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Hyperbilirubinemia and elevated C-reactive protein as predictive markers for appendiceal perforation in acute appendicitis: A prospective observational study

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Ethics Committee Approval
Ethical approval was obtained from the Institutional Academic Ethics Committee (approval number: ECR/531/Inst/MH/2014/RR-19; date: June 12, 2023). Informed consent was obtained from all participants.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Appendiceal perforation is a serious complication of acute appendicitis and contributes substantially to postoperative morbidity and prolonged hospital stay. Although imaging supports diagnosis, access may be limited in resource-constrained settings. This study evaluated the diagnostic utility of hyperbilirubinemia and elevated C-reactive protein (CRP) as cost-effective and readily available biomarkers for predicting appendiceal perforation.

Methods: This prospective observational study was conducted at Fortis Hospital, Mulund, Mumbai, from July 2023 to December 2024. Fifty adult patients with acute appendicitis who provided informed consent and underwent surgical management were included. Patients with liver disease, hepatobiliary malignancy, chronic alcoholism, hemolytic anemia, pregnancy, conservative treatment, or medications causing cholestasis were excluded. Preoperative serum bilirubin and CRP levels were measured and correlated with intraoperative and histopathological findings.

Results: The mean age of the 50 enrolled patients was 31.94 (14.12) years, 30 (60%) were male, and 15 (30%) had perforated appendicitis. The mean serum bilirubin level was 1.42 (0.19) mg/dL in the perforation group and 1.06 (0.21) mg/dL in the non-perforation group ($P < 0.001$). The mean CRP level was significantly higher in the perforation group than in the non-perforation group [243.3 (45.9) mg/L vs. 135.8 (51.3) mg/L; $P < 0.001$]. Receiver operating characteristic curve analysis showed strong diagnostic performance, with an area under the curve of 0.90 for bilirubin and 0.92 for CRP.

Conclusion: Elevated serum bilirubin and CRP levels are reliable non-invasive markers for predicting perforated appendicitis and may be particularly valuable in settings where advanced imaging is unavailable.

Keywords: appendicitis, appendiceal perforation, hyperbilirubinemia, C-reactive protein, predictive biomarkers, general surgery

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Introduction

Acute appendicitis is a leading cause of emergency abdominal surgery. With a lifetime risk of approximately 7-10% [1], the disease imposes a substantial healthcare burden. Timely diagnosis and surgical intervention are essential to prevent complications such as gangrene, perforation, and intra-abdominal abscess, which increase morbidity, length of hospital stay, and healthcare costs [2]. Despite advances in diagnostic imaging, perforation may still occur, particularly in patients with atypical symptoms or delayed diagnosis. Papandria et al. [3] reported that the risk of perforation increased with delayed recognition and surgery. Therefore, reliable biochemical markers that can help stratify patients at high risk of complicated appendicitis remain clinically important.

C-reactive protein (CRP) is an acute-phase reactant produced mainly by the liver in response to inflammatory cytokine stimulation, and its level rises rapidly during bacterial and surgical infections [4]. Hyperbilirubinemia may also occur in severe appendiceal inflammation, particularly in the absence of hepatobiliary disease, because bacterial endotoxemia and inflammatory cholestasis can impair bile transport. Previous studies have evaluated the predictive value of bilirubin and CRP in acute appendicitis [5-9]. However, prospective data assessing the combined clinical utility of these markers in an Indian adult population remain limited. This study aimed to evaluate the diagnostic potential of hyperbilirubinemia and elevated CRP levels for predicting appendiceal perforation.

Materials and methods

Study design

This prospective observational study was conducted in the Department of General Surgery at Fortis Hospital, Mulund, Mumbai, and was prepared in accordance with the STROBE reporting principles. The study period was from July 2023 to December 2024. The participants comprised a convenience sample of 50 adult patients presenting with clinical signs of acute appendicitis and undergoing surgical management. Informed consent was obtained from all participants.

Diagnosis was supported by clinical examination and radiological imaging, including ultrasonography or computed tomography when clinically indicated. Intraoperative findings and histopathology reports confirmed the diagnosis. The inclusion criteria were age older than 18 years and acute appendicitis confirmed by intraoperative and histological evaluation. The exclusion criteria were liver dysfunction or hepatobiliary malignancy, chronic alcohol use or hemolytic anemia, pregnancy, conservative management of appendicitis, and use of medications associated with cholestasis.

Data collection and variables

Clinical symptoms, demographic data, laboratory values, including total serum bilirubin and CRP levels, and imaging findings were recorded. Blood samples were collected on admission and processed in the hospital laboratory. CRP was measured using immunoturbidimetry, and bilirubin was estimated using the diazo method. The primary outcome was the association of serum bilirubin and CRP levels with appendiceal perforation in acute appendicitis. The secondary outcome was the diagnostic accuracy of these markers.

Statistical analysis

Continuous data were expressed as mean (standard deviation) and compared using the unpaired t-test. Categorical data were expressed as numbers and percentages and compared using the chi-squared test or Fisher's exact test, as appropriate. Receiver operating characteristic (ROC) curves were plotted to assess diagnostic accuracy. A *P*-value less than 0.05 was considered statistically significant. Data were analyzed using GraphPad InStat v3.0.

Results

Demographics and clinical presentation

The mean age of the 50 patients was 31.94 (14.12) years. Most patients were in the 18-30-year age group, and 30 (60%) were male. Abdominal pain was the most common symptom and was present in all patients, followed by vomiting in 14 (28%), nausea in 10 (20%), fever in 8 (16%), and less frequent symptoms such as anorexia, bloating, and loose stools. On clinical examination, right lower-quadrant tenderness was the most consistent finding, whereas guarding and rebound tenderness were observed in a smaller proportion of patients.

Perforated appendicitis was observed in 15 (30%) patients based on intraoperative and histopathological findings. The remaining 35 (70%) patients had non-perforated appendicitis. Patients with appendiceal perforation had higher serum bilirubin and CRP levels than patients without perforation. Biomarker levels are summarized in Table 1. The mean serum bilirubin level was 1.42 (0.19) mg/dL in the perforation group and 1.06 (0.21) mg/dL in the non-perforation group ($P < 0.001$). The mean CRP level was 243.3 (45.9) mg/L in the perforation group and 135.8 (51.3) mg/L in the non-perforation group ($P < 0.001$).

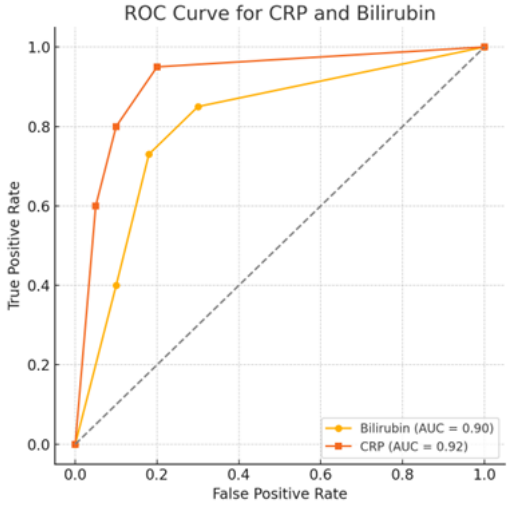
On ROC curve analysis, serum bilirubin showed an area under the curve (AUC) of 0.90. A cutoff value of 1.25 mg/dL yielded a sensitivity of 73.3% and a specificity of 82.4%. CRP showed an AUC of 0.92, and a cutoff value of 223 mg/L yielded a sensitivity of 80.0% and a specificity of 100.0% (Figure 1).

Table 1. Serum biomarker levels

Parameter	Perforated appendicitis	Non-perforated appendicitis	*P*-value
Mean serum bilirubin (mg/dL)	1.42 (0.19)	1.06 (0.21)	<0.001
Mean CRP (mg/L)	243.3 (45.9)	135.8 (51.3)	<0.001

CRP: C-reactive protein. $P < 0.05$ was considered statistically significant.

Figure 1: ROC curve for CRP and bilirubin



Discussion

The findings of this prospective observational study support the hypothesis that elevated serum bilirubin and CRP levels are significantly associated with appendiceal perforation in patients with acute appendicitis. This distinction is clinically important because perforated appendicitis increases the risk of sepsis, prolongs recovery, and may lead to complications such as intra-abdominal abscess and bowel obstruction [2]. In the present cohort, both biomarkers were higher in patients with perforated appendicitis than in those with non-perforated disease, and both showed strong diagnostic performance on ROC analysis.

The biological plausibility of hyperbilirubinemia in complicated appendicitis has been attributed to inflammatory and endotoxin-mediated impairment of hepatocellular bile transport in the absence of primary hepatobiliary disease [6-8]. Our findings are consistent with those of Pinate et al. [5], Nomura et al. [6], Akai et al. [7], and Eren et al. [8], who reported associations between elevated bilirubin, increased CRP, and complicated or severe appendicitis. The observed AUC values for bilirubin and CRP also align with prior diagnostic evidence suggesting that these markers can support clinical risk stratification, although they should not replace clinical judgment or imaging when imaging is available [9].

The practical value of serum bilirubin and CRP lies in their availability, low cost, and rapid measurement. In resource-limited settings where computed tomography may not be readily accessible, these markers may help identify patients who require closer observation, expedited imaging, or early operative prioritization. Their interpretation should nevertheless remain contextual and integrated with symptoms, physical examination, and radiological findings when available.

This study has limitations. It was a single-center study with a relatively small sample size, which may limit generalizability. The study did not evaluate other inflammatory markers, such as procalcitonin, neutrophil-to-lymphocyte ratio, or scoring systems, and no long-term follow-up of postoperative complications was performed. Future multicenter studies with larger samples should validate these findings and assess whether combinations of biochemical markers and clinical scoring systems can improve diagnostic accuracy for complicated appendicitis.

Conclusion

Serum bilirubin and CRP are significant predictors of appendiceal perforation in patients with acute appendicitis. Elevated levels of these markers should raise clinical suspicion and may support timely surgical decision-making. Their ease of measurement, availability, and low cost make them particularly valuable in rural or under-resourced healthcare settings.

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