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ASSOCIATION BETWEEN ACUTE APPENDICITIS AND HYPERBILIRUBINEMIA

Original Research

Najmul Hassan[1]*, Wajeeha Batool[1], Mansoor Hassan[1], Muttahir Asim Niaz[1], Sohail Saqib Chatha[1], Muhammad Salman Khalique[1], Muhammad Saqlain[1]
[1]CMH Sialkot, Pakistan.
Corresponding Author: Najmul Hassan, CMH Sialkot, Pakistan, najmulhassan836@gmail.com
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ABSTRACT

Background: Acute appendicitis is one of the most common causes of acute abdomen requiring emergency surgical intervention. Complicated appendicitis, such as gangrene or perforation, significantly increases morbidity and mortality. Early diagnosis is crucial to improving outcomes, but no single diagnostic test is definitive. Hyperbilirubinemia has recently emerged as a potential biomarker for acute appendicitis, particularly in complicated cases. Evaluating its diagnostic accuracy can aid in the timely management of this condition, especially when integrated with clinical and laboratory assessments.

Objective: To study the association and diagnostic accuracy of hyperbilirubinemia in patients presenting with acute appendicitis.

Methods: This prospective observational study was conducted at the Department of Surgery, Combined Military Hospital Sialkot, from September 2023 to July 2024. A total of 163 patients aged 12-60 years with a clinical diagnosis of acute appendicitis, who underwent appendectomy, were included. Pre-operative serum bilirubin levels were analyzed to determine their association with acute appendicitis. Post-operative histopathological examination served as the gold standard for diagnosis. Data on demographics, clinical presentation, and laboratory findings were collected and analyzed using descriptive and diagnostic statistics, including sensitivity, specificity, positive predictive value, and negative predictive value.

Results: Of the 163 patients, 103 (63.2%) were male and 60 (36.8%) were female, with a male-to-female ratio of 1.7:1. The mean age was 27.47 ± 11.33 years. Hyperbilirubinemia was detected in 114 (69.1%) patients, of which 111 (97.4%) were true positives and 3 (2.6%) were false positives. Among patients with acute appendicitis, 78 (70.2%) had uncomplicated appendicitis, while 33 (29.85%) had complicated appendicitis (gangrene or perforation). Hyperbilirubinemia demonstrated a sensitivity of 78.17%, specificity of 85.71%, positive predictive value of 97.37%, negative predictive value of 36.73%, and diagnostic accuracy of 79.14%.

Conclusion: Hyperbilirubinemia showed a significant association with acute appendicitis, particularly in complicated cases. Its diagnostic accuracy suggests it can serve as a valuable pre-operative adjunctive marker, enhancing the timely diagnosis and management of acute appendicitis.

Keywords: Appendicitis, Biomarkers, Complicated appendicitis, Diagnosis, Diagnostic accuracy, Hyperbilirubinemia, Sensitivity and specificity.

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INTRODUCTION

Acute appendicitis (AA) is one of the most commonly encountered causes of acute abdomen in emergency surgical settings, with a lifetime risk of 7-8% (1). Since its initial description by Reginald Herber Fitz in 1886, extensive research has focused on its etiology, diagnosis, and management strategies (3). The prevalence of AA in the literature is reported to range from 24-28.6%, with the highest incidence occurring between the second and fourth decades of life. Approximately 70% of cases present before the age of 30, with a slight male predominance and a male-to-female ratio of 1.3:1 (2, 4).

The condition arises from the inflammation of the vermiform appendix, frequently necessitating emergency surgical intervention. Typically, the clinical progression of AA begins with colicky abdominal pain, followed by nausea or vomiting, and subsequently pain migration to the right lower quadrant. While this classical presentation is well recognized, various clinical conditions, particularly in females and children, can mimic AA by causing pain in the right iliac fossa, adding to the diagnostic challenge (5). Accurate and timely diagnosis is critical, as delays or errors in management can lead to severe complications such as perforation, abscess formation, sepsis, and peritonitis, significantly increasing associated morbidity and mortality. Studies have shown that the incidence of appendiceal perforation ranges from 13-37%, particularly in extreme age groups, with mortality rates escalating from 0.3% in uncomplicated cases to 6% in complicated or perforated appendicitis (6). To mitigate such outcomes, surgeons often consider a negative appendectomy rate of 20-30% to be acceptable (7).

Despite advancements in diagnostic modalities, AA remains a diagnostic dilemma, often relying on clinical judgment. Experienced surgeons can achieve a diagnostic accuracy of up to 80% based on history, physical examination, and laboratory investigations (8). However, even expert evaluations are prone to misdiagnosis or oversight in certain cases. Radiological tools such as ultrasound and computed tomography have significantly improved diagnostic sensitivity, specificity, and accuracy, reportedly achieving rates of 85-99% (9). However, their use is often limited by cost, time, and accessibility, necessitating the exploration of alternative diagnostic measures. Various scoring systems, including the Alvarado score, Appendicitis Inflammatory Response (AIR) score, Adult Appendicitis score, Pediatric Appendicitis Score (PAS), and Raja Isteri Pengiran Anak Saleha Appendicitis (RIPASA) score, have been developed to support pre-operative diagnosis. These tools incorporate clinical symptoms, signs, and laboratory findings such as leukocytosis, neutrophilia, and elevated C-reactive protein levels. While these systems enhance diagnostic accuracy, they are not stand-alone solutions and serve primarily as adjuncts to clinical evaluation.

Recent research has highlighted hyperbilirubinemia as a promising biomarker for diagnosing acute and complicated appendicitis. Bacterial invasion of the appendix is thought to trigger the release of pro-inflammatory cytokines, such as tumor necrosis factor-alpha and interleukin-6, which reach the liver via the portal circulation, inducing hepatic inflammation and altering blood flow. This pathophysiological mechanism may explain elevated bilirubin levels in appendicitis cases, particularly those involving complications such as perforation or abscess formation (10). While numerous international studies have investigated the diagnostic value of hyperbilirubinemia, most focus on its predictive role in perforated appendicitis, leaving gaps in understanding its broader applicability. Moreover, there is limited local data to establish definitive guidelines linking AA with elevated serum bilirubin levels. Addressing this gap is crucial, as incorporating hyperbilirubinemia into diagnostic protocols could aid in early detection and timely management, ultimately improving patient outcomes.

In light of these considerations, this study seeks to evaluate the association between hyperbilirubinemia and AA, with a focus on both uncomplicated and complicated cases. By examining its diagnostic potential, the research aims to contribute to more accurate and efficient diagnostic strategies, reducing overall morbidity and mortality in acute appendicitis.

METHODS

This prospective observational study was conducted in the Department of Surgery at Combined Military Hospital Sialkot over a period of ten months, from September 2023 to July 2024. A total of 162 patients were enrolled, with the sample size calculated using the WHO sample size calculator. Parameters included a 95% confidence interval, a 5% margin of error, and an acute appendicitis (AA) prevalence of 22.8% (11). Participants were selected through a non-probability consecutive sampling technique. Written informed consent was

obtained from all participants prior to inclusion in the study. In cases involving minors, consent was obtained from their parents or legal guardians. Ethical approval was granted by the hospital's ethical review committee before the commencement of the study (ERC/01/2024).

The study included patients aged 12-60 years, regardless of gender, who were clinically diagnosed with AA upon admission and underwent surgical intervention. Exclusion criteria were applied to eliminate confounding factors, and patients with conditions such as viral or alcoholic hepatitis, a history of jaundice or liver disease, acquired or congenital biliary disorders, cholelithiasis, blood dyscrasias, hemolytic disease, or malignancy of the hepatobiliary system were excluded. Additionally, pregnant females, individuals using hepatotoxic drugs, and patients with operative findings of appendicular masses or abscesses were not included.

Each patient underwent a thorough clinical assessment, including a detailed history and physical examination focusing on key symptoms such as right iliac fossa pain, anorexia, nausea, vomiting, tenderness, and rebound tenderness. Baseline investigations were conducted in the hospital laboratory before surgery. These included a complete blood count, C-reactive protein levels, liver function tests, and hepatitis serology. Pre-anesthesia assessments were also performed. Appendectomy was carried out for all patients, and appendix specimens were sent for histopathological examination to confirm the diagnosis. Hyperbilirubinemia was defined as a bilirubin level exceeding 1.2 mg/dL. Histopathological examination served as the gold standard for diagnosing AA.

All relevant patient data, including demographic information, clinical features, laboratory results, intraoperative findings, and histopathological reports, were recorded on a structured proforma. Statistical analysis was performed using SPSS version 26. Descriptive statistics were applied to calculate both quantitative and qualitative variables. Frequencies and percentages were calculated for categorical data such as gender and histopathological diagnoses, while quantitative variables, including age and duration of pain, were expressed as means and standard deviations. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy of hyperbilirubinemia were calculated using a 2×2 contingency table, with histopathological findings as the gold standard.

RESULTS

Of the 163 patients included in the study, 103 (63.2%) were male, and 60 (36.8%) were female, resulting in a male-to-female ratio of 1.7:1. The mean age of the patients was 27.47 ± 11.33 years, with the majority (63.19%) aged between 12 and 30 years. The most common clinical presentation was pain in the right lower quadrant, reported by 156 (95.7%) patients, followed by anorexia in 108 (66.3%), nausea or vomiting in 89 (54.6%), and fever in 79 (48.5%). On examination, tenderness in the right lower quadrant was present in 147 (90.2%), while rebound tenderness was observed in 132 (81%). Laboratory investigations showed that 96 (58.9%) patients had leukocytosis, and hyperbilirubinemia was detected in 114 (69.1%). The mean duration of symptoms before presentation was 1.91 ± 1.11 days.

Histopathological analysis revealed that 142 (87.1%) patients had acute appendicitis, including 106 (65%) cases of acute inflamed appendicitis, 14 (8.6%) gangrenous appendicitis, and 22 (13.5%) perforated appendicitis. Hyperbilirubinemia was detected in 78 (73.58%) of acute inflamed cases, 13 (92.85%) of gangrenous cases, and 20 (90.90%) of perforated cases. Among the 21 (12.9%) patients with normal appendices, hyperbilirubinemia was present in 3 (14.2%), indicating a low false-positive rate. These results suggest a strong association between hyperbilirubinemia and complicated appendicitis, such as gangrenous or perforated cases, compared to uncomplicated or normal findings.

The diagnostic accuracy of hyperbilirubinemia for acute appendicitis was assessed against histopathological findings. Hyperbilirubinemia demonstrated a sensitivity of 78.17%, a specificity of 85.71%, and a diagnostic accuracy of 79.14%. The positive predictive value was 97.37%, reflecting its high reliability in confirming acute appendicitis. However, the negative predictive value was lower at 36.73%, indicating limited utility in excluding the diagnosis. Statistically significant results (p=0.001) highlight hyperbilirubinemia as a valuable adjunctive diagnostic marker, particularly in complicated cases of appendicitis.

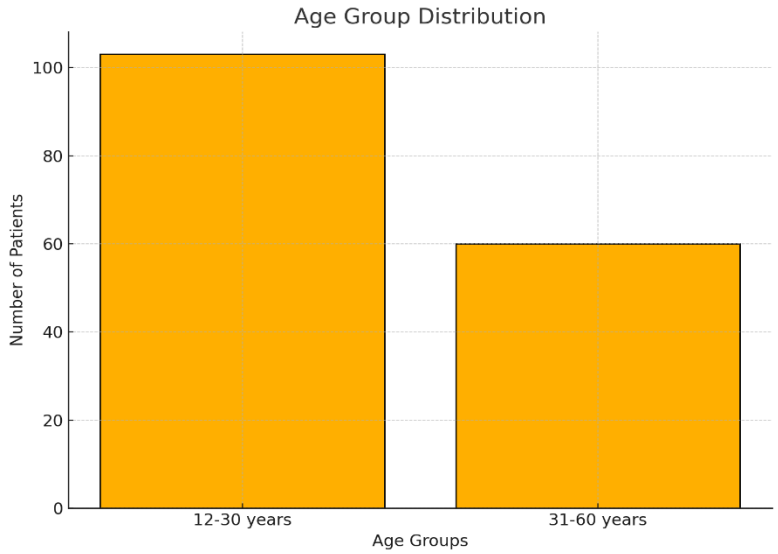

Figure 1 Age Group Distribution

The baseline characteristics of the 163 patients included in the study revealed a mean age of 27.47 ± 11.33 years, with the majority (63.19%) aged between 12 and 30 years.

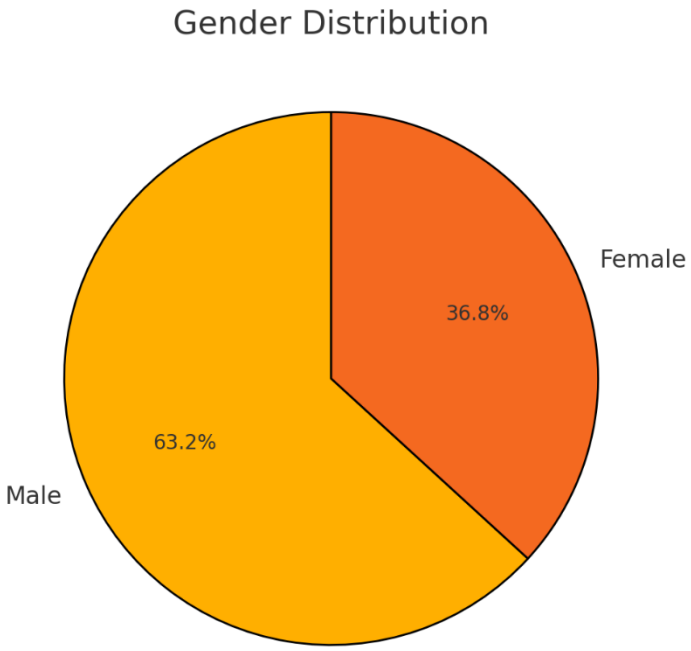

Figure 2 Gender Distribution

There was a male predominance, with 103 (63.2%) males and 60 (36.8%) females, yielding a male-to-female ratio of 1.7:1.

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Table 1: Baseline characteristics of patients

Characteristics	Value
Total patients (n)	163
Common presentation n (%)	
Pain RLQ	156 (95.7%)
Anorexia	108 (66.3%)
Nausea / Vomiting	89 (54.6%)
Fever	79 (48.5%)
Tenderness RLQ	147 (90.2%)
Rebound tenderness	132 (81%)
Leukocytosis (WBC)	96 (58.9%)
Hyperbilirubinemia	114 (69.1%)
Duration of symptoms (days), mean±SD	1.91 ± 1.11
Histopathological findings	
Normal	21 (12.9%)
Acute inflamed	106 (65%)
Gangrenous	14 (8.6%)
Perforation	22 (13.5%)

The most common clinical presentation was pain in the right lower quadrant, observed in 156 (95.7%) patients, followed by anorexia in 108 (66.3%), nausea or vomiting in 89 (54.6%), and fever in 79 (48.5%). On examination, tenderness in the right lower quadrant was present in 147 (90.2%) patients, and rebound tenderness was noted in 132 (81%). Leukocytosis was detected in 96 (58.9%) of patients, and hyperbilirubinemia was present in 114 (69.1%). The mean duration of symptoms prior to presentation was 1.91 ± 1.11 days. Histopathological findings confirmed normal appendices in 21 (12.9%) cases, acute inflamed appendicitis in 106 (65%), gangrenous appendicitis in 14 (8.6%), and perforated appendicitis in 22 (13.5%). These findings highlight the predominance of acute and complicated appendicitis in the study population, along with a high prevalence of hyperbilirubinemia.

Table 2: Association of hyperbilirubinemia with histopathological variants of AA

Histopathological findings	Total number of cases	Hyperbilirubinemia present
Acute inflamed	106	78 (73.58%)
Gangrenous	14	13 (92.85%)
Perforated	22	20 (90.90%)
Normal	21	3 (14.2%)

Histopathological examination of the 163 cases revealed that 106 (65%) patients had acute inflamed appendicitis, of which hyperbilirubinemia was detected in 78 (73.58%) cases. Among the 14 (8.6%) cases of gangrenous appendicitis, hyperbilirubinemia was present in 13 (92.85%) patients. Similarly, out of 22 (13.5%) perforated appendicitis cases, 20 (90.90%) exhibited hyperbilirubinemia. In contrast, among the 21 (12.9%) patients with normal appendices, only 3 (14.2%) demonstrated hyperbilirubinemia. These findings

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suggest a strong association between elevated bilirubin levels and complicated forms of appendicitis, such as gangrene and perforation, compared to normal or uncomplicated cases.

Table 3: Diagnostic accuracy of hyperbilirubinemia for AA

		AA (Histopathology Findings)		
		Present	Absent	p-value
Hyperbilirubinemia	Present	111 (97.4%)	3 (2.6%)	0.001
	Absent	31 (63.3%)	18 (36.7%)	
Sensitivity = 78.17%				
Specificity = 85.71%				
Positive predictive value = 97.37%				
Negative predictive value = 36.73%				
Diagnostic accuracy = 79.14%				

The diagnostic accuracy of hyperbilirubinemia for acute appendicitis (AA) was evaluated against histopathological findings, demonstrating statistically significant results (p=0.001). Hyperbilirubinemia was present in 111 (97.4%) of patients with histopathologically confirmed AA and only 3 (2.6%) of those without AA, indicating a low false-positive rate. Conversely, 31 (63.3%) patients with AA had normal bilirubin levels, while 18 (36.7%) of patients without AA also exhibited normal bilirubin levels. The sensitivity and specificity of hyperbilirubinemia for diagnosing AA were 78.17% and 85.71%, respectively. The positive predictive value (PPV) was exceptionally high at 97.37%, reflecting the strong reliability of hyperbilirubinemia in confirming AA. However, the negative predictive value (NPV) was relatively low at 36.73%, suggesting limited utility in ruling out AA. Overall, the diagnostic accuracy of hyperbilirubinemia for AA was calculated to be 79.14%, underscoring its potential as an adjunct diagnostic marker, particularly for confirming the condition.

DISCUSSION

Acute appendicitis (AA), if not diagnosed and treated promptly, is associated with significant morbidity and mortality. Early diagnosis and timely surgical intervention are critical in improving clinical outcomes. While clinical judgment plays a decisive role in pre-operative diagnosis in most cases, a subset of cases continues to challenge surgeons due to atypical presentations. Despite the availability of diagnostic modalities such as ultrasonography, computed tomography, laparoscopy, and laboratory investigations, approximately 15% of cases remain misdiagnosed, often culminating in complications such as perforation (12). No single diagnostic test other than histopathological examination following surgery has been established as definitive, and various scoring systems have been developed over time to aid diagnosis. These systems, which integrate clinical signs, symptoms, and laboratory parameters, have demonstrated variable diagnostic accuracy. Over recent years, serum bilirubin has emerged as a promising biomarker for predicting AA, particularly in complicated cases.

The findings of this study demonstrated that hyperbilirubinemia was present in 114 (69.1%) patients. Among these, 111 (97.4%) cases were histopathologically confirmed as AA, indicating a high positive predictive value of 97.37%. Hyperbilirubinemia supported the diagnosis in 73.58% of uncomplicated appendicitis cases and 91.66% of complicated cases, such as perforated and gangrenous appendicitis. Diagnostic performance metrics revealed a sensitivity of 78.17%, specificity of 85.71%, and an overall diagnostic accuracy of 79.14%. These findings align with prior research that has established hyperbilirubinemia as a valuable diagnostic tool. Studies conducted by Anum S et al. and Kolanjiappan B et al. reported even higher diagnostic accuracies and sensitivities, particularly in complicated cases (13, 18). In contrast, studies such as those by Ahmed FA and Chambers et al. found no significant correlation between elevated bilirubin levels and AA, indicating that the role of hyperbilirubinemia remains context-dependent and may be influenced by confounding variables such as underlying liver conditions (20, 21).

The strengths of this study include the systematic evaluation of hyperbilirubinemia as a diagnostic marker, its relatively large sample size, and its comprehensive analysis of both uncomplicated and complicated appendicitis cases. However, several limitations should be acknowledged. As a single-center study conducted over a limited timeframe, the findings may lack generalizability. Subclinical causes of hyperbilirubinemia, such as Gilbert's syndrome, were not ruled out, which could have influenced the results. Additionally, the study did not account for coexisting infections or hepatic conditions that might affect bilirubin levels, introducing a potential bias.

A comparative study conducted by Eren T et al. in 2020 assessed the diagnostic utility of hyperbilirubinemia alongside traditional inflammatory markers such as leukocytosis and C-reactive protein (CRP) in predicting complicated appendicitis. The study involved 250 patients who underwent appendectomy and demonstrated that hyperbilirubinemia had a significantly higher specificity (88.6%) for detecting perforated appendicitis compared to leukocytosis (71.2%) and CRP (79.4%). Sensitivity for hyperbilirubinemia, however, remained comparable to leukocytosis at 75.4%, indicating its superior reliability as a confirmatory marker rather than an initial screening tool. Furthermore, the study highlighted that combining hyperbilirubinemia with other markers enhanced diagnostic accuracy to 91.3%, supporting its integration into routine diagnostic protocols for acute appendicitis. These findings corroborate the growing recognition of hyperbilirubinemia as a valuable marker for complicated appendicitis, complementing existing diagnostic tools for improved patient outcomes (23).

Despite its limitations, this study contributes to the growing evidence supporting the use of hyperbilirubinemia as an adjunctive diagnostic marker for AA, particularly in resource-limited settings. Serum bilirubin is a readily available, cost-effective investigation that, when combined with clinical judgment and other diagnostic tools, can enhance the accuracy of AA diagnosis and potentially improve patient outcomes. Future multi-center studies with larger cohorts and broader inclusion criteria are recommended to validate these findings and establish standardized guidelines for the clinical use of hyperbilirubinemia in AA diagnosis.

CONCLUSION

Hyperbilirubinemia has shown significant potential as a diagnostic marker for acute appendicitis, particularly in identifying complicated cases such as perforation and gangrene. Its ability to complement clinical assessment and other diagnostic tools makes it a valuable pre-operative adjunct, enhancing diagnostic accuracy and aiding timely decision-making. By integrating hyperbilirubinemia into routine diagnostic protocols, clinicians may improve early detection and management of acute appendicitis, ultimately reducing associated morbidity and mortality.

AUTHOR CONTRIBUTIONS

Author	Contribution
Najmul Hassan*	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Wajeeha Batool	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Mansoor Hassan	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Muttahir Asim Niaz	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Sohail Saqib Chatha	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Muhammad Salman Khalique	Data Collection and Analysis Has given Final Approval of the version to be published
Muhammad Saqlain	Contributed to Analysis and Data Collection Has given Final Approval of the version to be published

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