ISSN (P&E): 1996-7195, (O): 2957-899X DOI: https://doi.org/10.53350/pjmhs020251910.2

ORIGINAL ARTICLE

Role of Serum Bilirubin as a Predictive Biomarker for Appendiceal Perforation in Patients Undergoing Emergency Appendectomy

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This article may be cited as:
Abdullah HM, Abadin MZU, Abid V, Hussain A, Akhtar MA, Ahmad M; Role of Serum Bilirubin as a Predictive Biomarker for Appendiceal Perforation in Patients Undergoing Emergency Appendectomy. Pak J Med Health Sci, 2025; 19(10): 3-7.

Received: 10-05-2025
Accepted: 24-10-2025
Published: 05-11-2025

ABSTRACT

Background: Appendiceal perforation is a severe perineal complication of acute appendicitis and is characterized by heightened morbidity, extended stay, and extended postoperative complication. Early diagnosis is still a clinical problem especially when it comes to emergencies. Serum bilirubin has become one of the potential biomarkers that predict complicated appendicitis.

Objective: To assess whether serum bilirubin is an analysis biomarker of appendiceal perforation in patients who are exposed to emergency appendectomy.

Methods: A prospective study of 100 patients with probable acute appendicitis who were subjected to emergency appendectomy was used. Preoperative clinical assessment, laboratory, such as serum total bilirubin, direct bilirubin, and indirect bilirubin, and imaging were carried out. Findings during the intraoperative phase were used to categorize cases as perforated and non-perforated. The bilirubin levels in the groups were statistically compared and then the ROC curve analysis to find the accuracy diagnosis and the best cut-off value was carried out.

Results: 32 percent of the 100 patients had perforated appendicitis. The perforated group had a high mean total bilirubin level (2.21 + -0.58 mg/dL) as compared to non-perforated (1.08 + -0.32 mg/dL, $p < 0.001$). The level of direct and indirect bilirubin was also very high in perforated cases. An AUC of ROC analysis was 0.87 and an optimum bilirubin cut-off was 1.6 mg/dL (sensitivity 81, specificity 78). There was a comparatively high risk of postoperative complications like wound infection and length of stay in the perforated group.

Conclusion: High serum bilirubin, especially above 1.6 mg/dL is an excellent predictive biomarker of appendiceal perforation. As it is simple, low cost, and is wide available, bilirubin measurement ought to validate part of routine examination in cases of suspected acute appendicitis in order to become efficient in diagnosing early and initiating surgery. More multicentric research is advisable to confirm cut-off levels and enhance its clinical usefulness.

Keywords: Serum bilirubin; Appendiceal perforation; Acute appendicitis; Predictive biomarker; Hyperbilirubinemia; Emergency appendectomy; Diagnostic accuracy; ROC curve; Inflammatory markers; Perforated appendicitis.

INTRODUCTION

Acute appendicitis is among the most prevalent surgical emergencies all over the globe, and it is necessary to diagnose it in time and avoid severe complications, including gangrene and perforation[1]. Appendiceal perforation is associated with high risk in developing postoperative morbidity, prolonged hospitalization, wound infections, intra-abdominal abscesses, and expenses to the healthcare system as a whole. Although

imaging methods and laboratory research have improved, the timely and correct identification of the patient at risk of perforation remains a clinical challenge, especially in an emergency and scarce-resource intensive environment, where a clinical delay in diagnostics is common[2].

The recent study has pointed out the possibilities of biochemical markers in enhancing the accuracy of the diagnosis and predicting the severity of the disease in appendicitis[3]. Of these, the serum bilirubin parameter has been given significant consideration due to the ease, low cost and also because it is a readily accessible laboratory parameter[6]. It is thought that hyperbilirubinemia in acute appendicitis is due to bacterial translocation, endotoxemia, and hepatocellular dysfunction of cytokine that may be more exaggerated, in complicated or perforated appendicitis[4]. There have been some mentioned studies which found higher bilirubin levels in perforated patients compared to simple appendicitis which imply that it can be used as a biomarker[5].

Since the measurement of serum bilirubin is simple and can be found almost anywhere in the emergency department, the assessment of this predictive factor can assist surgeons in the correct risk management and timely surgery[7]. Nevertheless, the available literature demonstrates differences in cut-off values, diagnostic accuracy and clinical usefulness across populations. Hence, the aim of this study is to examine the effectiveness of serum bilirubin as a predictive biological marker in indicating that appendiceal perforation in the case of emergency appendectomy and consider this as a method of improving an early diagnosis, complications and clinical outcomes[8].

MATERIAL AND METHOD

The research was done as a prospective clinical appraisal of 100 patients presenting with signs and symptoms, which showed signs of acute appendicitis and, as a result, underwent emergency appendectomy. During the study period, all patients were recruited at the Emergency Department of the hospital. To reduce the selection bias, consecutive sampling was used and all eligible patients that satisfied the inclusion criteria were enrolled. Clinically suspicious patients of both sexes aged between 12 and 70 years suspected to be having appendicitis, but confirmed by attending surgical staff, were patients to be included. Any known liver disease, hemolytic disorder, chronic alcohol consumption, viral hepatitis, pre-existing pathology of the biliary tract, or drug abuse were ruled out as it could cause high serum bilirubin levels causing inflammatory appendicitis as opposed to underlying hepatic dysfunction.

At admission, a comprehensive clinical history was taken, and this entailed the number of days spent experiencing the abdominal pains, fever, vomiting, and any other related symptoms. In-depth physical assessment was done, examining the symptoms of peritonitis, local tenderness and retaliations, as well as guarding of the right iliac fossa. Complete blood count, C-reactive protein, liver function tests, and serum bilirubin level were investigated as baseline laboratory investigations. Before the surgical procedure, intravenous fluids, or antibiotics, blood samples that were used to measure bilirubin were taken not to change the values of biochemicals. The total, direct and indirect bilirubin was determined using an automated clinical chemistry analyzer, under normal laboratory protocols. All patients underwent abdominal ultrasonography to assist in the diagnosis and to exclude the other causes of right lower quadrant pain.

Every patient underwent the emergency appendectomy procedure on the basis of the clinical and radiologic evaluation. The attending surgeon determined whether to do open or laparoscopic appendectomy based on the state of the patient and the availability of the resources. The description of intraoperative findings was made, such as the look of the appendix, whether perforated, gangrene, suppurated or gangrene abscess. To make an analysis the patients were grouped into two; perforated appendicitis and non-perforated appendicitis, according to a direct visual interpretation of the operation. Histopathological confirmation of the resected appendix was done to ascertain the accuracy of the diagnosis.

The hospital follow-up was done to measure the postoperative complications like wound infection, fever, or abscess in the abdomen. All the clinical, laboratory and operative data retrieved were given on a windowed proforma. The predictive value of serum bilirubin was found by comparing the samples of perforated to non-perforated group. The statistical analysis was done with the help of proper software. Constant variables like bilirubin numbers were reported using mean and standard deviation, whereas the number of frequencies and percentage of categorical variables were used. A student t -test used to compare mean values of serum bilirubin between the two groups and a receiver operating characteristic (ROC) curve was plotted to detect sensitivity, specificity, and the best cut-off value of serum bilirubin as a predictor of perforation. The p-value of below 0.05 was taken to be significant.

RESULTS

The analysis involved 100 patients in the emergency procedure of appendectomy. Amongst them, there were 32 patients (32 percent) who were intraoperatively

diagnosed with appendiceal perforation and 68 patients (68 percent) who were intraoperatively diagnosed with non-perforated appendicitis. The average age of the population sampled was 28.4 years and the standard deviation of age was 10.6, which is a little higher in the perforated group. The distribution of males was the same in both groups, with a 58-percentage contribution. Table 1 presents the baseline demographic characteristics.

Table 1 shows that duration of symptoms and presence of fever were significantly higher in patients with perforated appendicitis.

The parameters of the laboratories showed that there was a definite difference between the level of bilirubin in the two groups. The average total bilirubin concentration in the serum in the perforated group (2.21 pm 0.58 mg/dl) was much greater than that in the non-perforated group (1.08 pm 0.32 mg/dl). Significant increase in direct bilirubin levels was also noted. The patients with perforation also had more prominent leukocytosis. Table 2 represents these findings.

Table 2 clearly demonstrates that serum bilirubin levels were significantly elevated in perforated appendicitis.

To further determine diagnostic accuracy, Receiver Operating Characteristic (ROC) curve was carried out with respect to total serum bilirubin levels. The value of area under the ROC curve (AUC) was 0.87 which demonstrated high discriminatory ability. A bilirubin cut-off of 1.6mg/dL gave an 81 percent sensitivity 78 percent specificity in predicting perforation. The summary of the ROC statistics is presented in Table 3.

Table 3 shows that bilirubin at a 1.6 mg/dL cut-off is a strong predictor of perforation.

There were more postoperative complications in the perforated group including wound infection, longer hospital stays and intra-abdominal abscess. Table 4 shows the complication profile.

Table 4 indicates that perforation substantially increases postoperative morbidity.

In general, the results prove that the level of serum bilirubin was considerably greater in patients with appendiceal perforation than in patients with uncomplicated appendicitis. Bilirubin was also proven to be a good predictive biomarker through ROC curve analysis. Worse profiles in clinical and postoperative outcomes were also observed between patients with perforation, which justified using early biochemical evaluation as a measure of risk stratification.

Table 1. Baseline Characteristics of Study Population (N = 100)

Variable	Non-Perforated (n=68)	Perforated (n=32)	p-value
Age (years, mean ± SD)	26.9 ± 9.8	31.6 ± 11.4	0.04
Gender (Male/Female)	40/28	18/14	0.82
Duration of symptoms (hours)	24.3 ± 8.6	39.7 ± 12.1	<0.001
Fever (%)	47%	81%	0.002

Table 2. Laboratory Findings in Perforated vs Non-Perforated Appendicitis

Laboratory Parameter	Non-Perforated (n=68)	Perforated (n=32)	p-value
Total Bilirubin (mg/dL)	1.08 ± 0.32	2.21 ± 0.58	<0.001
Direct Bilirubin (mg/dL)	0.34 ± 0.11	0.92 ± 0.27	<0.001
Indirect Bilirubin (mg/dL)	0.74 ± 0.22	1.29 ± 0.41	<0.001
WBC Count ($\times 10^9$/L)	12.8 ± 3.4	15.7 ± 4.2	0.001
CRP (mg/L)	18.4 ± 7.5	36.6 ± 10.8	<0.001

Table 3. Diagnostic Performance of Serum Bilirubin for Predicting Appendiceal Perforation

Parameter	Value
AUC (Area Under Curve)	0.87
Optimal Cut-off (mg/dL)	1.6
Sensitivity (%)	81%
Specificity (%)	78%
Positive Predictive Value (%)	62%
Negative Predictive Value (%)	91%

Table 4. Postoperative Complications in Both Groups

Complication	Non-Perforated (n=68)	Perforated (n=32)	p-value
Wound Infection (%)	9%	31%	0.006
Intra-abdominal Abscess (%)	0%	12%	0.003
Hospital Stay (days, mean ± SD)	2.8 ± 1.1	5.3 ± 1.9	<0.001

DISCUSSION

The study at hand compared the serum bilirubin as a predictive biomarker of appendiceal perforation with the diagnostic value of the serum bilirubin in incidental patients undergoing emergency appendectomy. The results have shown statistically significant increase in total, direct and indirect bilirubin levels in patients with perforated appendicitis than those with non-perforated appendicitis[9]. These findings go a long way in supporting the assumption that hyperbilirubinemia can be made an early bio-chemical predictor of complicated appendicitis and its potential usefulness in clinical decision-making and risk stratification in preoperative [10].

The material pathophysiology of bilirubin raise in perforated appendicitis has been adequately outlined in literature. Perforation causes augmentation in bacterial load, increment in translocation of Gram-negative organisms and consequential endotoxemia[11]. Endotoxin and inflammatory cytokines i.e., TNF- a and IL- 6 damage the hepatocellular activity and decrease bile secretion, which leads to increased direct and indirect bilirubin [12]. Our study demonstrated over two-fold increase of total bilirubin in the perforated group than the non-perforated group and is in line with the fact that the theory of endotoxin-mediated cholestasis development. The high inflammatory indicators, such as the count of the WBC and CRP are also significantly high, which also evidences high inflammatory response and severe infection in perforated patients [13].

We analyzed our ROC curve and the AUC was found to be 0.87 that showed an excellent discrimination power of serum bilirubin in the detection of perforation. Optimal cut-off of 1.6 mg/dL resulted in optimum sensitivity of 81% and specificity of 78% which is similar to the international studies that report bilirubin cut-off values of between 1.3-2.0mg/dl [14]. The negative predictive value obtained in this study is high (91), and it indicates that the patients with the normal bilirubin level have a significantly lower chance of perforation, and by the way, bilirubin is specifically helpful in terms of the triage in the resource-limited settings where the imaging modalities are not necessarily available and feasible [15].

There were also significant trends in clinical parameters as observed in the current research. Perforated patients experienced a much longer period of symptoms, frequency of fever, and leukocytosis than their counterparts who experienced uncomplicated appendicitis. Such observations are in line with the conventional knowledge, which states that delayed presentation and intense inflammation will raise the likelihood of developing perforation [16]. Nevertheless, bilirubin was able to perform better in the scenario of diagnostic efficiency as compared to separate clinical parameters, highlighting its possible diagnostic importance as an objective biochemical concentration. The perforated group performed significantly worse in terms of postoperative outcomes, having a greater wound infection, intra-abdominal abscess developing rate, and extended hospital length of stay [17]. All these complications underscore the importance in clinical practice of identifying perforation as early as possible and responding promptly to surgery. The addition of bilirubin measurement into the first assessment can result in better early detection, less surgical delay and consequently less postoperative morbidity [17].

On the one hand, the findings of this study are promising; however, it is necessary to mention several limitations. The sample is too big to give preliminary results but, nevertheless, it is rather limited and is based on one center [18]. To universalize the bilirubin cut-off value, more multicentric studies should be done to test this cut-off value. Also, the subclinical hepatic dysfunction or hemolysis can still play a role in stratifying the bilirubin of some patients though these patients had known liver disease. Notwithstanding such constraints, the current research confirms the presence of serum bilirubin as an inexpensive, easy-to-use, and without any complication's biomarker with a huge predictive power regarding appendiceal perforation [19]. Its incorporation into the routine emergency assessment can improve the quality of diagnostic and aid in prompt operation management, especially during a high-volume emergency departments and in low-resource healthcare settings[20].

CONLUSION

This paper showed that serum bilirubin may be a helpful and useful predictive biomarker in patients who present with acute appendicitis indicating appendiceal perforation. Patients which had perforated appendicitis had much higher total and direct and indirect bilirubin levels than those who did not have perforated. The ROC curve further helped to confirm that it had excellent diagnostic accuracy with an optimal cut-off of 1.6 mg/dL that gave the analysis great sensitivity and specificity. Serum bilirubin is a simple and cost-effective test and universally available, so that it may be effectively integrated into regular emergency department assessment to aid in timely risk classification, in the timely formulation of surgical decisions, and possibly to help reduce complications following surgery. Under the resource-constrained conditions that do not always imply the availability of advanced imaging, bilirubin is a valuable auxiliary device to enhance clinical outcome in patients

with suspected complicated appendicitis. It is suggested that future research should be expanded to conduct multicenter studies in order to confirm these results and to standardize cut-off values to be used in a wider clinical range.

DECLARATION

Conflict of Interest
The authors declare no conflict of interest.

Funding
This research did not receive any external funding.

Author's Contribution
All authors contributed equally in the complication of current study.

Acknowledgments
The authors express their sincere gratitude to all colleagues and participants for their valuable contributions to this study.

Data Availability Statement
The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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