



Evaluation of hyperbilirubinemia as a predictor of complicated acute appendicitis

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Abstract: Background: Acute appendicitis is one of the most common presentations in emergency department and appendectomy is considered to be one of the most frequently performed surgeries worldwide. The decision whether or not to operate, is key in the management of acute appendicitis. **Aim of the Work:** to evaluate the value of serum bilirubin measurement in cases of complicated acute appendicitis. **Patients and Methods** This prospective study was conducted on 80 patients with signs, symptoms and laboratory findings consistent acute appendicitis. They had open or laparoscopic appendectomy in the emergency department in Ain Shams University hospitals, Ain Shams University and two other private hospitals from November 2017 to April 2018. **Results:** the sensitivity of the total serum bilirubin as a predictor for complication in acute appendicitis was found to be 82.35% with the negative predictive value of 93.3%, and the specificity was 95.45% while positive predictive value of 87.5%. while the sensitivity of WBC levels with cut off value of 14.2×10^3 was found to be 76.74%. Accordingly, total serum bilirubin, in this study, is proved to be highly accurate and sensitive in predicting complication of acute appendicitis. The test is fast, cost-effective and easily accessible. In comparison, WBC levels is only moderately sensitive (76.74%). However, the complication in cases of acute appendicitis should be dealt with careful examination, history taking and investigations as there is no single investigation stand solely for proper diagnosis and appendicitis remains a clinical diagnosis. **Conclusion:** Diagnostic accuracy of hyperbilirubinemia in diagnosing complicated appendicitis is acceptable with high specificity and has dramatically improved our ability of accurate diagnosis of complicated appendicitis and the need for CT scans and MRI can be reduced and unnecessary delay in appendectomy can be avoided. It is recommended that hyperbilirubinemia is used as a screening marker for complicated appendicitis, aiding in accurate, timely diagnosis and management.

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Key words: hyperbilirubinemia, acute appendicitis, serum bilirubin.

1. Introduction

Appendicitis is one of the most typical causes of right iliac fossa pain and surgical emergencies requiring emergency treatment, and appendectomy remains among the most frequently performed urgent surgeries worldwide.(1) Often, it's tough to diagnose appendicitis properly because there may be atypical symptoms and signs of appendicitis. Different clinical signs and symptoms perpetually mimic the diagnosis of acute appendicitis, as there are variety of causes resulting in pain in right iliac fossa notably in female patients. diagnosing acute appendicitis clinically remains a typical surgical problem.

Correct diagnosis will be assisted by extra testing or expectant management or both. These may delay appendectomy and may result in perforation with raised morbidity and hospital stay. A safe alternative seems to be appendectomy as shortly as the condition is suspected, a technique that will increase the number of unneeded appendectomies. (2)

One of the most common and feared

complications of the acute appendicitis is perforation of appendix. the general rate of perforated appendix is 25.8%, children <5 years old, patients >65 years old have the highest rates of perforation (45% and 51, respectively).(3)(4). The perforation of appendix may results in high incidence of infection postoperatively and prolonged hospital stay.(5) To decrease the morbidity and mortality of perforated appendix, a preoperative diagnosis of perforation should be sought as soon as possible. to stop the harmful effects of perforated appendix, a surgeon needs diagnostic tools which can signal perforation of appendix at the early stages, to avoid the delay in the management of perforated. A new diagnostic test added to the spectrum is hyperbilirubinemia, due to the fact that elevated total serum bilirubin has been found to signal perforation.(6)(7). hyperbilirubinemia in patients with appendicitis may have a prediction for potential diagnosis of appendiceal perforation. The sensitivity of elevated total serum bilirubin is almost like that of elevated total white blood cell count and CRP

however specificity of elevated total serum bilirubin is more higher when compared to elevated WBC's and C-reactive protein.(8) This study was undertaken to evaluate the sensitivity, specificity and predictive value of serum hyperbilirubinemia in acute appendicitis and its possible complications.

Aim of the work: The aim of the present study is to evaluate the value of serum bilirubin measurement in cases of complicated acute appendicitis.

2. Patients and methods

This prospective study was conducted on eighty patients who presented with clinical features of acute appendicitis to the Emergency unit in Ain shams university hospitals and two other private hospitals and subjected to the inclusion and exclusion criteria in the period from November 2017 to April 2018.

The study included all patients diagnosed as acute appendicitis, appendicular perforation or recurrent appendicitis clinically on admission. While patients with hemolytic anemia and patients with Congenital or Acquired hepatobiliary disease were excluded from the study.

Methods

All patients presenting to the surgical outpatient department (OPD) and emergency department (ED) throughout the study period with pain within the right iliac fossa with duration less than 7 days were included. Ethical committee approval was guaranteed before the start of study & standards of good clinical practices were followed during this study. Patients were enlightened concerning the study and a written consent was obtained. They were clinically assessed for signs and symptoms of acute appendicitis. The diagnosis was made on the basis of history, clinical examination, and Alvarado scoring system is employed to evaluate all patients as a clinical scoring system. laboratory reports including white blood cell (WBC) count, total and direct bilirubin levels, and routine pre-operative laboratory investigations were withdrawn. All the standard recommended precautions were taken throughout processing of samples.

Provisional imaging by pelvi-abdominal ultrasound scan is done as adjunctive diagnostic tool in all patients with acute abdominal pain.

Typically, menstrual history and pregnancy test are requested along with proper gynecological evaluation.

All patients with positive findings in examination or investigations, are re-examined by senior consultant for the management decision.

Complementary to ultrasound scans, additional CT with IV contrast can be requested for query cases or cases with complicated appendicitis. Proper hydration is done as precaution for minimizing the nephropathic risks and normal creatinine level is a

perquisite. Scan result is reviewed by radiology and general surgery physicians. In general, patients receive proper intravenous antibiotics and IV analgesics, preoperatively. Cases with appendicular mass are managed conservatively and are not included in our study unless operated upon secondary to failure of conservative treatment. appendectomy is performed through muscle splitting incision at the McBurney point.

All patients were operated in the emergency operation theatre and per-operative findings were recorded and specimens were sent for histopathology to confirm the diagnosis.

Statistical analysis

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 23. ROC curves and optimal cut off points were obtained using Youden index in Med Calc software version 19. The quantitative data were presented as mean, standard deviations and ranges when parametric and median, inter-quartile range (IQR) when data was non parametric. Also, qualitative variables were presented as number and percentages. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following: P-value > 0.05: Non significant (NS), P-value < 0.05: Significant (S) and P-value < 0.01: Highly significant (HS).

3. Results

The sample was divided into 3 pathology groups according to the histopathological examination results.

Table 1. Descriptive statistics for pathology groups

	Count	Percent
Negative cases	19	23.8%
Acute non complicated cases	44	55.0%
Acute complicated cases	17	21.3
Total	80	100.0

Correlation between pathology groups, WBC's and total serum bilirubin

The correlation between the pathology groups and white blood cells was found to be highly significant with a P value of.002 for white blood cells.

The WBC's values differ according to the operative diagnosis, which could be shown by studying the mean within the three diagnoses. The lower values of WBC's were recorded in the negative operative diagnosis with average 9.58, while the highest values were recorded within the complicated appendix cases with an average 15.32. The average values of the non-complicated appendicitis were 12.52 which is closer to the mean of the sample, and that could be explained easily as more than 50% of the sample are non-complicated appendicitis cases.

However, the minimum and maximum range values of WBC's were recorded within the negative case, the WBC's value recorded higher values within the complicated appendicitis and non-complicated appendicitis relative to the negative cases. (Table 2)

The bilirubin value is confirmed to be highly significant, as its p-value is less than 0.001. The values of bilirubin were significantly high within the cases diagnosed as complicated appendicitis compared to the negative cases and non-complicated appendicitis. (Table 2)

Table 2. Correlation between pathology groups and laboratory results

		Pathology groups			Test value	P-value	Sig.
		Negative	Appendicitis non complicated	Complicated			
		No. = 19	No. = 44	No. = 17			
WBCs	Mean ± SD	9.58 ± 5.84	12.52 ± 3.86	15.32 ± 5.02	6.895*	0.002	HS
	Range	3 – 28	4 – 23	3.9 – 23.5			
Bil. Total	Median (IQR)	0.36 (0.3 – 0.55)	0.5 (0.4 – 0.64)	1.2 (1.1 – 1.36)	29.384#	0.000	HS
	Range	0.19 – 1.4	0.1 – 1.4	0.4 – 1.75			
Bil Direct	Median (IQR)	0.08 (0.06 – 0.11)	0.07 (0.03 – 0.11)	0.2 (0.16 – 0.37)	24.757#	0.000	HS

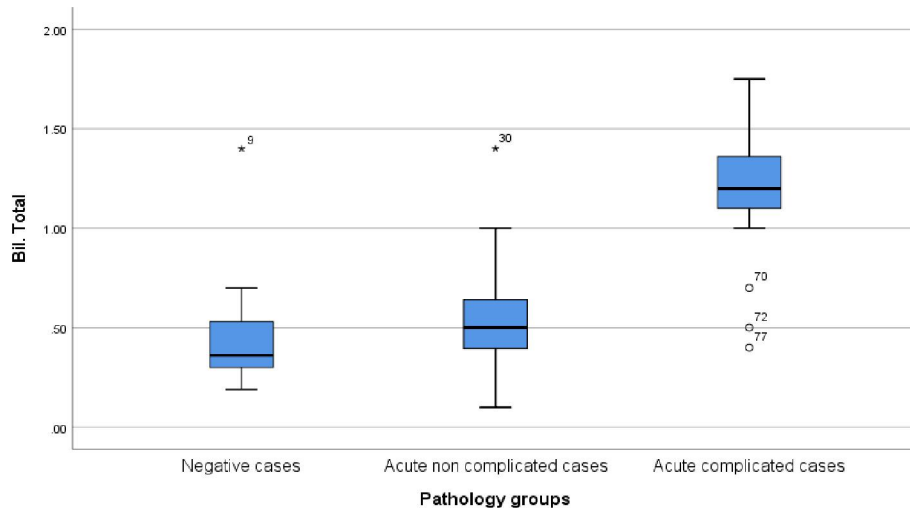


Figure 1. Total bilirubin in different pathology groups

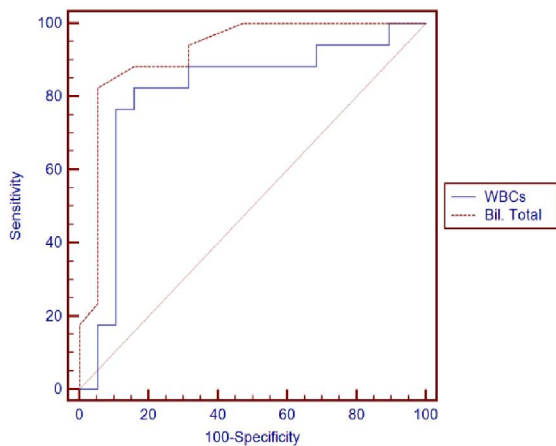


Figure 2. Receiver operating characteristic curve for WBCs and total serum bilirubin levels in differentiating the negative group and complicated group.

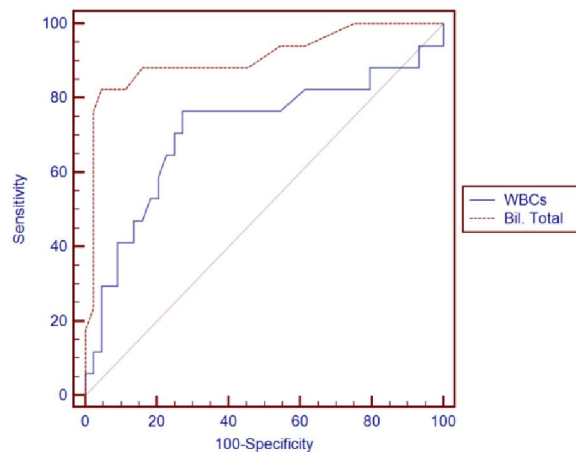


Figure 3. Receiver operating characteristic curve for WBCs and total serum bilirubin levels in differentiating the acute non complicated group and complicated group.

Diagram (Figure 1) show the distribution of bilirubin between different pathology groups.

Receiver operating characteristic (ROC) curves were used to demonstrate the correlation between the WBC's and total bilirubin with pathology groups.

1. Comparison between negative and complicated group in relation to WBC's and total bilirubin

Both WBC's and total bilirubin were found to be significant in comparison between the negative group

and complicated group as indicated by the following ROC curve. (Figure 2)

2. Comparison between acute non complicated and complicated group in relation to WBC's and total bilirubin

Total bilirubin was found to be more significant than WBC's in comparison between the acute non complicated group and complicated group as indicated by the following ROC curve. (Figure 3)

Table 3. Sensitivity and specificity for WBCs and total bilirubin in differentiating the negative group and the complicated group

Variables	Cut off point	AUC	Sensitivity	Specificity	+PV	-PV	Accuracy	P-Value
WBCs	> 10.5	0.808	82.35	84.21	82.4	84.2	66.56	0.0002
Bil. Total	> 0.7	0.920	82.35	94.74	93.3	85.7	77.09	<0.0001

Optimal cut-off points (the point of maximum sensitivity and specificity) of $>10.5 \times 10^3$ for WBC's and > 0.7 mg/dl for total bilirubin were observed from analysis of the ROC curve using Youden index. (Table 3).

Table 4. Sensitivity and specificity of WBC's and total bilirubin between non complicated and complicated cases

Variables	Cut off point	AUC	Sensitivity	Specificity	+PV	-PV	Accuracy	P-Value
WBCs	> 14.2	0.712	76.47	72.73	52	88.9	49.20	0.0135
Bil. Total	> 0.92	0.908	82.35	95.45	87.5	93.3	77.81	<0.0001

Optimal cut-off points (the point of maximum sensitivity and specificity) of $> 14.2 \times 10^3$ for WBC's and $>.92$ mg/dl for bilirubin were observed from the analysis of the ROC curve using Youden index.

4. Discussion

Appendicitis is usually uncomplicated in most cases. However, non-perforated appendicitis is often cured by open or laparoscopic appendectomy followed by a brief recovery period, a complicated appendicitis could cause a life-threatening condition on the patient health. The diagnosis of perforation as early as attainable improves the outcomes, and facilitate the decision of the surgeon to operate sooner and prepare for a difficult operation(9). in addition, the diagnosis of complicated appendicitis might change the operative approach from the regular McBurney's incision to laparotomy(10).

It is still a challenge to diagnose appendicitis properly, this is as a result of the clinical presentation may be vague, and there is a lack of specific laboratory test for diagnosing acute appendicitis. Meanwhile, a lot of scoring systems and laboratory tests are present as a diagnostic help, clinical examination and assessment are the most vital decision-making factors for the preoperative diagnosis of perforation. This is often a really difficult task for the surgeon to achieve and therefore the question of complication or not is often not answered until the operation.

The CT scan is extremely specific however it lacks the sensitivity needed as the diagnosis of

complication or perforation cannot be established based on CT findings unless abscess or additional luminal gas is present (11)(12). Laboratory Tests like white blood cell and C-reactive protein are useful in the course of constructing a diagnosis. although, they each have very low specificity(13).

No single imaging scan or laboratory test is capable to dependably diagnose acute appendicitis. Instead, a combination of history, examination and laboratory with imaging investigations is employed to establish the diagnosis and choose the management. Although abdomen and pelvis CT is accurate in diagnosing acute appendicitis. In many studies, its routine use has not established to improve diagnosis accuracy or reduce the rate of negative appendectomies. additionally, it may lead to delay in final treatment with additional complications postoperatively, longer hospital stays, and exaggerated costs. furthermore, it is not always available for such use in all hospitals.(14)

New emerging interest has appeared for non-operative management of non-complicated appendicitis using antibiotics and conservative treatment(15). For this reason, a reliable test to differentiate between complicated and non-complicated appendicitis is extremely needed.

The attention to the increased WBC's was noticed because it is a well-known marker for inflammation and inflammatory process. An increase in inflammatory markers including white blood count (mainly neutrophils) and C-reactive protein, are sensitive for appendicitis but not specific. On the other hand, this increase in inflammatory markers is not immediate and patients particularly those with short presentation will have normal laboratory tests (16).

Serial blood tests over a period of 24- hour, provides higher diagnostic sensitivity. Lau et al, found that white blood cell count was raised in 81.4% with a specificity of 77.3% that was comparable to our present study (17).

Regarding Demographics, the rates of gender and mean age of patient were not considerably different in previous studies. The male to female ratio between patients in our study was nearly 1:1. The distribution of gender, 46.2% males and 53.8% females, along with the average age 27 years old were in line with demographics from previous studies (18)

Perforation typically happens in approximately 20% to 30% of patients with appendicitis (19). The rate of complicated appendicitis in this study was 21.3% which was similar to a study by Michael Sand, in which, the rate of complicated appendicitis was 21 % (20). And another study by Ramasamy Ramu T which showed the rate of complicated appendicitis of 29% (21).

Hyperbilirubinemia, which is an increased quantity of bilirubin within the blood, either as a result of excess bilirubin production or modification of bilirubin clearance, has been identified as a laboratory indicator for helping the preoperative diagnosis of a perforated appendicitis. both mechanisms, enhanced production and change of clearance of bilirubin, result in accumulation of bilirubin and would possibly play a role in hyperbilirubinemia of patients with appendiceal perforation.

A range of bacterial infections were shown frequently to be associated with hepatic dysfunction to the extent of abnormalities in bile acid constitution and bile flow. which finally may result in hyperbilirubinemia, this is a well-known side effect of bacterial infection particularly in patient with sepsis. Patients with sepsis and those with extrahepatic bacterial infection, like in perforated appendicitis, show a pro-inflammatory cytokine and nitric oxide-triggered cholestasis by dysfunction of hepatocellular and ductal bile formation (22).

Moreover, the commonest bacterial species isolated from the appendiceal wall of patients with acute appendicitis are *E. coli* and *bacteroides fragilis*, both of them are shown to impair hepatocyte microcirculation, inducing sinusoidal injury as shown in a rat liver model(23). Additionally, *E coli* infection

was proved induce hemolysis of erythrocytes (24). This results in an exaggerated bilirubin load in infected individuals, that likely promotes hyperbilirubinemia.

In 1976, Miller and Irvine identified *E coli* in peritoneal cultures in a prospective series of appendectomies in patients with acute appendicitis and jaundice (25). Later on, in 2007, Estrada et al discovered that patients with acute suppurative appendicitis have less hyperbilirubinemia than patients with perforated appendicitis or necrotizing appendicitis. They delineated the probability of appendiceal perforation to be three times higher for patients with hyperbilirubinemia compared with those with normal bilirubin levels.

On the other hand, Estrada et al reported that increased bilirubin could also be related to appendiceal perforation and showed that a lot of patients with a perforated or gangrenous appendix had hyperbilirubinemia compared to those with acute simple appendicitis (26). Sand et al in 2009 showed that hyperbilirubinemia had a specificity of 86% for perforation or gangrene, compared with a specificity of only 35% for C-reactive protein Furthermore, Sand *et al.* reported a specificity of 86% for bilirubin in perforated appendicitis compared with WBC 55%. WBC was more sensitive 0.96 % than bilirubin (0.7) (20).

In 2011 Emmanuel et al studied a total of 472 patients whose age ranged from 5 years to 82 years with a mean age of 27 years, that correlates with this study(27). They found that hyperbilirubinemia has a sensitivity of 60% and specificity of 70% in detection of complication in acute appendicitis. Furthermore, in 2013, A large study by Giordano *et al.* found that hyperbilirubinemia had a sensitivity of 49% and specificity of 82% with an odds ratio of 4.42 for predicting perforation in appendicitis(28).

Later on, in 2018, Ramasamy Ramu initiated a study on 311 patients and found the sensitivity of bilirubin in detection of complication in acute appendicitis to be 89.6% and specificity to be 71.4%. Comparable with these results, the current study found total serum bilirubin level to be sensitive 82.4% and specific 95.5% in predicating perforated complicated appendicitis.

This year, in 2019, Iftikhar et al initiated a study on between age of 12 and 60 years and gender distribution of 54.05 males, and 45.95 females which is comparable to the age and gender distribution in this study. They found that the overall specificity, sensitivity, negative predictive value, positive predictive value and diagnostic accuracy of Hyperbilirubinemia in diagnosing complicated appendicitis was 95.45%, 56.60%, 84.56%, 83.33% and 84.32% respectively.(7)

This study shows that bilirubin can help to diagnose patients who are more prone to have gangrenous or perforated appendicitis (complicated appendicitis). It should be used along with other clinical findings and other laboratory investigations to identify patients with complicated appendicitis at early stages. In addition to high specificity for diagnosing acute appendicitis, increased bilirubin in patients with appendicitis indicates a higher chance of a perforated or gangrenous appendix.

5. Conclusion

Bilirubin is a simple and cost-effective biochemical marker that can be done easily and rapidly in routine pre-operative investigations. Using the bilirubin value together with clinical examination and imaging will help in diagnosis of complication of appendicitis in the form of perforation and gangrene. It is also concluded that bilirubin showed high sensitivity and specificity and positive predictive value in diagnosis of acute non complicated appendicitis.

Based on the above, patients with signs and symptoms of acute appendicitis and hyperbilirubinemia should be considered as complicated and rapidly managed using the appropriate operative technique for such complication. This also will decrease the morbidity and mortality associated with the delay in management of complicated appendicitis.

This study concludes that diagnostic accuracy of hyperbilirubinemia in diagnosing complicated appendicitis is acceptable with high specificity and has dramatically improved our ability of accurate diagnosis of complicated appendicitis and the need for CT scans and MRI can be reduced and unnecessary delay in appendectomy can be avoided. It is recommended that hyperbilirubinemia is used as a screening marker for complicated appendicitis, aiding in accurate, timely diagnosis and management.

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