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Clinical Implications of Serum Bilirubin and Procalcitonin in the Diagnosis of Acute Appendicitis

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ABSTRACT

Acute appendicitis remains a common surgical emergency with challenges in prompt and accurate diagnosis. Serum biomarkers have garnered attention for their potential role in aiding diagnostic accuracy. This paper aims to update the clinical implications of serum bilirubin and procalcitonin levels in diagnosing acute appendicitis. A systematic review of literature was conducted, encompassing studies that investigated the relationship between serum bilirubin and procalcitonin levels and acute appendicitis. The search strategy included electronic databases, resulting in a comprehensive analysis of relevant articles. The findings suggest a notable association between elevated serum bilirubin levels and the presence of acute appendicitis. Furthermore, procalcitonin exhibited promising diagnostic potential, demonstrating a significant correlation with the severity of appendicitis. Subgroup analyses revealed varied sensitivity and specificity values, indicating the need for further refinement in clinical application. The integration of serum biomarkers, specifically bilirubin and procalcitonin, into the diagnostic algorithms of acute appendicitis could potentially enhance the accuracy of clinical assessments. However, limitations in existing studies, such as heterogeneity in patient populations and differing assay methodologies, emphasize the necessity for standardized protocols and larger prospective trials. In conclusion, serum bilirubin and procalcitonin levels show promise as adjunctive tools in diagnosing acute appendicitis. Their incorporation into clinical practice warrants careful consideration and validation through larger-scale studies to delineate their precise diagnostic utility, thereby potentially optimizing patient care pathways in the context of this prevalent surgical condition.

Keywords : Acute appendicitis, Bilirubin, Procalcitonin, Diagnosis, Clinical implications

INTRODUCTION

Acute appendicitis represents one of the most common surgical emergencies worldwide, necessitating prompt diagnosis and intervention to prevent potentially severe complications. Despite advancements in diagnostic imaging modalities and clinical evaluation, accurately discerning appendicitis at its early stages remains a challenge. Consequently, there exists a continuous quest for reliable and efficient diagnostic tools to aid clinicians in timely decision-making and appropriate management [1]. In recent years, the exploration of serum biomarkers has emerged as a promising avenue for improving the diagnostic accuracy of acute appendicitis. Among these biomarkers, serum bilirubin and procalcitonin have garnered substantial interest due to their potential role in reflecting inflammatory and infectious processes, respectively, within the appendiceal microenvironment [2]. The significance of serum bilirubin lies not only in its established role as a marker of hepatic function but also in its suggested association with inflammatory conditions, including appendicitis. Elevated bilirubin levels have been hypothesized to correlate with the severity and progression of inflammatory processes within the appendiceal tissue, prompting investigations into its potential utility as a diagnostic indicator in acute appendicitis [3]. Similarly, procalcitonin, a precursor of the hormone calcitonin, has gained recognition as a marker of bacterial infections. Elevated levels of procalcitonin have been observed in various systemic infections,

and recent studies have explored its potential relevance in identifying the presence and severity of bacterial-induced inflammation in appendicitis [4]. This paper aims to critically evaluate the clinical implications of serum bilirubin and procalcitonin levels in the diagnosis of acute appendicitis. By synthesizing and analyzing available literature, this study seeks to elucidate the potential roles of these serum biomarkers, individually and in combination, in augmenting the accuracy and efficiency of diagnosing acute appendicitis. Additionally, it aims to address existing gaps in research, emphasize the strengths and limitations of current evidence, and propose directions for future investigations to enhance diagnostic strategies in this critical surgical condition.

Overview and pathophysiology of appendicitis.

Appendicitis is the most frequent acute abdomen worldwide, and its burden has been changing.

In 2019, it was reported that the prevalence varied between 8.7 (95% UI 6.9 to 11.0) and 229.9 (95% UI 180.9 to 291.0) per 100,000 people worldwide with more than 17.7 million people affected [5]. Ethiopia, India, and Nigeria were among the areas with the greatest increases in the increases prevalence rate between 1990 and 2019 [5]. Luminal obstruction is thought to represent the main pathogenic event in the majority of patients with acute appendicitis [6]. Fecaliths, lymphoid hyperplasia, foreign things, parasites, and primary and metastatic tumors (carcinoid, adenocarcinoma, Kaposi sarcoma, and lymphoma) are a few possible causes [7].

This hypothesis proposes that blockage causes inflammation, increasing intraluminal pressures, and finally ischemia. The surrounding tissues, such as the peritoneum and pericecal fat, become inflamed as a result of the appendix's distension [7]. Eventually, the inflamed appendix perforates if left untreated. True appendiceal calculi, which are hard, noncrushable, calcified stones, are less frequent than appendiceal fecaliths, which are hard but crushable concretions, but they have been linked to perforating appendicitis and periappendiceal abscess more frequently. Younger people, whose lymphoid tissue is more numerous than that of older people, appear to be more susceptible to this occlusion's pathogenesis [8]. Due to the appendix's limited luminal capacity, rapid distension occurs, and intraluminal pressures can reach 50 to 65 mm Hg. Due to the cecal localized ileum's inflammatory process, this appendiceal disease causes the cecum to expand [9]. When luminal pressure rises beyond 85 mm Hg, the venules that drain the appendix become thrombosed, and when arteriolar inflow persists, vascular congestion and appendix engorgement become visible. When the mucosa gets hypoxic and starts to ulcerate, the mucosal barrier is compromised, which allows intraluminal bacteria to invade the appendiceal wall. Gram-negative bacteria make up the majority of bacteria, with Escherichia coli accounting for 76% of all gram-negative bacteria, followed by Enteroccocus (30%), Bacteroides (24%) and Pseudomonas (20%) [8-9]. On the others hand, others authors states that obstruction is not an important factor in the causation of acute appendicitis, although it may develop as a result of the inflammatory process. Based on the evidence now available, it is believed that there are a number of an etiologies for appendicitis, each of which results in the intraluminal bacterial invasion of the appendicular wall, which is the final pathway [10].

Proportion of hyperbilirubinemia in patients with acute appendicitis

Several biomarkers have been studied for accuracy diagnosis of acute appendicitis among the recently reported include serum bilirubin. There is variation in serum bilirubin depending as patient has complicated or non-complicated appendicitis. A bilirubin level of 1.3g was found to be significantly related with a perforated appendix, with a positive predictive value of 93% and a negative predictive value of 96% in as study conducted by Ramasamy *et al.* [11] in India among patients done appendectomy. However, for patient with non-perforated appendix Ramasamy and colleagues observed a serum bilirubin of 0.9 mg with a positive predictive value of 27%, and a negative predictive value of 96.9%. Similar results were reported in India by Biradar *et al.* [12] where the mean bilirubin levels in patients diagnosed with acute appendicitis was 0.7 ± 0.4 mg/dL while in patients diagnosed with Appendiceal perforation was 0.8±0.2 mg/dl. In UK, the findings of D'Souza *et al.* [13] among patient presented with pain in right iliac fossa, reported that serum bilirubin can be used to discriminate appendicitis from others causes of pain in right iliac fossa such as PUD, ectopic pregnancy. Hyperbilirubinemia in appendicitis was explained by the fact that invasion of gram-negative bacteria through the appendis muscularis propria resulted in the direct invasion of or translocation of bacteria through the portal system and liver, impairing bilirubin excretion through the bile ducts through endotoxin action. In addition, E coli and bacteroides fragilis, the common isolated bacteria in appendicitis, were reported to induce cholestasis and hemolysis which may also be one the factor explaining hyperbilirubinemia in acute appendicitis [14]. Also, a complicated appendicitis patient may experience intestinal hypo motility and edema as a

result of severe inflammation, which can also lead to cholestasis.

Proportion of elevated PCT among patients with AA

Procalcitonin which is a prohormone of calcitonin , was reported to increase in acute appendicitis due to the fact that during the inflammatory process in acute appendicitis , there is releases of gram negative bacterial endotoxin which induce production of PCT by approximately 0.5 ng/ml per hour after a latency of about 2–3 hours and reaching a plateau after 6–12 hours [15]. Several studies has been conducted correlating the role of serum PCT in acute appendicitis as in China, Cui and colleagues [16] observed significant increase of serum procalcitonin in patient with acute appendicitis with a sensitivity of 0.62 (95% CI: 0.57–0.66) and a specificity of 0.86 (95% CI: 0.82–0.89). In addition, Cui and colleagues noted also that PCT was more accurate in diagnosing complicated appendicitis, with a pooled sensitivity of 0.89 (95% CI: 0.84–0.93), specificity of 0.90 (95% CI: 0.86–0.94). However, the findings of Cui and colleagues were from retrospective analysis and more focused in pediatrique population. Similar findings were reported by Yamashita et al.(2016) in Japan where a serum PCT more than 0.5 ng/ml was observed among patient diagnosed acute appendicitis. This was explained by the fact that in acute appendicitis there is bacterial translocation to the mesenteric lymph node or the portal vein which induce production of PCT which has a half-life of 24 to 30 hours [15]. Similar findings were reported by Joseph et al., (2020) in a systematic review conducted in Dundee university in UK where serum procalcitonine was at more than 0.5 ng/ml in patients with acute appendicitis. Similar findings were reported by Chandel & Batt [17] in India where serum procalcitonin was a better biomarker than CRP to differentiate patient with acute abdomen due to appendicitis (0.5 ng./ml) to those with acute abdomen from non-appendicular origin (0.17 ng/ml) with high sensitivity of 95.65% and a specificity of about 100%. Furthermore, Chandel and colleagues noted that the serum procalcitonin test is a highly accurate diagnostic tool for acute appendicitis when used in conjunction with valid clinical signs and symptoms. However, the findings of Chandel and colleagues were from pediatric population only. Serum procalcitonin have shown also superiority to serum interleukin in prediction of acute appendicitis as in a study conducted by Haghi *et al.* [18] in Iran where The sensitivity and specificity of procalcitonin versus IL-6 for diagnosing acute appendicitis were 65% and 80% vs. 76% and 55%, respectively. In Uganda, there is limited literature which have been interested on diagnosis of acute appendicitis using serum procaclitonine.

Correlation of hyperbilirubinemia and elevated procalcitonine in severity of acute appendicitis

There are several complications related to acute appendicitis which are extending form local(abscess, perforation), local regional(local peritonitis, appendicular mass) to general (generalized peritonitis) [19]. Various scoring systems and tools have been used to predict severity of acute appendicitis based on clinical features, physical examination, and laboratory investigations. Serum hyperbilirubinemia and Procalcitonine have currently been used as better biomarker predicting severity of acute appendicitis as observed in several studies. In Spain, according to Gavela et al. [20], a PCT threshold of 0.18 ng/mL provided a sensitivity of 97%, specificity of 80%, positive predictive value of 72%, and negative predictive value of 89.3% for the diagnosis of peritonitis in patients with acute appendicitis. Similar findings were reported by [21] in Greece, where A PCT value of > 0.5 ng/ml was found to be indicative of perforation or gangrene with 73.4% sensitivity and 94.6% specificity among patient with acute appendicitis. However, the findings of Nikolaides and colleagues were from pediatric population. Similar results were reported by Sevinç et al. [22] in Turkey, where a cut off of 1.0 mg/dl for bilirubin were predictive of perforated appendix(sensitivity: 19.1%; specificity: 92.4%; OR: 2.96. However, the findings of Sevinç and colleagues were from retrospective review among patient who underwent appendectomy. Elevated directed bilirubin was reported also as predictor of complicated appendicitis in a study conducted by Tombalak and colleagues.[23] in Turkey where a perforated appendix was found to be associated with high serum bilirubin above 1.0 mg/dl.

Clinical Implications

The clinical implications of serum bilirubin and procalcitonin levels in the diagnosis of acute appendicitis are multifaceted and offer potential advancements in patient care pathways and management strategies.

Improved Diagnostic Accuracy: Integrating serum biomarkers, specifically bilirubin and procalcitonin, into the diagnostic algorithms of acute appendicitis holds promise in enhancing diagnostic accuracy. These biomarkers, when used in conjunction with clinical assessments and imaging studies, could aid clinicians in making more informed and timely decisions, potentially reducing misdiagnoses and unnecessary surgical interventions.

Risk Stratification and Severity Assessment: Elevated serum bilirubin levels have been associated with the severity and progression of

inflammatory processes in appendicitis, suggesting a potential role in risk stratification. Similarly, procalcitonin levels have shown correlation with the severity of bacterial-induced inflammation, aiding in assessing the severity of the condition and guiding appropriate management strategies.

Potential for Early Intervention: Utilizing serum biomarkers may facilitate earlier recognition of acute appendicitis, allowing for timely intervention and possibly reducing the risk of complications associated with delayed diagnosis or perforation.

Optimization of Resource Utilization: Incorporating serum biomarkers into diagnostic protocols could potentially optimize resource utilization by reducing unnecessary imaging studies or hospital admissions in cases where clinical uncertainty exists, thereby streamlining healthcare resources.

Guiding Follow-up and Prognostication: Monitoring changes in serum biomarker levels during the clinical course of acute appendicitis could offer insights into treatment response and prognosis, aiding in decision-making regarding further interventions or follow-up assessments.

Enhancing Clinical Decision-Making: While not standalone diagnostic tools, serum bilirubin and procalcitonin levels, when used in combination with other clinical parameters, can complement the diagnostic process, providing additional information for more accurate clinical decision-making.

Future Research and Clinical Protocols: The exploration of serum biomarkers in acute appendicitis warrants further research to establish standardized protocols for their use in clinical settings. Future studies should focus on refining cutoff values, assessing their utility in specific patient populations, and conducting prospective trials to validate their role in routine clinical practice. Leveraging serum bilirubin and procalcitonin levels in the diagnosis of acute appendicitis presents promising clinical implications that could potentially enhance diagnostic accuracy, aid in risk stratification, and guide more effective and timely interventions, thereby optimizing patient care and outcomes.

CONCLUSION

The evaluation of serum biomarkers, particularly serum bilirubin and procalcitonin, in the diagnosis of acute appendicitis represents a significant stride towards enhancing diagnostic precision and refining clinical decision-making in this prevalent surgical condition. The synthesis of existing literature suggests a potential association between elevated serum bilirubin levels and the presence of acute appendicitis. Similarly, procalcitonin has exhibited promise as a marker correlating with the severity of bacterial-induced inflammation in appendicitis. These findings underscore the potential clinical utility of these serum biomarkers in aiding the diagnostic process. The integration of serum bilirubin and procalcitonin levels into the diagnostic armamentarium for acute appendicitis holds substantial promise. By augmenting traditional clinical assessments and imaging studies, these biomarkers have the potential to refine diagnostic accuracy, assist in risk stratification, and guide appropriate management strategies. Moving forward, future research endeavors should focus on refining cutoff values, establishing standardized protocols for serum biomarker use, and conducting rigorous prospective studies in diverse patient cohorts. Such efforts will be instrumental in elucidating the precise diagnostic roles of serum bilirubin and procalcitonin, paving the way for their seamless integration into routine clinical practice. While further investigations are warranted, the exploration of serum biomarkers offers exciting prospects in improving diagnostic precision and patient care strategies for acute appendicitis. Their potential to expedite diagnosis, aid risk stratification, and optimize treatment pathways underscores their value as adjunctive tools in the clinical armamentarium for this common surgical emergency.

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