.156192
\]

\[
 n = 93.754248 \sim 94
\]

Statistical Analysis

Data were tabulated, coded then analysed using the computer program SPSS (Statistical package for social science) version 17.0 to obtain.

Results

In our study population of ninety-four patients included and found that thirty-six male patient (38%) and fifty-eight female patient (62%). The mean age (27.6) years, and according to post-operative histopathological reports eighty-one patients (86.2%) had an inflamed appendix and thirteen patient (13.8%) had normal appendix and thirty-six patients (38.3%) had simple inflamed appendix (which are catarrhal or acute on top of chronic appendicitis), thirty-eight patients (40.5%) had acute suppurative appendicitis and seven patients (7.4%) had gangrenous appendicitis, and thirteen patients (13.8%) had normal appendix. We found that Mean of serum total bilirubin 1.34 mg/dl with standard deviation 0.37 mg/dl. Serum total bilirubin distributed as following thirty-four patients (36.2%) had a total bilirubin less than 1.2 mg/dl, and 60 patients (63.8%) had total bilirubin more than 1.2 mg/dl. The mean total bilirubin in simple inflamed 1.14 mg/dl, in acute suppurative 1.53 mg/dl and gangrenous appendicitis 2.1 mg/dl (P<0.001).
Finally, Sensitivity, Specificity, Positive predictive value, Negative predictive value and accuracy were calculated from Statistical Analysis. Sensitivity and Specificity of bilirubin in predicting acute simple appendicitis, acute suppurative appendicitis and gangrenous appendicitis diagnosis were as follows: sensitivity 72.8%, specificity 92.3%, PPV 98.3%, NPV 35.3%, accuracy 75.5%.

### Table 1 Sex and age distribution.

| Gender | No  | %    |
|--------|-----|------|
| Male   | 36  | 38.3%|
| Female | 58  | 61.7%|
| Total  | 94  | 100.0%|

| Age/ years | Mean ± SD |
|------------|-----------|
| Gender     |           |
| Male       | 29.44 ± 9.84 |
| Female     | 26.60 ± 7.30  |
| Total      | 27.69 ± 8.43  |

SD: standard deviation

The overall mean age of all 94 patients was 27.69 ± 8.43 years (range from 19.26–36.12 years). The average age in males and females was 29.44 ± 9.84 years and 26.6 ± 7.3 years respectively.

### Table 2 Distribution of different types of appendicitis.

| Pathology       | No  | %    |
|-----------------|-----|------|
| Normal          | 13  | 13.8%|
| simple inflamed*| 36  | 38.3%|
| acute suppurative| 38  | 40.5%|
| gangrenous      | 7   | 7.4% |
| Total           | 94  | 100.0%|

*Simple inflamed include: catarrhal and acute on top of chronic appendicitis

Post-operative histopathological examination of removed appendix in 94 patients revealed that Normal appendix in 13 patients (13.8%), simple inflamed 36 (38.3%), acute suppurative 38 (40.5%), gangrenous 7 (7.4%).

Overall 94 patients mean serum total bilirubin was 1.34 mg/dl with SD of 0.37 mg/dl. 34 patients (36.2%) of all 94 patients were found to have normal bilirubin levels (≤1.2 mg/dl), while 60 patients (63.8%) had raised bilirubin levels (>1.2 mg/dl).

Mean total serum bilirubin in the normal appendix was 0.95 mg/dl, simple inflamed 1.14 mg/dl, acute suppurative 1.53 mg/dl and in gangrenous appendicitis 2.1 mg/dl. P value for simple inflamed appendix was 0.04 so bilirubin has no significance while P value in acute suppurative and gangrenous appendicitis was less than 0.001; so bilirubin has good significance in diagnosing acute appendicitis.

### Table 3 Mean and Standard Deviation of Total Bilirubin and its distribution.

| Total Bilirubin | Mean mg/dl | ±SD   |
|-----------------|------------|------|
| <1.2 mg/dl      | 34         | 36.2%|
| >1.2 mg/dl      | 60         | 63.8%|
| Total           | 94         | 100.0%|

SD: standard deviation

Among 36 patients whom have serum total bilirubin <1.2 mg/dl found 12 patients have normal appendix, 22 have simply inflamed. 2 patients have acute suppurative appendicitis, and no patient have gangrenous appendicitis, while among 58 patients have total serum bilirubin >1.2 mg/dl found one patient has normal appendix, 14 patients have simply inflamed, 36 acute suppurative appendicitis and 7 patients have gangrenous appendicitis.

When Cutoff value 1.15 mg/dl found that sensitivity 61%, Specificity 76.9%, PPV 88%, NPV 41.67%, Accuracy 65.3%, while cutoff value 1.35 mg/dl found that sensitivity 89.5%, Specificity 83.3%, PPV 85%, NPV 88.2%, Accuracy 88.2%, while cutoff value 1.85 mg/dl found that sensitivity 85.7%, Specificity 89.5%, PPV 60%, NPV 97.14%, Accuracy 88.89%.

### Discussion

Our study was taken up with this thought that is it possible to add serum total bilirubin as a new laboratory marker to aid in the diagnosis of acute appendicitis, decrease the removal of the normal appendix and to prevent impending complications of acute appendicitis.

This study population is ninety-four patients included and found that thirty-six male patient (38%) and fifty-eight female patient (62%). The mean age (27.6) years. While in Emmanuel et al. In his study including 472 patients, 254 patients (53.8%) were male and (46.2%) female and the mean age was (27) years [8]. While in Eren et al. study group of 162 patients consisted of 97 (60%) men and 65 (40%) women with a median age of 36 years [9]. So our study differed from another study as female more than males due to female have more other causes of a right iliac pain than males and this the cause that removal of normal appendix more in female patients.

In this study the according to histopathological reports eighty-one patients (86.2%) had an inflamed appendix and thirteen patient (13.8%) had a normal appendix. While Emmanuel et al In his study Regarding histopathological reports 386 patients (82%) had an inflamed appendix and 86 patient (18%) had normal appendix [8], in Eren et al study Histopathological examinations revealed inflamed appendix in 141 (87%) patients and twenty-one patients (13%) had normal appendix [9]. So removal of normal appendix still has significant incidence in our study and other studies.

In our study post-operative histopathological reports revealed that thirty-six patients (38.3%) had simple inflamed appendix (which are catarrhal or acute on top of chronic appendici-
### Table 4 Mean and SD of serum total bilirubin in different types of appendicitis.

| Pathology          | Normal  | simple inflamed | acute suppurative | gangrenous |
|--------------------|---------|-----------------|-------------------|------------|
| Total Bilirubin    | Mean    | ±SD             | P1                | P2         | P3         |
|                    | .95 mg/dl| .24             | .04               | <0.001     | <0.001     |
|                    | 1.14 mg/dl| .23             | <0.001            | <0.001     |            |
|                    | 1.53 mg/dl| .19             |                  |            |            |
|                    | 2.10 mg/dl| .20             |                  |            |            |

SD: standard deviation,  
P: Probability, Test used: one-way ANOVA  
P1: significance relative to Normal group,  
P2: importance relative to Simple inflamed group,  
P3: significance relative to acute suppurative group

### Table 5 Distribution of total serum bilirubin in different pathological types of appendicitis

| Pathology          | Normal  | simple inflamed | acute suppurative | gangrenous |
|--------------------|---------|-----------------|-------------------|------------|
| Total Bilirubin    | <1.2mg/dl| No              |                   |            |
|                    | %       | 33.3%           | 61.1%             | 0%         |
|                    | >1.2    | 1               | 14                | 36         |
|                    | %       | 7.7%            | 38.9%             | 94.7%      |

P: Probability, Test used: Chi-square test
Graph 1: Differentiations between Normal and different types of appendicitis according to serum total bilirubin.
Table 6 Differentiations between Normal and different types of appendicitis according to serum total bilirubin

| Total bilirubin | P | Cutoff value | Sensitivity | Specificity | PPV | NPV | Accuracy |
|-----------------|---|-------------|-------------|-------------|-----|-----|----------|
| Normal & Simple inflamed Appendicitis | 0.015 | 1.15 | 61.1% | 76.9% | 88% | 41.67% | 65.3% |
| Simple inflamed Appendicitis & Acute suppurative Appendicitis | <0.001 | 1.35 | 89.5% | 83.3% | 85% | 88.2% | 88.2% |
| Acute suppurative Appendicitis & Gangrenous Appendicitis | <0.001 | 1.85 | 85.7% | 89.5% | 60% | 97.14% | 88.89% |

In our study mean of serum total bilirubin 1.34 mg/dl with standard deviation 0.37 mg/dl. Serum total bilirubin distributed as following thirty-four patients (36.2%) had a total bilirubin less than 1 mg/dl, and 60 patients (63.8%) had total bilirubin more than 1.2 mg/dl. The mean total bilirubin in simple inflamed 1.14 mg/dl, in acute suppurative 1.53 mg/dl and gangrenous appendicitis 2.1 mg/dl (P<0.001). In Chaudhary et al. in his study including 50 patients, total serum bilirubin was raised in thirty-eight (76%) patients whereas twelve (24%) cases had normal serum total bilirubin level. Serum total bilirubin was more elevated in gangrenous and perforated appendix than those in acute appendicitis (P<0.001). The mean of serum total bilirubin in acute appendicitis cases without perforation or gangrene was 1.52 mg/dl, and the mean of serum total bilirubin in cases with perforated or gangrenous appendix was 3.62 mg/dl for gangrenous/perforated appendicitis [8]. In Eren et al. study found that total and direct bilirubin levels were associated with 36 times greater risk for appendicular gangrene/perforation [9]. Moreover, in Emmanuel et al. study The mean bilirubin levels were higher for patients with simple acute appendicitis compared to those with a non-inflamed appendix, and significantly more patients in this group had hyperbilirubinemia on admission (30% vs 12%, p<0.001). The odds of a patient with hyperbilirubinemia having simple acute appendicitis were over three times higher than those without hyperbilirubinemia. The specificity of hyperbilirubinemia for simple acute appendicitis was 88%, and its positive predictive value was 91%. Patients with a perforated or gangrenous appendix had higher mean bilirubin levels than those with simple acute appendicitis (2.3mg/dl vs 1.8mg/dl, p=0.01). Significantly more patients with a perforated or gangrenous appendix had hyperbilirubinemia than those with simple acute appendicitis (60% vs 30%, p<0.001). The specificity of hyperbilirubinemia for a perforated or gangrenous appendix was 70% [8]. So all studies found that elevated total serum bilirubin has good significance in the diagnosis of acute appendicitis.

In our study, the Sensitivity, Specificity, Positive predictive value, Negative predictive value and accuracy were calculated from Statistical Analysis. Sensitivity and Specificity of bilirubin in predicting acute simple appendicitis, acute suppurative appendicitis and gangrenous appendicitis diagnosis were as follows: sensitivity 72.8%, specificity 92.3%, PPV 98.3%, NPV 35.3%, accuracy75.5%. While in Emmanuel et al study when differentiating between simple inflamed appendix and non-inflamed appendix found that hyperbilirubinemia had sensitivity 30%, specificity 88%, PPV 91%, and NPV 24%, and when differentiating between simple inflamed appendix and gangrenous appendix found that hyperbilirubinemia had sensitivity 60%, specificity 70%, PPV 21% and NPV 92% [8].

Hence, we see that patients with acute suppurative appendicitis and gangrenous appendicitis had significantly elevated total serum bilirubin as compared to that of simple appendicitis. So we infer that patients with features suggestive of appendicitis...
with elevated serum total bilirubin are more susceptible to having acute suppurative appendicitis and gangrenous appendicitis than those with normal or slightly elevated total serum bilirubin.

**Conclusion**

Serum bilirubin levels appear to be a promising new laboratory marker for diagnosing acute appendicitis. However, diagnosis of appendicitis remains mostly still clinical. Hyperbilirubinemia seems to facilitate diagnosis of complicated AA in the absence of CT.

Patients with clinical signs and symptoms of appendicitis and with hyperbilirubinemia should be identified as having a higher probability of complicated appendicitis.

**Recommendations**

- Adding total serum bilirubin in routine investigations for all patients primary diagnosed as having acute appendicitis

**Authors’ Statements**

**Competing Interests**

The authors declare no conflict of interest.

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