Global Journal of Medical and Health Science
Volume 11, Number 4; October-December,2024;
ISSN: 2836-5577| Impact Factor: 7.76
https://zapjournals.com/Journals/index.php/Medical-Health/
Published By: Zendo Academic Publishing

DIAGNOSTIC VALUE OF SERUM BILIRUBIN IN PREDICTING COMPLICATION IN ACUTE APPENDICITIS; A PROSPECTIVE STUDY AT ABUBAKAR TAFAWA BALEWA UNIVERSITY TEACHING HOSPITAL BAUCHI, NIGERIA.

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Article Info
Keywords: Acute appendicitis, Perforated appendicitis, Serum Bilirubin, Hyperbilirubinemia, complicated appendicitis

DOI
10.5281/zenodo.14044752

Abstract
Background: Appendicitis is a common surgical emergency. Despite the increasing use of advanced imaging techniques, the rates of misdiagnosis of appendicitis (15%) and appendiceal rupture remain unchanged.
The significance of hyperbilirubinemia as a predictive factor of acute appendicitis has continued to gain attention in recent studies; however, its value in the diagnosis of perforated/gangrenous appendicitis has not been studied in our practice.
We studied the diagnostic value of serum bilirubin in predicting complications of acute appendicitis.
Methods: This prospective study was conducted at the Surgery Department of Abubakar Tafawa Balewa University Teaching Hospital (ATBUTH) Bauchi, Nigeria over a duration of three calendar years from January 2020 to December 2022.
Results: A total of 396 patients who met the predefined inclusion criteria were included in the analysis. The mean age of 24 ± 10 years, and the male-to-female ratio was 1.4:1. The majority of patients (63.7%) had non-perforated appendicitis. Notably, among the patients with a normal appendix, the percentage of female patients (69.44%) was significantly higher. 107 (29.72%) exhibited hyperbilirubinemia, and among the patients diagnosed with perforated appendicitis, 62 (86.11%) had hyperbilirubinemia. Significantly more patients with appendiceal perforation had hyperbilirubinemia than those with acute perforated appendicitis (86.11% vs. 17.36%, $p < 0.001$). Bilirubin demonstrated a higher specificity (97.29%) in detecting acute appendicitis, but it has a low sensitivity. A comparative analysis of serum bilirubin levels to discriminate between acute appendicitis and perforated/gangrenous appendicitis demonstrated sensitivity and specificity of 86.11% and 82.63%. A statistical analysis indicated that patients with perforated/gangrenous appendicitis were 4.96 times more likely to have hyperbilirubinemia than those with acute appendicitis.
Conclusions- There is a significant difference in bilirubin levels between the patients diagnosed with acute appendicitis and those diagnosed with perforated appendicitis. Bilirubin is a valuable armamentarium for the diagnosis of perforation or gangrene.

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1. INTRODUCTION

Acute appendicitis is the most commonly encountered disease in abdominal surgical emergencies, with approximately 250,000 cases reported in the United States and 40,000 in England each year[1,2]. Reports from Africa are consistently low at around 1%[3,4]. Worldwide, approximately one in every ten individuals will develop acute appendicitis during their lifetime[1]. The highest incidence of positive appendectomy (appendicitis) is found in persons aged 10-29yrs[1]. Males had higher rates of appendicitis than females for all age groups, with an overall rate ratio of 1.4:1[1].

The standard of care for acute appendicitis for over a century has remained early surgery[5]. This followed pioneering works by Reginald Fitz and Charles McBurney[6,7]. In 1886, Reginald Fitz awakened the medical Profession in America by discussing the importance of the vermiform appendix undergoing inflammation causing pelvic infections and coined the term appendicitis. He advocated for early appendicectomy[6] . In 1889, Charles McBurney emphasized the importance of early diagnosis and prompt surgical intervention. He also described the McBurney point and the incision that bears his name[7] . This treatment significantly reduced acute appendicitis mortality.

These seminar works predated the availability of antibiotics by 40 years. These studies were challenged soon after the advent of antibiotics, first in 1956 by Eric Coldrey[8] and more recently by several randomized studies demonstrating the effectiveness and safety of antibiotics alone for treating uncomplicated appendicitis[9–12]. There is no doubt that with advances in diagnostic imaging and better antibiotics coupled with growing evidence from several randomized trials and meta-analyses, the philosophy and practice of treatment of acute uncomplicated appendicitis is changing from mandatory prompt appendicectomy to selective treatment and a choice between medical and surgical treatment. As of today, this choice is largely value- and preference-dependent[13].

There is therefore a growing need to elucidate markers that could help in accurately selecting and monitoring patients (while on treatment) who may benefit from a solely medical treatment of uncomplicated acute appendicitis.

The role of Hyperbilirubinemia in differentiating between acute appendicitis and its complications (a key parameter in selecting patients for sole medical treatment) has attracted the attention of researchers in this field; however, results have been conflicting[14–17].

This gave the impetus to design this study to investigate the accuracy of these simple serum markers in diagnosing acute uncomplicated appendicitis (the subgroup of patients likely to benefit from medical treatment) and monitoring these patients during the course of medical treatment.

Justification

The growing evidence of antibiotic use as an effective alternative to prompt surgical intervention for acute uncomplicated appendicitis has increased the importance of identifying markers that can differentiate complicated from uncomplicated appendicitis.

This study was designed to fill this gap in the literature.

AIMS AND OBJECTIVES

Aim; The aim of this study was to evaluate the value of serum bilirubinemia as a diagnostic and monitoring tool for differentiating uncomplicated (Medical) and complicated (Surgical) appendicitis.

Hypothesis

Ho: Serum hyperbilirubinemia does not have good diagnostic accuracy for the diagnosis and monitoring of patients with uncomplicated appendicitis selected for medical treatment.

H_A: Serum hyperbilirubinemia has good diagnostic accuracy for the diagnosis and monitoring of patients with uncomplicated appendicitis and is suitable for medical treatment.

2. MATERIALS AND METHODS

Study area

This prospective study was conducted at the Surgery Department of Abubakar Tafawa Balewa University Teaching Hospital (ATBUTH), Bauchi. ATBUTH is a government-owned teaching hospital that offers multispecialty specialist care to patients in Northeastern Nigeria.

Study design

This will be a single-center, prospective, observational study conducted over a three-year period from January 2020 to December 2022.

Participants

Inclusion criteria;

1. All consecutive patients who provided consent during the study period underwent surgery with an initial clinical diagnosis of acute appendicitis who presented to the general and pediatric surgery units of the hospital.

Exclusion criteria

1. Appendectomy performed for other indications
2. History of alcoholic liver disease; hemolytic or liver diseases associated with hyperbilirubinemia; history of gastrointestinal or hepatopancreatobiliary malignancy in the past.

Sample size estimation

Estimation of sample size per center, considering that the study is a cross-sectional study and the primary outcome variable is quantitative, the following formula will be used[18]

$$n = \frac{Z_{1-\alpha/2}^2 SD^2}{d^2}$$

n = estimated sample size per center

$Z_{1-\alpha/2}$ = Standard normal deviation, which at 5% type 1 error (set for this study) is 1.96

SD = Standard deviation of hyperbilirubinemia in complicated appendicitis which is 19.61µmol/l, as shown by D'Souza et al[16]

d = absolute error (5%)

$$n = \frac{1.96^2 \times 19.61^2}{5^2}$$

$$= 59$$

Data collection

The method of data collection for this study was by direct observation, while the research instrument was a proforma designed for the study (Appendix I). The objective of the study was explained to the patient in order to obtain informed consent.

The demographic characteristics of the patients, relevant history and physical examination findings, presence of comorbidities, laboratory results including full blood count &differential (FBC&Diff), Fasting Blood Sugar (FBS), Serum Electrolyte urea & Creatinine(E/U/Cr), Liver function test, Abdominopelvic ultrasound (USS), intra-operative findings, and histologic analysis will be entered into the proforma.

The absolute values of serum bilirubin and leucocyte counts were entered. Patients will be categorized based on serum bilirubin levels into normal and elevated bilirubin using a cut off of 20µmol/l. Based on leucocyte count, patients were categorized into three; leucopenia (count less than 4000/ml), Normal (4-11,000/ml), and leukocytosis (>11,000/ml).

Intraoperative findings were reported, and patients were classified as having normal appendix, acute appendicitis, ruptured appendicitis with localized right iliac fossa peritonitis/abscess, and ruptured appendicitis with generalized peritonitis.

Histological analysis was performed, and patients were classified as having normal appendix, acute appendicitis, and perforated/gangrenous appendicitis.

Data analysis

All data were collected using Proforma, which was designed for this study. Data analysis was performed on a computer using the statistical package for social science (SPSS) version 20. Chicago II USA.

Continuous variables are presented as mean and standard deviation, whereas categorical variables are presented as absolute numbers and percentages.

2 2 table was constructed for appendicitis and bilirubin levels. Sensitivity, specificity, and odd ratio were computed for bilirubin levels in the diagnosis of acute and perforated appendicitis.
The level of significance was set at $P \leq 0.05$.

3. RESULTS

A total of 420 patients underwent appendectomy between January 2020 and December 2022. Of these, 396 patients met the predefined inclusion criteria and were thus included in the analysis.
The age of the patients ranged from 2 to 70 years, with an overall mean age of 24 ± 10 years.
Amongst the patient analysed 230 (58.08%) were male and 166 patients (41.91%) were female, a assigned male at birth (AMAB) ratio of 1.4:1. The overall occurrence rate of perforated appendicitis was 18.18%, with 50 cases occurring in males and 22 in females out of 72 cases. The majority of patients (63.7%) had non-perforated appendicitis, with 138 cases in males and 114 cases in females out of the total 252 cases. Notably, among the 36 patients with a normal appendix, the proportion of female patients (69.44%) was significantly higher than that of male patients (30.55%).
The average length of hospital stay among these patients was 3.27 ± 3.02 days. The rate of negative appendectomy was 9.09%.
The analysis to demonstrate the bilirubin levels in the different categories of intraoperative findings showed that out of the 396 eligible patients, 107 (29.72%) exhibited hyperbilirubinemia, with serum total bilirubin levels exceeding 20μmol/L. Among the 72 patients diagnosed with perforated appendicitis, 62 (86.11%) had elevated total bilirubin levels >20 μmol/L while 10 (13.89%) had normal levels (<20μmol/L). Significantly more patients with appendiceal perforation had hyperbilirubinemia than those with acute perforated appendicitis (86.11% vs. 17.36%, $p < 0.001$).

Nature Of Disease	Number Of Patients	Number Of Patients with Hyperbilirubinemia	Percentage Of Patients with Hyperbilirubinemia
Normal Appendix	36	1	2.8
Acute Appendicitis	288	50	17.36
Perforated/Gangrenous Appendicits	72	62	86.11
Total	396	113	28.53

TABLE 1: Distribution of the nature of the diseased appendix and the occurrence of hyperbilirubinemia

Test		**Acute appendicitis**	**Normal Appendix**			
Bilirubin	Elevated	50	1	Sensitivity	17.36	OR= 7.352941
				Specificity	97.29	
	Normal	238	35	PPV	98.03	
				NPV	12.82	

TABLE 2; Acute appendicitis vs. normal appendices

PPV: positive predictive value

NPV, negative predictive value

OR- Odds Ratio

Test		Perforated/Gangrenous appendicitis	Acute Appendix			
Bilirubin	Elevated	62	50	Sensitivity	86.11	OR= 29.512
				Specificity	82.63	
	Normal	10	238	PPV	55.35	
				NPV	95.96	

TABLE 3; Perforated/Gangrenous appendicitis vs. Acute appendices

PPV: positive predictive value

NPV, negative predictive value

OR- Odds Ratio

A comparative analysis of serum bilirubin between patients with normal appendix and those with acute appendicitis revealed that bilirubin demonstrated a higher specificity (97.29%) in detecting acute appendicitis; however, it had a low sensitivity (Table 2). The odds ratio for diagnosing acute appendicitis with serum bilirubin was 7.35.

A comparative analysis of serum bilirubin levels to discriminate between acute appendicitis and perforated/gangrenous appendicitis demonstrated sensitivity and specificity of 86.11% and 82.63%. An odd ratio of 29.5. A statistical analysis indicated that patients with perforated/gangrenous appendicitis is 4.96 times more likely to have hyperbilirubinemia than those with acute appendicitis.

4. DISCUSSION

Appendicitis is one of the most common surgical emergencies in modern medicine, and it can lead to serious complications, such as ileus, peritonitis, abscess, and even death, as well as significant costs to the healthcare system[16]. The incidence of appendicitis is approximately 233 per 100,000 people per year, and the lifetime incidence risk ranges from 6.7% to 8.6%[19]. Despite the increasing use of advanced imaging and noninvasive diagnostic techniques, such as ultrasound with graded compression, high-resolution helical CT, and laparoscopy, the rates of misdiagnosis of appendicitis (15%) and appendiceal rupture have remained unchanged[20]. These methods also have several noteworthy limitations, such as financial implications, exposure to radiation, operator dependence, allergy to contrasts, false-positive and false-negative diagnoses, and anesthesia exposure[20].

Surgery for uncomplicated acute appendicitis is typically associated with a low risk of complications, with a typically rapid and uneventful recovery. However, surgery can be associated with morbidity and mortality if the appendix is gangrenous or perforated. Perforated appendicitis is associated with the risk of severe complications, such as bacterial peritonitis, intra-abdominal abscess, portal pyemia, liver abscess, and sepsis. Early diagnosis is important to prevent complications. However, no clinical or laboratory test can accurately predict complicated appendicitis during the initial stages[20]. Therefore, there is a need to develop safe, affordable, accessible, and accurate diagnostic markers for early detection and management to reduce morbidity[20]. Serum bilirubin estimation appears promising, fulfilling several of these requirements, and gaining popularity[20].

The significance of hyperbilirubinemia as a predictive factor of simple acute appendicitis is not widely acknowledged. Nevertheless, several studies have found that hyperbilirubinemia is an indicator with a high specificity for perforated appendicitis. Our study showed that hyperbilirubinemia is a significant marker of simple acute appendicitis and not only for appendiceal perforation. Patients with hyperbilirubinemia exhibited a notably higher likelihood of having uncomplicated acute appendicitis than those with normal bilirubin levels[15–17,20]. The index study also identified hyperbilirubinemia as a potential predictive factor of appendiceal perforation in patients with appendicitis. More patients with appendiceal perforation or gangrene had hyperbilirubinemia than those with acute appendicitis (86.11% vs. 17.36%, $p < 0.001$)).

Several studies that have examined the discriminating value of serum bilirubin in diagnosing perforated and gangrenous appendicitis have consistently supported the predictive value of this marker.

Noh et al. conducted a study to evaluate a preoperative diagnostic marker in Korean children for the diagnosis of complicated appendicitis. Results showed that the risk of complicated appendicitis was significantly higher in patients younger than 10 years old. Preoperative white blood cell, CRP, and bilirubin levels have clinical value in diagnosing complicated appendicitis, with an HR of 2.0 to 2.5[21]. Sand et al. in their study of the diagnostic value of hyperbilirubinemia in perforated appendicitis found that patients with appendiceal perforation had a significantly higher mean bilirubin level than those with nonperforated appendicitis ($P < .05$)[22]. The specificity of hyperbilirubinemia for appendiceal perforation was 0.86 compared with 0.55 for the white blood count and 0.35 for the C-reactive protein. The sensitivity was 0.7 compared with 0.81 for the white blood count and 0.96 for C-reactive[22]. The authors concluded that patients with hyperbilirubinemia and clinical symptoms of appendicitis should be identified as having a higher probability of appendiceal perforation than those with normal bilirubin levels[22]. Kar et al[23] in a recent prospective study on hyperbilirubinemia as a possible predictor of appendiceal perforation in acute appendicitis and found that elevated total serum bilirubin could be used as a better predictor of appendiceal perforation in acute appendicitis than total white blood cell count. Similarly, Khalid et al[20] in their study on the Diagnostic Accuracy of Hyperbilirubinemia in predicting Appendicitis and Appendiceal perforation found that when comparing perforated appendicitis with non-perforated appendicitis, bilirubin showed a specificity of 80.97% and an odds ratio of 10.21. The likelihood of a patient with hyperbilirubinemia having perforated appendicitis was more than 10 times higher than that of patients without appendiceal perforation, suggesting its potential as a potential indicator for appendiceal perforation. WCC showed a specificity of 26.72% and an odds ratio of 4.28, whereas CRP had a specificity of 23.48% and an odds ratio of 4.91. They concluded that there is a significant association between bilirubin levels and appendicitis, highlighting its potential as a valuable marker for predicting appendicitis and appendiceal perforation. They also posited that the simplicity, cost-effectiveness, and diagnostic value of bilirubin assessment support its routine use in suspected cases of acute appendicitis[20].

The index study findings support the abovementioned findings regarding the diagnostic value of hyperbilirubinemia in acute appendicitis. This study showed that bilirubin demonstrated a high specificity (97.29%) in detecting acute appendicitis however, it has a low sensitivity (17.36%) (Table 2). The odds ratio for diagnosing acute appendicitis with serum bilirubin was 7.35. This suggests that patients with acute appendicitis are seven times more likely to have elevated serum bilirubin than those without. However, serum bilirubin is not a sensitive marker in diagnosing acute appendicitis. Our study also showed that serum bilirubin could discriminate between acute appendicitis and perforated/gangrenous appendicitis with sensitivity and specificity of 86.11% and 82.63%. An odd ratio of 29.5. A statistical analysis indicated that patients with perforated/gangrenous appendicitis is 4.96 times more likely to have hyperbilirubinemia than those with acute appendicitis.

LIMITATION OF STUDY

A single-center study with a small sample size impacts its generalizability. Therefore, we recommend conducting a multicenter study with preoperative bilirubin samples and a larger study population to overcome this limitation and strengthen our findings.

Conclusions/Recommendation

In this study, we observed a significant difference in bilirubin levels between patients diagnosed with acute appendicitis and those diagnosed with perforated appendicitis. Bilirubin is a valuable armamentarium for the diagnosis of perforation or gangrene. Therefore, we recommend including bilirubin levels in the evaluation of patients suspected of having acute appendicitis because of its simplicity, cost-effectiveness, and widespread availability. Bilirubin, in conjunction with clinical examinations and other laboratory tests, can enhance the evaluation of patients with suspected acute appendicitis or perforation/gangrene, especially in patients managed non-operatively.

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