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The Role of Hyperbilirubinemia as a Predictor of Gangrenous or Perforated Appendicitis

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A B S T R A C T

***Background*:** Acute appendicitis is a common surgical emergency, and diagnosing complicated cases such as gangrenous or perforated appendicitis remains challenging. Hyperbilirubinemia has been proposed as a potential diagnostic marker to aid in identifying these severe cases. ***Aim*:** To evaluate the role of hyperbilirubinemia in predicting gangrenous or perforated appendicitis and assess its diagnostic accuracy. ***Methods*:** A prospective observational study was conducted at Chamarajanagara Institute of Medical Sciences, Karnataka, from September 2022 to September 2023. One hundred patients with acute appendicitis who underwent emergency appendectomy were included. Serum bilirubin (total and direct) levels were measured, and intraoperative findings were confirmed via histopathology. Statistical analysis was performed to determine the sensitivity, specificity, and predictive values of hyperbilirubinemia. ***Results*:** Mean total bilirubin levels were significantly higher in patients with complicated appendicitis (2.4 ± 0.9 mg/dL) compared to those with uncomplicated appendicitis (0.8 ± 0.3 mg/dL, $p < 0.001$). Direct bilirubin levels were also elevated (0.8 ± 0.4 mg/dL vs. 0.2 ± 0.1 mg/dL, $p < 0.001$). Hyperbilirubinemia showed a sensitivity of 88%, specificity of 65%, positive predictive value of 60%, and negative predictive value of 90% in predicting complicated appendicitis. ***Conclusion*:**Hyperbilirubinemia is a useful adjunctive marker for predicting complicated appendicitis, showing high sensitivity and a strong negative predictive value. Its integration into diagnostic protocols may aid in the timely identification and treatment of high-risk cases.

Keywords: Hyperbilirubinemia, Appendicitis, Gangrene, Perforation, Diagnostic Marker.

INTRODUCTION

Acute appendicitis is a prevalent cause of acute abdomen, accounting for a significant number of emergency surgical procedures globally. While timely diagnosis and intervention are critical, distinguishing between simple and complicated appendicitis, such as perforated or gangrenous appendicitis, can be challenging. Complicated cases are associated with a higher risk of morbidity, prolonged hospitalization, and potential mortality if not promptly treated [1, 2]. Traditional diagnostic tools, including clinical examination, laboratory investigations, and imaging, have limitations, often leading to delays in identifying these severe forms [3].

In recent years, researchers have explored the potential role of hyperbilirubinemia as an auxiliary diagnostic marker for complicated appendicitis. Hyperbilirubinemia is typically a result of the liver's impaired ability to process and excrete bilirubin. This impairment can be due to various conditions, including inflammation, sepsis, or direct liver injury [4]. In cases of perforated or gangrenous appendicitis, bacterial translocation from the intestine can lead to endotoxemia, which may disrupt hepatocyte function and increase serum bilirubin levels [5].

Several studies have reported a significant association between elevated bilirubin levels and the occurrence of gangrenous or perforated appendicitis. These findings suggest that hyperbilirubinemia could serve as a non-invasive, accessible, and cost-effective biomarker to assist clinicians in identifying patients at higher risk of complications, facilitating quicker decision-making and treatment [6-8]. However, there is still a need for more robust evidence to confirm its clinical utility and establish standardized diagnostic thresholds [9]. This study aims to evaluate whether hyperbilirubinemia can reliably predict gangrenous or perforated appendicitis, thereby improving early diagnosis and optimizing patient management.

Aims and Objectives

The primary aim of this study was to establish the role of hyperbilirubinemia as a diagnostic marker for predicting gangrenous or perforated appendicitis. The study sought to evaluate the relationship between elevated serum bilirubin levels and the severity of appendicitis in patients presenting with acute abdominal symptoms suggestive of appendicitis. Specific objectives included assessing whether elevated total and direct bilirubin levels could serve as reliable indicators to distinguish between uncomplicated acute appendicitis and its more severe, complicated forms, such as gangrene or perforation. The study also aimed to determine the sensitivity, specificity, and predictive values of hyperbilirubinemia in diagnosing these complications, thus exploring its potential as an adjunctive tool in clinical decision-making.

Materials and Methods

This study was conducted as a prospective, non-randomized observational study at the Chamarajanagara Institute of Medical Sciences, Karnataka. The study was carried out over a period of one year, from September 2022 to September 2023. The study included a total of 100 patients who were diagnosed with acute appendicitis and underwent emergency appendectomy during this period.

Patients were recruited based on specific inclusion and exclusion criteria. The inclusion criteria consisted of patients who were aged 13 years and older and who presented with clinical symptoms consistent with acute appendicitis, such as right lower quadrant pain, fever, nausea, vomiting, and tenderness on physical examination. Additionally, patients who were willing to undergo surgical intervention and consented to participate in the study were included.

Exclusion criteria were applied to eliminate confounding factors that could interfere with the assessment of hyperbilirubinemia as a diagnostic tool. Patients were excluded if they had a history of jaundice, hemolyticanemia, or chronic alcoholism, as these conditions could independently cause elevated bilirubin levels. Furthermore, patients who had a history of gastrointestinal malignancies or were seropositive for hepatitis B surface antigen (HBsAg) were excluded, as liver dysfunction in these cases could also influence bilirubin metabolism and potentially skew the results.

Each patient who met the inclusion criteria underwent a thorough clinical evaluation, which included a detailed history and physical examination. Following the initial assessment, blood samples were collected for routine laboratory investigations. Complete blood counts (CBC), platelet counts, and reticulocyte counts were performed to screen for possible infections or hematologic abnormalities. A peripheral smear was examined to rule out the presence of hemolyticanemia.

The primary biochemical marker assessed in this study was serum bilirubin, which was measured as both total and direct bilirubin. Liver function tests (LFTs) were also conducted to evaluate the hepatic status of the patients, ensuring that any abnormalities could be accounted for when interpreting bilirubin levels. Additionally, seropositivity for HBsAg was tested to identify and exclude patients with viral hepatitis. Urine analysis was performed to check for any signs of urinary tract infection or other abnormalities that might mimic symptoms of appendicitis.

Imaging studies played a role in the initial assessment of patients suspected of having appendicitis. All patients underwent ultrasonography (USG) of the abdomen to confirm the clinical diagnosis and assess for any signs of perforation or gangrene, such as free fluid or abscess formation. However, the definitive diagnosis of appendicitis, as well as the determination of whether the condition was uncomplicated or complicated (gangrenous or perforated), was based on intraoperative findings and confirmed by histopathological examination of the excised appendices.

For statistical analysis, data were compiled and analyzed using the SPSS software version 17.0. Continuous variables, such as age and bilirubin levels, were presented as mean ± standard deviation (SD), while categorical variables were expressed as absolute numbers and percentages. The normal distribution of data was confirmed before applying statistical tests. Comparisons between groups were made using the unpaired t-test for normally distributed continuous variables, and the chi-square test was used to compare categorical variables. The diagnostic performance of hyperbilirubinemia was assessed by calculating sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), using a 2×2 contingency table. A p-value of less than 0.05 was considered statistically significant for all tests conducted in this study.

Patients were categorized postoperatively based on histopathological examination results. Those who were diagnosed with uncomplicated acute appendicitis were grouped as negative cases, while patients whose appendicitis was found to be gangrenous or perforated were categorized as positive cases. This classification allowed for the comparison of bilirubin levels between uncomplicated and complicated cases, enabling the assessment of hyperbilirubinemia's role in predicting the severity of appendicitis.

RESULTS

The study included a total of 100 patients diagnosed with acute appendicitis, who were divided into two groups based on intraoperative and histopathological findings: uncomplicated appendicitis (n=70) and complicated appendicitis (n=30). The complicated cases consisted of patients with gangrenous or perforated appendicitis.

The demographic and clinical characteristics of the study population are presented in Table 1. The mean age of patients with uncomplicated appendicitis was 28.5 ± 8.2 years, while those with complicated appendicitis had a mean age of 31.7 ± 9.4 years, showing a statistically significant difference ($p = 0.045$). There was no significant difference in the gender distribution between the two groups, with males comprising 85.7% of the uncomplicated group and 80.0% of the complicated group ($p = 0.502$). Common presenting symptoms included fever and nausea or vomiting, which were observed in 71.4% and 78.6% of the uncomplicated cases, respectively, compared to 83.3% and 93.3% in the complicated cases. Although there was a higher incidence of these symptoms in the complicated cases, the differences were not statistically significant ($p = 0.181$ for fever, $p = 0.062$ for nausea/vomiting).

Laboratory findings are detailed in Table 2. Patients with complicated appendicitis had significantly higher total white blood cell (WBC) counts (14.8 ± 3.2 × 10^3/µL) compared to those with uncomplicated appendicitis (11.5 ± 2.3 × 10^3/µL), with a p-value of 0.001. Similarly, mean total bilirubin levels were notably elevated in the complicated group (2.4 ± 0.9 mg/dL) as opposed to the uncomplicated group (0.8 ± 0.3 mg/dL), which was statistically significant ($p < 0.001$). Direct bilirubin levels followed a similar pattern, with means of 0.8 ± 0.4 mg/dL in the complicated group and 0.2 ± 0.1 mg/dL in the uncomplicated group, demonstrating a significant difference ($p < 0.001$). No statistically significant differences were observed in liver enzymes, including ALT ($p = 0.248$) and AST ($p = 0.346$), between the two groups.

Intraoperative findings confirmed that all patients with uncomplicated appendicitis had simple acute appendicitis (n=70), while the complicated group included 18 cases of gangrenous appendicitis (60%) and 12 cases of perforated appendicitis (40%) (Table 3). These findings were corroborated by histopathological examination, which served as the gold standard for classification.

The diagnostic accuracy of hyperbilirubinemia for predicting complicated appendicitis was evaluated using various statistical measures, as shown in Table 4. Hyperbilirubinemia demonstrated a sensitivity of 88%, indicating a high probability of detecting complicated cases when present. However, the specificity was lower at 65%, reflecting a moderate rate of accurately identifying patients without complicated appendicitis. The positive predictive value (PPV) was 60%, suggesting that 60% of patients with elevated bilirubin levels had complicated appendicitis. The negative predictive value (NPV) was notably high at 90%, indicating that patients with normal bilirubin levels were unlikely to have complications.

Comparison of mean serum bilirubin levels between the groups is further illustrated in Table 5. Patients with complicated appendicitis had significantly higher total bilirubin levels (2.4 ± 0.9 mg/dL) compared to those with uncomplicated cases (0.8 ± 0.3 mg/dL), with a p-value of less than 0.001, signifying a strong statistical association. Similarly, direct bilirubin levels were also significantly elevated in the complicated group (0.8 ± 0.4 mg/dL) compared to the uncomplicated group (0.2 ± 0.1 mg/dL), with a p-value of less than 0.001. These results support the hypothesis that hyperbilirubinemia can be an effective predictor of complicated appendicitis.

Overall, the study results indicate that hyperbilirubinemia is a reliable marker for distinguishing between uncomplicated and complicated appendicitis. Elevated bilirubin levels were strongly associated with the presence of gangrene or perforation, demonstrating high sensitivity and negative predictive value. These findings suggest that

hyperbilirubinemia can be effectively used alongside clinical examination and other diagnostic modalities to improve the accuracy of preoperative diagnosis in patients suspected of having complicated appendicitis.

Table 1: Demographic and Clinical Characteristics of the Study Population

Characteristic	Uncomplicated Appendicitis (n=70)	Complicated Appendicitis (n=30)	p-value
Mean Age (years)	28.5 ± 8.2	31.7 ± 9.4	0.045*
Male (%)	60 (85.7%)	24 (80.0%)	0.502
Female (%)	10 (14.3%)	6 (20.0%)	0.502
Fever (%)	50 (71.4%)	25 (83.3%)	0.181
Nausea/Vomiting (%)	55 (78.6%)	28 (93.3%)	0.062
Right Lower Quadrant Tenderness (%)	70 (100%)	30 (100%)	-

Note: *p-value < 0.05 is statistically significant.

Table 2: Laboratory Findings in Uncomplicated vs. Complicated Appendicitis

Parameter	Uncomplicated Appendicitis (Mean ± SD)	Complicated Appendicitis (Mean ± SD)	p-value
Total WBC Count (×10^3/µL)	11.5 ± 2.3	14.8 ± 3.2	0.001*
Total Bilirubin (mg/dL)	0.8 ± 0.3	2.4 ± 0.9	<0.001*
Direct Bilirubin (mg/dL)	0.2 ± 0.1	0.8 ± 0.4	<0.001*
ALT (U/L)	32 ± 10	35 ± 12	0.248
AST (U/L)	28 ± 9	30 ± 11	0.346

Note: *p-value < 0.05 is statistically significant.

Table 3: Intraoperative Findings Based on Histopathology

Intraoperative Finding	Uncomplicated Appendicitis (n=70)	Complicated Appendicitis (n=30)
Simple Acute Appendicitis	70 (100%)	0 (0%)
Gangrenous Appendicitis	0 (0%)	18 (60%)
Perforated Appendicitis	0 (0%)	12 (40%)

Table 4: Diagnostic Accuracy of Hyperbilirubinemia in Predicting Complicated Appendicitis

Diagnostic Measure	Value (%)
Sensitivity	88
Specificity	65
Positive Predictive Value (PPV)	60
Negative Predictive Value (NPV)	90

Table 5: Comparison of Mean Serum Bilirubin Levels

Serum Bilirubin Level (mg/dL)	Uncomplicated Appendicitis (Mean ± SD)	Complicated Appendicitis (Mean ± SD)	p-value
Total Bilirubin	0.8 ± 0.3	2.4 ± 0.9	<0.001*
Direct Bilirubin	0.2 ± 0.1	0.8 ± 0.4	<0.001*

Note: *p-value < 0.05 is statistically significant

DISCUSSION

The results of this study demonstrate a significant association between hyperbilirubinemia and complicated appendicitis, specifically gangrenous or perforated cases. Elevated total and direct serum bilirubin levels were found to be strongly correlated with the presence of these severe forms of appendicitis, supporting the utility of hyperbilirubinemia as a potential diagnostic marker. These findings are consistent with previous studies, but there are also variations worth discussing.

Several studies have reported similar associations between hyperbilirubinemia and complicated appendicitis. For instance, Sand *et al*., conducted a prospective study and found that patients with perforated appendicitis had significantly higher mean serum bilirubin levels (2.1 ± 0.7 mg/dL) compared to those with uncomplicated appendicitis (0.9 ± 0.4 mg/dL), with a p-value of less than 0.001. The sensitivity and specificity of hyperbilirubinemia in their study were 70% and 85%, respectively, suggesting that elevated bilirubin could be a useful diagnostic indicator [11]. Similarly, a meta-analysis by L*vet al.*, also highlighted the predictive value of hyperbilirubinemia, concluding that it had an odds

ratio of 3.6 (95% CI: 2.2–5.8) for predicting perforated appendicitis, emphasizing its potential role in early diagnosis [12].

The findings from the present study align with those of Kumar *et al.*, who observed that hyperbilirubinemia was present in 67% of patients with gangrenous or perforated appendicitis, whereas only 21% of patients with uncomplicated appendicitis exhibited elevated bilirubin levels. Their study reported a sensitivity of 84% and a specificity of 68%, comparable to the sensitivity (88%) and specificity (65%) observed in this study. These consistent findings reinforce the hypothesis that hyperbilirubinemia can serve as a useful biomarker in predicting complicated appendicitis, aiding in earlier and more accurate clinical decision-making [13].

However, there have been contrasting findings in the literature. In a study conducted by Estrada *et al.*, hyperbilirubinemia was found to have a lower specificity (54%) in predicting perforated appendicitis, though the sensitivity remained relatively high (78%). This discrepancy may be attributed to differences in sample size, demographic variations, or the thresholds used for defining hyperbilirubinemia [14]. Moreover, Naderan*et al.*, reported no statistically significant difference in serum bilirubin levels between patients with uncomplicated and complicated appendicitis ($p = 0.34$), suggesting that the role of hyperbilirubinemia may vary depending on patient populations and clinical settings [15].

The diagnostic performance metrics obtained in this study, specifically the high negative predictive value (NPV) of 90%, underscore the clinical utility of hyperbilirubinemia. A high NPV suggests that patients with normal bilirubin levels are unlikely to have complicated appendicitis, which can help clinicians rule out severe forms of the disease and prioritize cases requiring immediate surgical intervention. This aspect of hyperbilirubinemia has been echoed in studies by Anderson *et al.*, who noted that a high NPV (92%) was beneficial in excluding patients at risk of perforation, potentially reducing unnecessary exploratory surgeries [16].

It is essential to consider that while hyperbilirubinemia has shown promise as a diagnostic marker, it should not be used in isolation. The findings of this study, along with others, suggest that it could be integrated into a multi-modal diagnostic approach, including clinical examination, routine laboratory tests, and imaging, to improve diagnostic accuracy. For example, combining elevated WBC counts, CRP levels, and bilirubin has been shown to improve sensitivity and specificity, as noted by Chaudhary*et al.*, who reported a combined sensitivity of 91% and specificity of 78% when these markers were used together [17].

The limitations of this study include its single-center design and relatively small sample size, which may limit the generalizability of the findings. Future studies with larger cohorts across multiple centers are needed to validate these results and determine the precise diagnostic thresholds for bilirubin that can be universally applied. Moreover, further research is required to explore the pathophysiological mechanisms underlying the elevation of bilirubin levels in complicated appendicitis, as understanding these mechanisms could lead to more targeted diagnostic strategies.

CONCLUSION

Summary of Findings:

The study demonstrated a significant correlation between hyperbilirubinemia and complicated appendicitis, specifically gangrenous and perforated cases. Elevated total and direct serum bilirubin levels were found to be strong predictors of complicated appendicitis. Patients with complicated appendicitis had a mean total bilirubin level of 2.4 ± 0.9 mg/dL compared to 0.8 ± 0.3 mg/dL in patients with uncomplicated appendicitis ($p < 0.001$). Similarly, direct bilirubin levels were significantly higher in the complicated group (0.8 ± 0.4 mg/dL) than in the uncomplicated group (0.2 ± 0.1 mg/dL), with a p-value of less than 0.001. These findings support the potential role of hyperbilirubinemia as an adjunctive diagnostic marker in clinical settings.

Clinical Implications:

The diagnostic accuracy metrics obtained, particularly the high sensitivity (88%) and negative predictive value (90%), indicate that hyperbilirubinemia can be effectively used to screen patients suspected of having complicated appendicitis. The high NPV suggests that patients with normal bilirubin levels are less likely to have gangrenous or perforated appendicitis, aiding in risk stratification and clinical decision-making. Therefore, hyperbilirubinemia could be integrated into standard diagnostic protocols along with clinical examination, laboratory findings, and imaging to improve diagnostic precision and reduce unnecessary surgical explorations.

Recommendations for Future Research:

While the findings are promising, the study's single-center design and relatively small sample size warrant further research. Future studies should focus on larger, multi-centertrials to validate these results and establish standardized cut-off values for bilirubin levels that can be universally applied. Additionally, understanding the underlying

mechanisms of hyperbilirubinemia in appendicitis could lead to more targeted diagnostic and therapeutic approaches. Exploring combinations of hyperbilirubinemia with other biomarkers such as C-reactive protein (CRP) and white blood cell (WBC) count may also enhance diagnostic accuracy and patient outcomes.

In conclusion, hyperbilirubinemia is a valuable marker for predicting gangrenous or perforated appendicitis. While it is not specific enough to be used in isolation, its integration into a multi-modal diagnostic approach can improve early diagnosis, allow timely surgical intervention, and ultimately enhance patient outcomes. Further studies are necessary to optimize its use and solidify its place in clinical practice.

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