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Hyperbilirubinemia and Hyponatremia in Predicting Severity of Acute Appendicitis- Making Way for New Markers

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ABSTRACT

The study explores the use of hyperbilirubinemia (elevated bilirubin) and hyponatremia (low sodium) as predictive markers for the severity of acute appendicitis. Acute appendicitis, a common cause of emergency surgeries, can progress from mild to life-threatening stages, including perforation and abscess formation. Accurate staging is essential, yet challenging, due to overlapping symptoms with other abdominal issues and limitations in traditional imaging methods, such as CT scans, which, though effective, have constraints like cost and radiation exposure. This has spurred interest in laboratory markers that could provide a less invasive and cost-effective alternative. Hyperbilirubinemia and hyponatremia have emerged as potential indicators for severe appendicitis, reflecting the body's inflammatory response. Elevated bilirubin may result from liver involvement triggered by endotoxins from a severely inflamed appendix, while hyponatremia can occur due to electrolyte shifts in response to inflammation. In the study, data from patients with histopathologically confirmed acute appendicitis showed that both markers were associated with complicated appendicitis cases. Specifically, higher bilirubin levels and lower sodium levels correlated significantly with perforated or gangrenous appendicitis, achieving notable diagnostic accuracy. When combined, hyperbilirubinemia and hyponatremia displayed increased sensitivity and specificity, suggesting their value as complementary to traditional diagnostic methods. This combination approach achieved a sensitivity of 81.3%, specificity of 64.7%, and an area under the curve (AUC) of 0.80, providing a reliable adjunct in assessing appendicitis severity. While these markers show promise, they should be used alongside clinical and imaging assessments, not as standalone indicators, given their nonspecificity. Further research could refine their role in diagnostics, particularly in settings where CT may not be accessible, offering an efficient tool for early identification of complicated appendicitis.

INTRODUCTION

Appendicitis is one of the most common reasons for emergency surgery worldwide, often requiring prompt intervention to prevent life-threatening complications. The management of acute appendicitis largely depends on accurately diagnosing its stage, as the condition can vary from self-limiting to necessitating urgent surgical treatment. In its early stages, acute appendicitis may resolve without surgery, but if left untreated, it can progress to more complicated forms, such as perforation, peritonitis, or abscess formation, which require immediate surgical intervention. Therefore, determining the severity of appendicitis is crucial for appropriate clinical decision-making and optimal patient outcomes [1,2].

The diagnosis of acute appendicitis is often challenging due to its variable clinical presentation, which can overlap with other abdominal pathologies. This makes it difficult for clinicians to reliably distinguish between simple and complicated appendicitis based on clinical findings alone. Moreover, preoperative diagnosis is rarely definitive, and delays in diagnosis can lead to worsened outcomes, including increased rates of perforation and postoperative complications. To improve diagnostic accuracy and reduce these risks, several diagnostic approaches have been explored, including

laboratory tests, imaging modalities, and scoring systems. Despite the extensive research, no single method has proven to be entirely reliable as a standalone diagnostic tool. This is evident from studies showing that more than 20% of appendicitis diagnoses are missed when relying solely on traditional diagnostic methods [3,4].

Radiological imaging, particularly computed tomography (CT), remains the most valuable tool for diagnosing acute appendicitis. CT scans offer detailed insights into the appendicealmorphology and can identify complications such as perforation, abscess formation, or gangrene. However, while CT is highly effective in detecting complicated appendicitis, its availability, cost, and exposure to radiation limit its use in certain patient populations. This has prompted ongoing efforts to find additional biomarkers or diagnostic indicators that could help predict the severity of appendicitis, offering a more cost-effective and less invasive approach [5,6].

In recent years, there has been growing interest in the potential role of laboratory markers, such as hyperbilirubinemia and hyponatremia, in predicting the severity of acute appendicitis. Hyperbilirubinemia, characterized by elevated serum bilirubin levels, is typically associated with liver dysfunction or biliary obstruction. However, its presence in the context of acute appendicitis has led to speculation that it could reflect the inflammatory response or hepatic involvement in complicated appendicitis. Although only a few studies have specifically investigated the relationship between hyperbilirubinemia and complicated appendicitis, early evidence suggests that elevated bilirubin levels could be a useful adjunct to other diagnostic modalities. However, it is important to note that elevated bilirubin can also occur in other abdominal inflammatory conditions, such as cholecystitis or pancreatitis, making it a nonspecific marker for appendicitis. Therefore, its role as a standalone predictor for complicated appendicitis requires further exploration [7,8].

Similarly, hyponatremia, or low serum sodium levels, has been identified as an independent risk factor for acute appendicitis. It is thought that the body's inflammatory response during appendicitis may cause changes in electrolyte balance, leading to sodium depletion. Hyponatremia has been associated with more severe forms of appendicitis, including perforated and gangrenous appendicitis, but its diagnostic value for predicting complications remains inconclusive. Some studies have suggested that hyponatremia could be a reliable indicator of severe appendicitis, particularly in patients presenting with systemic signs of infection or sepsis. However, the diagnostic accuracy of hyponatremia in predicting complicated appendicitis has not been fully established, with conflicting results in the literature. As with hyperbilirubinemia, hyponatremia is not specific to appendicitis and can occur in a variety of other clinical conditions, including dehydration, heart failure, and renal disease [9,10].

The use of hyperbilirubinemia and hyponatremia as adjunctive markers for predicting the severity of acute appendicitis is still in its early stages. While these markers show promise, they should not be relied upon in isolation for making clinical decisions. Rather, they could be integrated into existing diagnostic frameworks, alongside clinical findings and imaging studies, to improve the overall accuracy of appendicitis diagnosis. Further research is necessary to better understand the pathophysiological mechanisms linking these markers to complicated appendicitis and to determine their potential utility in clinical practice [11,12].

While imaging techniques such as CT remain the gold standard for diagnosing acute appendicitis, the search for additional biomarkers to predict the severity of the condition continues. Hyperbilirubinemia and hyponatremia represent promising avenues for future research, offering the potential to enhance preoperative diagnostic accuracy and guide clinical decision-making. However, the challenge lies in establishing their role as reliable, specific markers for complicated appendicitis. As the understanding of these markers deepens, they may become valuable tools in conjunction with traditional diagnostic methods, ultimately improving patient outcomes in the management of acute appendicitis [13,14].

The present study evaluated the diagnostic effectiveness of hyperbilirubinemia, hyponatremia, and their combined use in predicting complicated appendicitis. It also explored the characteristics of patients with different stages of acute appendicitis to assess the potential of these markers in identifying more severe forms of the condition.

MATERIAL AND METHODS

This prospective observational study was conducted at the Department of general surgery, at a tertiary care hospital from January 2021 and December 2023. Ethical approval has been obtained from the Ethical Approval Committee of tertiary care hospital.

Study Population:

The study population consisted of patients admitted for acute appendicitis, who underwent surgery and had postoperative histopathological confirmation of acute appendicitis. Data were extracted from their medical records available in a computer-based hospital information system. Exclusion criteria included pregnancy, appendicular neoplasm, hemolytic disease, and known hepatocellular carcinoma. These criteria ensured a focused analysis on patients with confirmed acute appendicitis without complicating factors.

Data Analysis:

Data analysis included patient demographics (sex, age), serum sodium levels, total bilirubin (TBIL) levels, histopathology, and type of surgery. The stage of appendicitis was categorized based on histological findings as early

acute, acute suppurative, acute necrotizing gangrenous with perforation, or other types. The primary outcome, complicated appendicitis, was defined by intraoperative findings of acute necrotizing gangrenous appendicitis with perforation. Hyperbilirubinemia was defined as TBIL >20 µmol/L, and hyponatremia as serum sodium <135.0 mEq/L.

RESULTS

The study included a male-to-female ratio of 1.71:1, with a mean age of 24.6 ± 12.4 years. The mean serum total bilirubin (TBIL) level was 17.36 ± 7.87 µmol/L, and the mean serum sodium level was 134.63 ± 2.82 mEq/L. The most common type of appendicitis observed was acute suppurative appendicitis.

Table 1: Appendicitis Staging

Staging of Appendicitis	Frequency	Percentage
Early	14	14.43
Suppurative	70	72.16
Complicated	12	11.64
Other	1	0.97

The mean total bilirubin (TBIL) level was significantly higher, and the mean sodium level was significantly lower in patients with complicated appendicitis compared to those with uncomplicated appendicitis, with p-values of 0.031 and 0.047, respectively.

The levels of total bilirubin (TBIL) (odds ratio: 1.098, 95% CI: 1.052-1.147) and serum sodium (odds ratio: 0.743, 95% CI: 0.646-0.855) were found to be associated with complicated appendicitis (CA).

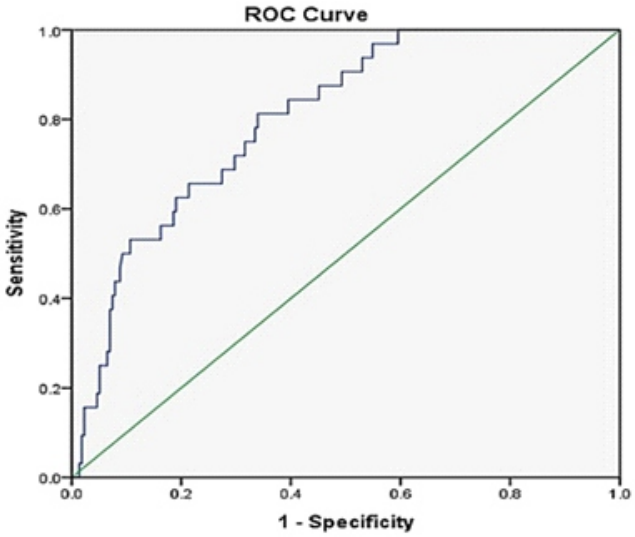

Figure 1: ROC Curve

The combination of hyperbilirubinemia and hyponatremia improved diagnostic efficacy, achieving a sensitivity of 81.3%, specificity of 64.7%, positive predictive value (PPV) of 25.5%, negative predictive value (NPV) of 95.9%, and an area under the curve (AUC) of 0.80.

DISCUSSION

An early and accurate diagnosis of complicated appendicitis is crucial for ensuring timely surgical intervention, which significantly improves clinical outcomes. The ability to identify complicated appendicitis early can prevent the progression to severe complications, such as perforation, peritonitis, or sepsis, all of which are associated with increased morbidity and mortality. Prompt recognition of these complications reduces the risk of postoperative infections, minimizes the need for additional interventions, and shortens hospital stays, ultimately enhancing patient recovery. While clinical signs and symptoms remain essential for diagnosing appendicitis, the increasing reliance on imaging techniques such as computed tomography (CT) has greatly improved the diagnostic sensitivity for complicated appendicitis. CT scans are particularly useful in identifying complications like perforation, abscess formation, or gangrene, allowing for a more accurate and timely diagnosis. However, despite the efficacy of CT in diagnosing complicated appendicitis, it is not without limitations. CT imaging is expensive, requires access to specialized equipment, and exposes patients to radiation. These factors make it less feasible in some clinical settings, especially in resource-limited environments, and raise concerns regarding the overuse of radiation in young patients. Additionally, there are instances where CT imaging may still be inconclusive or fail to detect early signs of complicated appendicitis, necessitating the search for additional diagnostic markers that can complement existing methods [15,16,17].

In this context, laboratory markers such as hyperbilirubinemia and hyponatremia have emerged as potential adjuncts in predicting the severity of acute appendicitis. Hyperbilirubinemia, characterized by elevated total bilirubin (TBIL) levels, has been identified as a promising marker for complicated appendicitis. It is thought that hyperbilirubinemia may arise due to the systemic infla-

-mmatory response associated with appendicitis, particularly in cases where the appendix becomes perforated or gangrenous. In these more severe forms of the disease, endotoxins released by the inflamed appendix may contribute to liver dysfunction, impairing biliary excretion and leading to increased bilirubin levels in the bloodstream. Several studies have reported that TBIL levels greater than 20 µmol/L are commonly observed in patients with complicated appendicitis, suggesting that hyperbilirubinemia may serve as a diagnostic indicator of disease severity. Moreover, research has shown that patients with acute perforated appendicitis tend to have significantly higher bilirubin levels compared to those with uncomplicated appendicitis. This correlation further supports the potential role of hyperbilirubinemia as a marker for distinguishing between simple and complicated forms of appendicitis [18,19].

Although the association between hyperbilirubinemia and complicated appendicitis is well-documented, it is important to note that elevated bilirubin levels are not specific to appendicitis alone. Hyperbilirubinemia can also occur in a range of other abdominal inflammatory conditions, including cholecystitis, pancreatitis, and even liver diseases. Therefore, while hyperbilirubinemia may be useful in identifying complicated appendicitis, it cannot be relied upon as a sole diagnostic marker. The challenge lies in differentiating between these various conditions that may also present with elevated bilirubin levels, making it necessary to consider other diagnostic factors, such as clinical symptoms, imaging findings, and laboratory tests, to reach an accurate diagnosis [20].

Hyponatremia, defined as a serum sodium level below 135 mEq/L, has also been identified as a potential marker for predicting complicated appendicitis. The relationship between hyponatremia and appendicitis is believed to stem from the body's response to inflammation. During acute appendicitis, particularly in the presence of complications such as perforation or gangrene, the systemic inflammatory response can lead to fluid shifts and electrolyte imbalances, including a decrease in sodium levels. Studies have shown that hyponatremia is more common in patients with complicated appendicitis, particularly those with perforated or gangrenous appendicitis. Some research has suggested that hyponatremia may be an independent predictor of disease severity, with a lower sodium threshold (e.g., below 136 mEq/L) correlating with higher odds of complicated appendicitis. However, there is variability in the reported strength of this association. For example, some studies have reported an odds ratio of 2.8 for hyponatremia as a predictor of complicated appendicitis, while others have found higher odds ratios, such as 3.2. These discrepancies suggest that while hyponatremia may serve as a useful indicator of complicated appendicitis, further research is needed to refine its diagnostic utility and establish definitive thresholds [21].

The combination of hyperbilirubinemia and hyponatremia may offer a more reliable diagnostic approach than either marker alone. By integrating these two markers, clinicians may be able to improve the diagnostic accuracy and predictive value for complicated appendicitis. This combination could enhance the ability to distinguish between uncomplicated and complicated appendicitis, enabling more timely interventions and better management of the condition. For instance, patients with both elevated TBIL levels and low serum sodium may be more likely to have complicated appendicitis, which would prompt closer monitoring and potential early surgical intervention. The sensitivity, specificity, and positive and negative predictive values of these markers in combination have been shown to be favorable, further supporting their potential role in clinical practice [22,23].

However, it is important to note that hyperbilirubin emia and hyponatremia, like all diagnostic markers, should not be used in isolation. They must be considered in conjunction with clinical findings, imaging results, and other laboratory tests to ensure accurate diagnosis. These markers can be particularly valuable in resource-limited settings where advanced imaging techniques may not be readily available, providing a less expensive and non-invasive means of assessing the severity of appendicitis. Nonetheless, their role should be viewed as complementary to other diagnostic tools, rather than as standalone diagnostic criteria [24].

The identification of reliable biomarkers for predicting the severity of acute appendicitis remains a critical area of research. Hyperbilirubinemia and hyponatremia both show promise as potential markers for complicated appendicitis, offering valuable diagnostic insights when used in conjunction with traditional clinical and imaging methods. While these markers have demonstrated diagnostic potential, further studies are needed to better define their thresholds, optimize their use in clinical practice, and determine their role in combination with other emerging markers. Ultimately, integrating these biomarkers into the diagnostic workflow could improve the early detection and management of complicated appendicitis, leading to better patient outcomes and more efficient healthcare delivery [25].

CONCLUSION

The combination of hyponatremia and hyperbilirub inemia provided significant discriminatory value in diagnosing complicated appendicitis (CA). Total bilirubin (TBIL) and serum sodium levels can serve as useful adjunctive parameters in identifying perforated or necrotizing appendicitis, aiding in the early detection and assessment of disease severity. This combination enhances diagnostic accuracy and may support clinical decision-making in managing complicated cases of appendicitis.

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