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Research Article

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Serum Bilirubin Level as a Laboratory Marker in Acute Appendicitis

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Abstract

Background: *Acute appendicitis is the most common acute abdominal condition.*
For many decades the diagnosis has depended mainly on clinical examinations, laboratory investigations such as leukocytosis, and abdominal sonography. Occasionally it can be challenging to reach the diagnosis, as there many differential diagnoses for right iliac fossa pains, especially in women. Thus, there is an encouraging demand for laboratory markers for the diagnosis.
Objective: *Our study aims to the assessment of total serum bilirubin level as a laboratory marker for diagnosing acute appendicitis.*
Methods: *A prospective study collected data from 500 patients. All patients' demographic details, duration of symptoms, vital data, and blood samples were collected on admission for full blood count, and liver function tests including bilirubin. All the removed appendices will be sent for histopathological examination and were classified into 5 groups according to the histological diagnosis, variable from no pathological findings in the First group, to acute necrotizing appendicitis in the fifth group.*
Results: *There were highly major differences between each group as regards the duration of symptoms in hours till the time of taking the samples. There was no difference between the patients regarding the temperature, and the pulse rate, but Total serum bilirubin (TSB) was ≥1.00 (mg/dl), with a sensitivity of 58% and specificity of 82%, with a diagnostic accuracy of 70%. White blood cells (WBCs) were≥11 (×103/µL), with a sensitivity of 68% specificity of 66%, and diagnostic accuracy of 67%.*
Conclusion: *TSB is a valuable indicator of patients having acute appendicitis, with higher specificity than WBCs.*

Keywords: *Serum Bilirubin, acute Appendicitis, Laboratory marker.*

Introduction

Appendectomy is the far most common general surgical operation. However, it is not uncommon for surgeons to face difficulties in diagnosis of appendicitis, and also in determining the proper timing for surgery as appendicitis takes numerous clinical presentations ranging from slight abdominal pain up to more serious forms such as bowel obstruction (especially in extremes of age), and frank peritonitis [1].

For decades the history and clinical examination were the main criteria for acute appendicitis diagnosis. However, this was associated with fallacies of missing some cases ranging from 8-22% in males to 15-42% in females. The perforated appendix is associated with an increase in morbidity and mortality rates up to 47% & 3% respectively. Consequently, a lot of effort was carried out to increase the accuracy of the diagnosis of appendix inflammation to avoid either unnecessary surgery or missing the atypical cases and to determine the proper timing of surgery. This was done through laboratory tests and radiological investigations [2].

Estimation of WBCs and serum C reactive protein (CRP) is the most commonly used investigation for diagnosis. However, there is no cut-off could be detected for CRP, and we still have cases of acute appendicitis with normal values of both markers [3].

As regards, radiology for the diagnosis of appendicitis, ultrasound, and computed tomography (CT) scans are the best radiologic modalities for diagnosing acute appendicitis. The overall ultrasound sensitivity ranges from 78% to 83%. Furthermore, there are situations, in which CT scan Usage is not applicable and/or not desirable such as in children and pregnant women [4,5].

Recently, total serum bilirubin (TSB) has gained interest as a marker for inflammation of the appendix, and raised bilirubin levels were linked to more severe forms of appendicitis and even perforation. Sand et al. [6], studied 538 patients who were proven histologically to have appendicitis. The raised bilirubin levels in those patients showed a positive relation with appendiceal perforation with a sensitivity of 70%and a specificity of 86%. These figures when compared with those of WBCs and CRP seem to be more diagnostic. Also, similar results were obtained by Farooqui et al.[7], in their study.

Our work aimed to carry out a prospective study to assess the relationship between the TSB level and histologically proven acute appendicitis, and a comparison between the sensitivity and specificity of this marker and the well-established marker (WBCs).

Patients and Methods

All adult patients, males, and females aged (18-60 years) presenting to the Emergency Departments of our hospital in the duration from June 2019 to June 2022 who were diagnosed as having acute appendicitis will be assessed for eligibility. The exclusion criteria included patients who have a history of liver diseases, abnormal liver function tests, hemolytic blood diseases, congenital metabolic syndromes, and congenital, & acquired biliary radicle diseases.

All patients' demographic details, duration of symptoms, and vital data will be collected using a pro forma. Blood samples will be collected on admission for the routine laboratory work-up Full blood count, liver function tests including TSB level.
All the removed appendices will be sent for histopathology, to be evaluated by a single senior pathologist.

The histological examination will be categorized into five groups: (sand et al. [6])

1) Normal histological Findings.
2) Reactive follicular hyperplasia /chronic inflammation.
3) Acute inflammation, intact mucosa, and the infiltrate of inflammatory cells are mild to moderate degrees.
4) Perforated appendix (Macroscopically or histologically).
5) Acute necrotizing appendicitis.

Statistical Analysis:

Data analysis was done by using Statistical Program for Social Science (SPSS) version 20.0. For multiple comparisons between different variables, we used (ANOVA). A Chi-square test and ROC curve were used to realize the overall predictivity and the best cut-off value of the sensitivity and specificity. A significant *P* value was considered if it ≤ 0.05.

Results

Our retrospective collected data for 500 patients's majority of them are male 390 (78%) and 110 females (22%), mean age was 21.98±1.89, all were classified into 5 groups according to the histological diagnosis as in (Table 1).

Table 1: Demographic data distribution among the study groups.

Group	Number	Age (Years) range / Mean	Gender N (%) 500	
			F	M
I	30	17-26 21.33±2.09	6 20%	24 80%
II	170	18-31 22.15±2.03	42 24.7%	128 75.3%
III	160	17-32 22.09±2.14	32 20%	128 80%
IV	62	17-24 21.65±1.54	14 22.6%	48 77.4%
V	78	21-24 21.92±1.01	16 20.5%	62 79.5%
Total	500	21.98±1.89	110 22%	390 78%
ANOVA		0.930		
p-value		0.447	0.458	
Chi-square			0.640	

Results show no significant difference between groups related to their age (years), and gender. As regards the duration of symptoms in hours till the blood tests were taken are highly statistically significant differences between each group varying from a minimum of 12 hours in the first &second groups up to 24-72 hours in the fourth & fifth groups as in (Table 2).

There was no considerable difference between groups according to the temperature which reached up to 38.5 ^{O}C in the second & third groups, and the maximum was 39^{O} C in the fourth &fifth groups. the same for the pulse rate variable reached 78-105 beats /minute in the fourth group & 82-110 beats/minute in the fifth group. For laboratory investigations, there was no considerable difference between groups related to Alanine transaminase (ALT) IU/l. On the contrary, considerable differences in the WBCs between each group high reached the level of 23000(×10^3/µL) in the fourth & fifth groups.

The TSB shows a highly considerable difference between groups it was 0.5-2.1mg/dl in the fourth group & 0.7 -2.2 mg/dl in the fifth group (Table 2).

Table 2: Comparison according to Duration of symptoms, Temperature, Pulse, ALT, WBCs& TSB.

Group (Numbers of patients)	Duration of symptoms. hours Range/ Mean ±SD	Temp. ^{O}C Range /Mean ±SD	Pulse/min Range /Mean ±SD	ALT (IU/L) Range /Mean ±SD	WBCs ($\times10^3/\mu L$) Range /Mean ±SD	TSB (mg/dl) Range /Mean ±SD
I (n:30)	12-36 24.00±7.86	37.3-38 37.59±0.24	73-90 82.93±5.95	17-23 20.80±.21	5600-15000 10160.00±2434.22	0.3-1.3 0.69±0.29
II (n:170)	12-48 24.24±8.13	37-38.5 37.63±0.43	70-100 84.46±6.80	9-29 19.68±3.93	10000-16600 10868.82±2786.49	0.3-1.64 0.88±0.36
III (n:160)	12-48 27.18±11.19	37-38.5 37.66±0.31	72-100 90.0±5.19	12-28 21.13±3.67	9800-19000 12408.73±3081.58	0.4-1.9 1.07±0.40
IV (n:62)	24-72 41.81±16.65	37.2-39 37.89±0.47	78-105 91.35±6.62	7-28 21.48±4.51	10000-23000 13919.35±4621.07	0.5-2.1 1.26±0.49
V (n:78)	24-72 46.26±15.07	37-39 38.15±0.54	82-110 96.67±6.53	17-28 21.77±2.64	7800-23000 15271.67±3108.56	0.7-2.2 1.47±0.43
ANOVA	34.040	0.319	0.789	1.874	16.402	19.952
p-value	<0.001	0.865	0.533	0.271	<0.001	<0.001
ALT: Alanine transaminase, WBCs: White blood cells, & TSB: total serum bilirubin						

Table 3: Diagnostic Performance of T. Bilirubin (mg/dl) and WBCs ($\times10^3/\mu L$) in discrimination of uncomplicated appendicitis and complicated appendicitis.

Items	Cut-off	Sen.	Spe.	PPV	NPV	Accuracy
T. Bilirubin	≥1.00	58.0%	82.0%	76.3%	66.1%	70.0%
WBCs	≥11000	68.0%	66.0%	66.7%	67.3%	67.0%

The Receiver operating characteristic (ROC) curve cut-off value of TSB was ≥1.00 (mg/dl), with a sensitivity of 58% specificity of 82% positive predictive value (PPV) of 76.3%, and a negative predictive value (NPV)of 66.1% diagnostic accuracy of 70% (Table 3& Figure 1).

In comparison to WBCs which were ≥11 ($\times10^3/\mu L$), with a sensitivity of 68% specificity of 66% PPV of 66.7%, a negative predictive value of 67.3% diagnostic accuracy of 67%. (Figure 1)

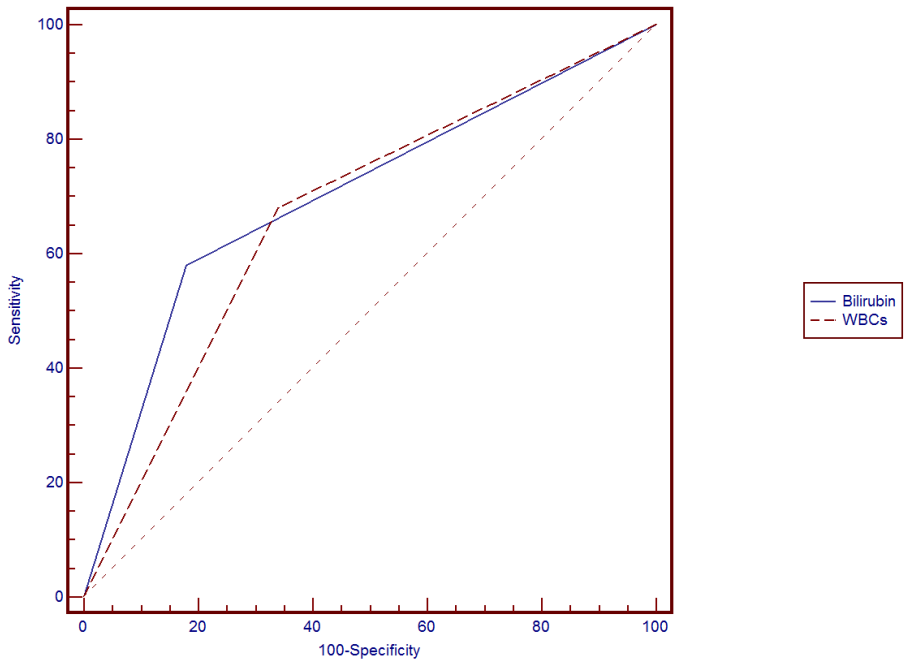

Figure 1: ROC curve for TSB (mg/dl), and WBCs($\times10^3/\mu L$) sensitivity& specificity

Discussion

Acute appendicitis is the commonest cause of acute abdomen, however, no reliable specific laboratory test for the definite diagnosis [8]. Occasionally it can be challenging to reach a diagnosis, as there may not be typical symptoms and signs of appendicitis, and many differential diagnoses for right iliac fossa pains, especially in women [9]. Delays in the diagnosis and surgical intervention can be complicated by perforated appendix and peritonitis with high morbidity and long hospital stay [10]. The prevalence of perforated appendicitis is increasing and has

reached 13 – 37%. This leads to a significant increase in morbidity as wound infection and peritonitis up to 47%, and mortality of 3% [7]. Thus, there is an encouraging demand for laboratory markers for the diagnosis.

In our study population, the age ranges from 18-60 years, with a mean age was (21.98) years. Most of the patients were between 20-50 years old. In comparison to a study by Dipen Patel et al. (2014), 62% of patients between 20-40 years old. As regards gender we found that 390 patients (78%) were males while 110 patients were females, with a male-to-female ratio was 3.5:1 more than in other studies by Dipen Patel et al. [11], done on 100 patients the ratio was 2.4:1, and Marudanayagam et al. [12] study on 2660 patients was 1.5:1. The explanation in our study that it was done in a military hospital where most of the patients in this age group are males.

There was a higher different correlation between groups according to the duration of symptoms till the time of admission and taken blood samples, as the duration increases the degree of inflammation increases. Some hospitals attempted to reduce surgical operations done during the night times, provided that acute appendicitis is uncomplicated **[13].** Peritonitis due to a perforated appendix always mandates an immediate emergency operation [13,14]. There was no difference according to the temperature between groups which reached up to 38.5°C in groups II and III, and the maximum was 39°C in groups V &VI. The same for the pulse rate variable reached 78-105 beats /minute in group IV & 82-110 beats/minute in the group.

ALT was within the normal range in 100% of the cases included in our study, in comparison to the study by Chaudhary et al. [9], ALT was normal in 80% of cases and slightly elevated in 20% of cases.

Diagnosis of appendicitis according to Serum bilirubin:
Raised TSB levels were linked to complicated appendicitis [15]. Many mechanisms leading to high TSB levels in inflammatory response have been described as haemolysis, due to bacteremia, and endotoxemia which results in reduced bilirubin excretion. Inhibition of bile salt transport mechanisms by cytokine-mediated form bacterial endotoxin leads to cholestasis [16].
The invasion of *Escherichia coli* organisms into the muscularis propria of the appendix and then into the portal venous circulation and liver tissues interfering with the excretion of the bile causes increasing in TSB [17]. therefore, high TSB level is due to bacteraemia occurring in both complicated and non-complicated appendicitis [8].

We also made a comparison between groups according to TSB level and we found the following: among the 500 patients, the TSB level was raised by 58%, whereas 42% had a normal level. As the degree of appendicitis increases, the mean level of elevation of TSB increases. As the degree of inflammation of the appendix increases the number of cases with hyperbilirubinemia increases.in our study TSB was high in 3 patients in group I, 79 Patients in group II, 80 Patients in group III,56 patients in group IV & 72 Patients in group V.

The sensitivity, specificity, PPV, and NPV were 58%, 82% 76.3% 66.11% respectively.
We found in our study that the patients with complicated appendicitis either gangrenous or perforated have significantly more hyperbilirubinemia (elevated TSB levels > 1 mg/dL) than those with uncomplicated cases.

High TSB is a predictive marker for perforated appendix diagnosis [17,18], and the levels double increased in gangrenous appendicitis [19].

In our study, a TSB of ≥1.0 mg/dl sensitivities were 58% for diagnosis & specificity was 82%, in comparison to other studies were 27%, 96% [20], 30%,88% [8], and 69%,56% [7], respectively. In the study by Sevinç et al. [21], the specificity for diagnosis was 81.4%& 92.4% for acute appendicitis, and perforated appendicitis respectively. Conversely, the sensitivity was very low it was 19% &34% for acute appendicitis and perforated appendicitis respectively, and he noted that direct bilirubin, not TSB was more accurate. The same was noted by Eren et al. [15], who noticed a 36-fold greater risk for perforated appendix or gangrene seen with elevated direct bilirubin levels.

Sand et al. [6], studied those who were proven histologically to have appendicitis. The raised bilirubin levels in those patients showed a positive relation with appendiceal perforation with a sensitivity of 70% and a specificity of 86%. These figures when compared with those of WBCs and CRP seem to be more diagnostic.

Comparing our study results with other studies according to bilirubin level it seems to be in concordance with many retrospective studies like Sevinc et al. [21], Eren et al. [15], and Sand et al. [6] studies.

Diagnosis of appendicitis according to the WBCs count:
According to the WBCs count the comparison between the five groups showed a high considerable difference between groups according to WBCs. As the degree of inflammation of the appendix increases, the total WBCs increase as shown in (Table 2). Also, the percentage of patients in each group increases. The sensitivity, specificity, and PPV of WBCs in our study were 68%, 66%, and 66.7% respectively. On comparing our results with other studies, it seems to be in concordance with a study by Jahan et al. [22], which revealed sensitivity, specificity, and PPV of 76.6%, 80%, and 82.5% respectively. Another study by Rafiq et al. [23]**,** reported a higher sensitivity of 87% and 92% specificity with a cutoff value of 11900/mm [3].
The total leukocyte count was found elevated at>11.000/cmm in 68% of the patients. the same percentage of 68%, in the study by Dipen Patel et al. [11], and was higher at 93% in the study by Emmanuel et al [8].

In comparing bilirubin to WBCs, for diagnosis of appendicitis:
In our study, TSB specificity was 82%, the same as D'Souza et al. [20], study in complicated appendicitis but with a higher sensitivity in his study it was 70% in comparison to our study which was 58%. For WBCs specificity was higher in our study was 66%, in comparison to the study by D'Souza et al. [20], which was 34 %, but the sensitivity was lower at 68% in our study in comparison to his study which was 80%.

Recently, a novel score called Shabir's "SMART-LAB" score. The name of the score is abbreviations, includes radiological investigation as abdominal ultrasonography(S), clinical symptoms, as para-umbilical pains migratory to right iliac fossa (M), anorexia (A), and signs as rebound tenderness (R), tenderness (T), Laboratory investigations as leucocytosis (L), Acute phase protein CRP (A), and TSB(B). Total Serum bilirubin is taken 3 points out of 14 points which is the maximum score [24].

Conclusion

In acute appendicitis besides the clinical physical examinations, TSB is a valuable indicator for the diagnosis of patients with higher specificity than WBCs.

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Conflict of Interest: there are no conflicts of interest.

Ethical approval: The study was approved by The Faculty of Medicine, Ain Shams University Research Ethics Committee.

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