

Diagnostic Efficacy of Procalcitonin, C-reactive Protein, and Bilirubin in Acute Appendicitis and its Complications

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Abstract

Introduction: Acute appendicitis is the most common abdominal emergency encountered in general surgery.

Purpose: In this study, diagnostic accuracy of Procalcitonin, C-Reactive Protein (CRP), Bilirubin as a biomarker in acute appendicitis and its complications have been analyzed. 82 patients with clinical diagnosis of acute appendicitis or appendiceal perforation were studied. Method: The serum Procalcitonin, C-Reactive Protein (CRP), and Bilirubin were carried out in all the patients. The diagnosis was confirmed USG reports and intra-operative findings and those differing from the pre-operative diagnosis were excluded from the study.

Results: 53 patients (64.6%) were males while the remaining 29 patients (35.4%) were females. The mean age in our study population (82 patients) was 25.9 ± 11.5 years. The average age in females 27.8 ± 12.6 years was slightly higher than males 24.9 ± 10.8 years. 65 patients (79.3%) were diagnosed as acute appendicitis pre-operatively while 17 patients (20.7%) were diagnosed with Appendiceal perforation. The mean level of procalcitonin, C-Reactive Protein (CRP), Bilirubin were found to have increased in both acute appendicitis and appendiceal perforation. The mean procalcitonin levels in patients diagnosed with acute appendicitis was 2.2 ± 0.9 ng/mL (range, 0.8– 3.4 ng/mL) while in patients diagnosed with Appendiceal perforation was 2.7 ± 0.8 ng/mL (range, 1.5– 4.6 ng/mL). The mean bilirubin levels in patients diagnosed with acute appendicitis was 0.7 ± 0.4 mg/dL (range, 0.09– 1.6 mg/dL) while in patients diagnosed with Appendiceal perforation was 0.8 ± 0.2 mg/dL (range, 0.5– 1.2 mg/dL). The mean CRP levels in patients diagnosed with acute appendicitis was 1.4 ± 0.5 mg/dL (range, 0.5– 2.2 mg/dL) while in patients diagnosed with Appendiceal perforation was 1.8 ± 1.1 mg/dL (range, 0.9– 6.0 mg/dL). Sensitivity of Procalcitonin, C-Reactive Protein (CRP) and bilirubin in predicting acute appendicitis and appendiceal perforation diagnosis was 64.6%, 41.54% and 16.9% respectively.

Conclusion: The findings indicate that procalcitonin is a useful marker of acute appendicitis with abscess and/or perforation than CRP and Serum bilirubin.

Key words: Acute appendicitis, Appendiceal perforation, C-reactive protein, Hyperbilirubinemia, Procalcitonin

INTRODUCTION

Acute appendicitis is the most common abdominal emergency encountered in general surgery. The diagnosis of appendicitis can be difficult, occasionally taxing the

skills of even the most experienced surgeon. Admiss^[1] estimated the incidence of acute appendicitis in the United States population to be 11 cases per 10,000 populations annually. The disease is slightly more common in males, with a male:female ratio of 1.4:1. In a lifetime, 8.6% of males and 6.7% of females can be expected to develop acute appendicitis. Young age is a risk factor, as nearly 70% of patients with acute appendicitis are < 30 years of age. The highest incidence of appendicitis in males is in the 10–14-year-old age group (27.6 cases per 10,000 population), while the highest female incidence is in the 15–19-year-old age group (20.5 cases per 10,000 population).

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Patients at extremes of age are more likely to develop perforated appendicitis. Overall, perforation was present in 19.2% of cases of acute appendicitis. This number was significantly higher, however, in patients under 5 and over 65 years of age. Although less common in people over 65-years-old, acute appendicitis in the elderly progress to perforation >50% of the time.^[1] In most of the cases, the diagnosis can be made clinically by assessing the symptoms and physical findings and confirmed by laboratory tests and ultrasonography (USG). However, diagnosis is difficult sometimes even after all these tests and in such doubtful cases either the diagnosis is missed or patients normal appendix is operated on, leading to an increase in mortality and morbidity.^[2] No reliably specific marker for acute appendicitis has been identified till now. A raised white cell count is not specific for appendicitis and although C-reactive protein (CRP) is commonly used in the assessment of suspected appendicitis, its specificity varies markedly between studies and may only significantly raise once appendiceal perforation takes place.^[3] Cases presenting with non-specific abdominal pain and acute appendicitis are extremely common in general surgery, accounting for about 75% of admissions due to acute abdominal complaints. Furthermore, the rate of negative appendectomies in these cases is about 30%, leading to increased morbidity and risk of incisional hernia. Whereas delayed diagnosis and treatment of patients with acute appendicitis may lead to several complications that are potentially life threatening, such as perforation, peritonitis, sepsis, small bowel obstruction, urinary retention, and abdominal abscess formation. Recently, elevation in serum bilirubin was reported, but the importance of the raised total has not been stressed in acute appendicitis and appendiceal perforation.

The endotoxin of *E. coli* has been shown *in vivo* to affect physiological bile flow, which led to the theory that hyperbilirubinemia may possess inferential potential in the preoperative early diagnosis of appendix perforation^[4] elevated serum bilirubin level will help in the early and accurate diagnosis of acute appendicitis and in predicting its serious complications, most importantly the perforation. It is hypothesized that an association exists between hyperbilirubinemia, CRP, and procalcitonin (PCT) in acute appendicitis and its complications such as appendicular perforation. In the context of above discussion, there is a need for the study to conclude whether the serum bilirubin and CRP and PCT can be considered as a new laboratory marker to aid in the diagnosis of acute appendicitis and if so, does it have the predictive capacity to warn us about appendicular perforation. In this paper, the diagnostic accuracy of PCT, CRP, and bilirubin as a biomarker in acute appendicitis and its complications was examined.

MATERIALS AND METHODS

A total of 82 patients admitted in Shri B. M. Patil Medical College Hospital and Research Center, Vijayapura, diagnosed with acute appendicitis during the period of September 2016–August 2018 will be taken for the study. Patient suspected clinically to have acute appendicitis and its complications such as perforated appendicitis and appendicular abscess are evaluated with PCT, CRP, and bilirubin levels and their diagnostic accuracy was evaluated. Patients with history of jaundice or liver disease, acquired or congenital biliary diseases and HbsAg and HCV positive were excluded from the study. The following tests were carried out for patients diagnosed as acute appendicitis or perforation.

Investigation:

1. Complete blood count.
2. Serum bilirubin.
3. CRP.
4. Seropositivity for HbsAg and HCV.
5. USG of abdomen and pelvis.
6. Procalcitonin.

Chi-square (χ^2) test was used for association between two categorical variables.

The difference of the means of analysis variables between two independent groups was tested by unpaired *t* test. Sensitivity and specificity was analyzed to check relative efficiency. If $P < 0.05$, then the results were considered to be statistically significant otherwise; it was considered as not statistically significant. Data were analyzed using SPSS software v.23.0. and Microsoft office 2007.

RESULTS

Results show that out of the 82 patients enrolled for the study, 53 patients (64.6%) were males while the remaining 29 patients (35.4%) were females. The mean age in our study population (82 patients) was 25.9 ± 11.5 years. Out of 82 patients, 65 patients (79.3%) were diagnosed as acute appendicitis preoperatively while 17 patients (20.7%) were

Table 1: Comparison of mean study parameters by clinical diagnosis

Parameters	Acute appendicitis	Appendiceal perforation	P value
	Mean±SD	Mean±SD	
Procalcitonin	2.2±0.9	2.7±0.8	0.317
Total bilirubin	0.7±0.4	0.8±0.2	0.238
CRP	1.4±0.5	1.8±1.1	0.078

CRP: C-reactive protein

diagnosed with appendiceal perforation. The mean level of PCT, CRP, and bilirubin was found to have increased in both acute appendicitis and appendiceal perforation [Table 1]. On USG, 68 patients (82.9%) were diagnosed as acute appendicitis while 14 patients (17.1%) were reported as normal USG findings. None, however, were diagnosed as appendiceal perforation on USG.

According to Figures 1-3, among the patients diagnosed with acute appendicitis preoperatively ($n = 65$), 42 patients (64.6%) were found to have elevated PCT (>1.5 ng/mL) while only 23 patients (35.4%) had normal PCT levels (≤ 1.5 ng/mL). In patients diagnosed with appendiceal perforation ($n = 17$), 16 patients (94.1%) had elevated

PCT (>1.5 ng/mL). Thus, hyper PCT was found in most of the patients diagnosed with acute appendicitis (64.6%) or appendiceal perforation (94.1%). Among the patients diagnosed with acute appendicitis preoperatively ($n = 82$), 11 patients (16.9%) were found to have elevated bilirubin (>1.0 mg/dL) while only 54 patients (83.1%) had normal bilirubin levels (≤ 1.0 mg/dL). In patients diagnosed with appendiceal perforation ($n = 17$), 2 patients (11.8%) had bilirubin elevated (>1.0 mg/dL). Thus, hyper bilirubinemia was found in less number of the patients diagnosed with acute appendicitis (16.9%) or appendiceal perforation (11.8%). Among the patients diagnosed with acute appendicitis preoperatively ($n = 82$), 27 patients (41.5%) were found to have elevated CRP (>1.5 mg/dL) while only

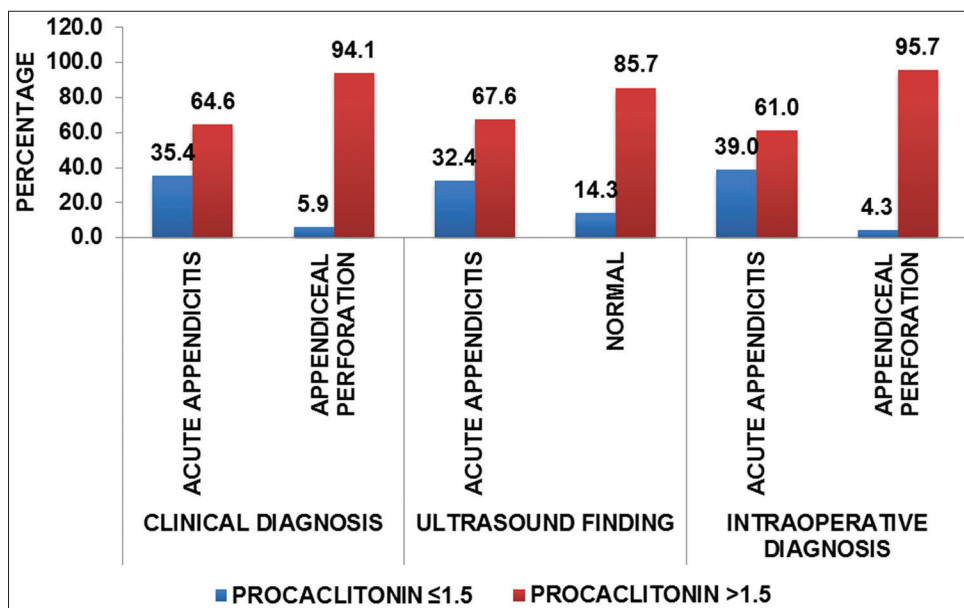


Figure 1: Levels of procalcitonin by study groups

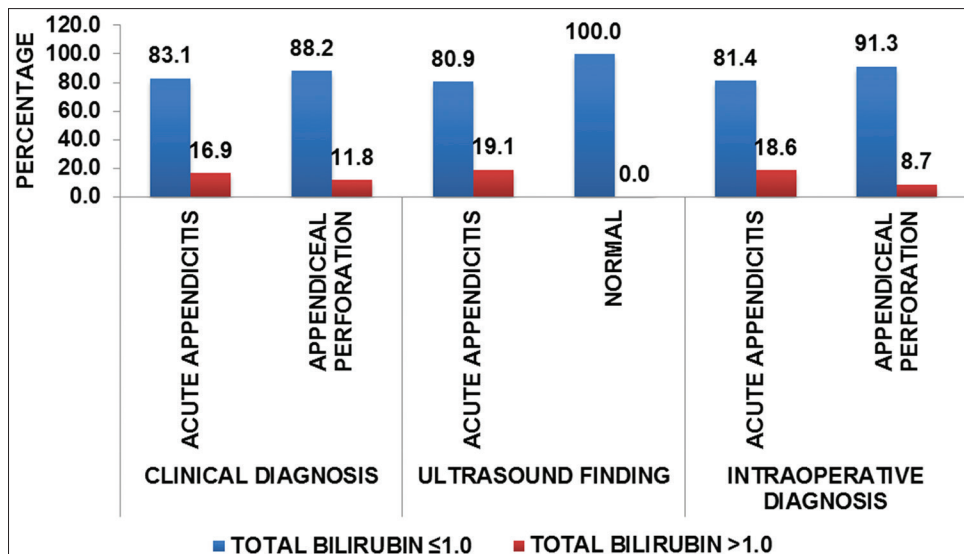


Figure 2: Levels of bilirubin by study groups

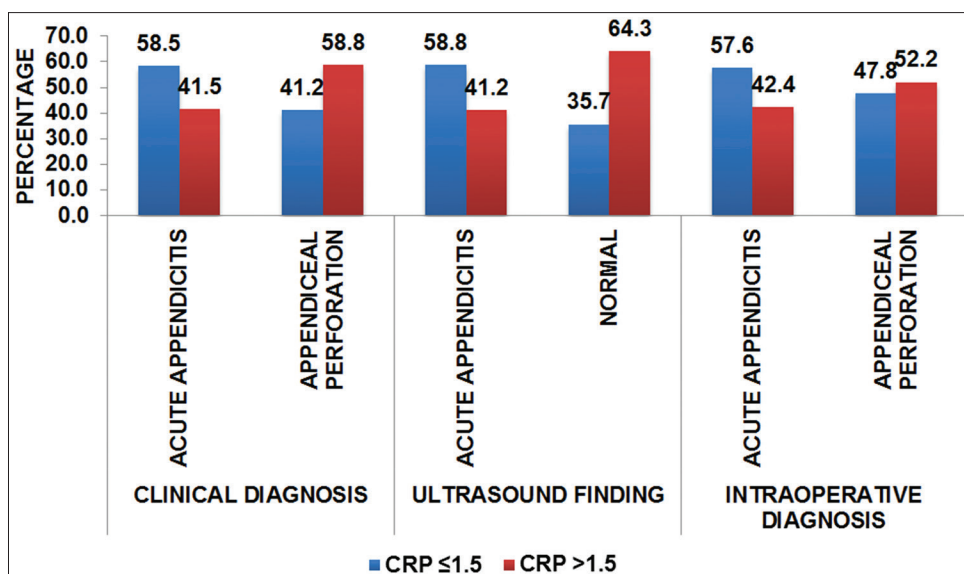


Figure 3: Levels of C-reactive protein by study groups

38 patients (58.5%) had normal CRP levels (≤ 1.5 mg/dL). In patients diagnosed with appendiceal perforation ($n = 17$), 10 patients (58.8%) had CRP elevated (> 1.5 mg/dL). Thus, hyper CRP was found in most of the patients diagnosed with acute appendicitis (41.5%) or appendiceal perforation (58.8%). The total leukocyte count was found elevated in just 49 patients (59.8%) of the total 82 patients. The mean of TLC count in all patients was $11922.6 \pm 2572.8/\text{mm}^3$ (range, 7692–12380.79/ mm^3), in which the highest percentage constituted neutrophils with 82.65% followed by 10.92% by lymphocytes.

The sensitivity, specificity, positive predictive value, negative predictive value, and odds ratio were calculated in Table 2. Sensitivity of PCT, CRP, and bilirubin in predicting acute appendicitis and appendiceal perforation diagnosis was 64.6%, 41.54%, and 16.9%, respectively.

DISCUSSION

Acute appendicitis is the most common cause of “acute abdomen” in young adults. Appendectomy is the most frequently performed urgent abdominal operation and is often the first major procedure performed by a surgeon in training. About 8% of people in western countries have appendicitis at some time in their lifetime.^[5] The peak incidence of acute appendicitis is in the second and third decade of life. It is relatively rare in infants and becomes increasingly common in childhood and early adult life. The incidence of appendicitis is equal in males and females before puberty. In teenagers and young adults, the male – female ratio increases to 3:2 at age. The lifetime rate of appendectomy is 12% for men and 25% for women, with approximately 7% of all people

Table 2: Diagnostic efficacy of procalcitonin total bilirubin and CRP

Diagnostic efficacy	Procalcitonin (%)	Total bilirubin (%)	CRP (%)
Sensitivity	64.62	16.92	41.54
Specificity	5.88	88.24	41.18
PPV	72.41	84.62	72.97
NPV	4.17	21.74	15.56
Accuracy	52.44	31.71	41.46
Odds ratio	0.11	1.53	0.50

CRP: C-reactive protein

undergoing appendectomy for acute appendicitis during their lifetime.^[6,7] Obstruction of the lumen is believed to be the major cause of acute appendicitis. Fecoliths are the usual cause of obstruction. Less-common causes are hypertrophy of lymphoid tissue, tumors, and intestinal parasites.^[8] The bacteriology of normal appendix is similar to that of normal colon. The principal organism seen in normal appendix, in acute appendicitis, and in perforated appendicitis is *Escherichia coli* and *Bacteroides fragilis*. However a wide variety of both the diagnosis of acute appendicitis is essentially clinical; however, a decision to operate based on clinical suspicion alone can lead to the removal of normal appendix in 15–30% of cases. The premise that it is better to remove a normal appendix than to delay diagnosis does not stand up to close scrutiny, particularly in the elderly. Hence, the diagnosis of appendicitis still remains a dilemma in spite of the advances in various laboratory and radiological investigations. A new tool to help in the diagnosis of acute appendicitis would thus be welcome. Serum PCT concentrations are positively correlated with severity of infection. Adequate antibiotic treatment leads to decreasing PCT levels. Serum PCT level elevation will help in the accuracy of clinical diagnosis of acute

appendicitis and more importantly help in foreseeing and preventing impending complications of acute appendicitis. Patients with appendiceal perforation had high levels of PCT, CRP and bilirubin as compared to that of acute appendicitis. So we infer that, patients with features suggestive of appendicitis with high range of PCT are more susceptible of having appendiceal perforation than those with normal or slightly elevated level. Sand *et al.* in his study found the mean bilirubin levels in patients with appendiceal perforation to be significantly higher than those with a non-perforated appendicitis. Sensitivity of PCT, CRP, and bilirubin in predicting acute appendicitis and appendiceal perforation diagnosis was 64.6%, 41.54%, and 16.9%, respectively. Less specificity for PCT was found due to less number of appendicitis cases with normal level. Similarly, positive predictive value, negative predictive value, and accuracy of PCT, CRP, and bilirubin in predicting acute appendicitis and appendiceal perforation diagnosis were highest for PCT followed by CRP and bilirubin. The odds ratio was calculated to be 0.11 for PCT, 0.5 for CRP, and 1.53 for bilirubin. The sensitivity in our study was at par with Kafetzis *et al.*^[8] in which, he found the sensitivity and specificity in his study of hyper PCT for predicting appendiceal perforation to be 73.4% and 94.6%, respectively.

CONCLUSIONS

The findings indicate that PCT is a useful marker of acute appendicitis with abscess and/or perforation than CRP and serum bilirubin. Serum PCT levels appear to be a promising

new laboratory marker for diagnosing acute appendicitis; however, diagnosis of appendicitis remains essentially still clinical. Its levels come out to be a credible *aid* in diagnosis of acute appendicitis and would be helpful investigation in decision-making. Patients with clinical signs and symptoms of appendicitis and with hyper PCT should be identified as having a higher probability of appendiceal perforation suggesting, serum PCT levels have a predictive potential for the diagnosis of acute appendicitis and appendiceal perforation.

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