Original Article

A study of C-reactive protein and D-dimer in patients of appendicitis

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Abstract

Background: Acute appendicitis is the most common abdominal surgical emergencies across the world. **Objective:** The aim of this study was to determine the value of C-reactive protein (CRP) and D-dimer as diagnostic markers of acute appendicitis. **Study Design:** It was a Prospective observational clinical study. **Method:** The present study was carried out in General Surgical Unit of University Hospital, Institute of Medical Sciences, Banaras Hindu University, Varanasi from September 2015 to July 2017. All data including patient's demography, clinical examination, laboratory test results, and appendix histology were summarized. Receiver operating characteristic (ROC) curve of TLC, CRP, and D-dimer was analyzed. **Results:** Total 65 patients who presented with periumbilical pain or pain in right iliac fossa (RIF) were included in the study. The mean age of the patients was 31.18 ± 14.59 years (range: 15 to 65 years) with male : female ratio was 2.21:1. The most common symptom was pain in right iliac fossa (100%) followed by nausea/vomiting (69.2%). The mean leucocyte count, CRP, and D-dimer levels were significantly raised in appendicitis group as compared to negative appendicectomy group ($P = 0.025$, $P = 0.036$, and $P = 0.025$, respectively). The receiver operating characteristic (ROC) curve for TLC was not helpful for differentiating between appendicitis and negative appendicitis ($P = 0.073$). In addition, D-dimer was helpful for differentiating between appendicitis and negative appendicitis ($P = 0.002$). However, CRP was also found to be helpful for differentiating between appendicitis and negative appendicitis ($P = 0.030$). **Conclusion:** The diagnosis of appendicitis remains multifactorial and biochemical markers like CRP and D-dimer may help to guide the surgeon in the decision making.

Keywords: Appendicitis, C-reactive protein, D-dimer

Introduction

Acute appendicitis is the most common abdominal surgical emergencies and worldwide appendicectomy is the most frequently performed emergency procedure.[1-3] The accuracy of the clinical diagnosis is approximately 80%, which corresponds to a negative appendectomy rate of around 20%,[4] but in the past few years, several inflammatory markers have been used for the diagnosis of acute appendicitis. Leukocyte count and C-reactive protein (CRP) are the most commonly used laboratory tests and in recent years, D-dimer has been used as a novel biomarker for the diagnosis of acute appendicitis.[5] The aim of this study was to determine the value of C-reactive protein (CRP) and D-dimer as diagnostic markers of acute appendicitis.

Material and Methods

This is a prospective study enrolled 65 patients which was done after obtaining ethical approval from the Ethical Committee of Institute of Medical Sciences, Banaras Hindu University from August 2015 to July 2017. Patients with age group < 15 and > 65 years, pregnant women, and patients having history of

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previous abdominal surgery or diagnosis of appendicular lump or other abdominal conditions such as perforation peritonitis, ovarian malignancy, pancreatitis, etc., were excluded from the study. The diagnosis of acute appendicitis was based on the clinical examination findings of acute abdomen, laboratory tests, and abdominal ultrasonography or computed tomography.

Blood samples were taken immediately after admission for measuring leukocyte count, CRP, and D-dimer levels. The patient was then subjected to laparoscopic/open appendicectomy and the specimen was sent for histopathological examination. After that, patients were divided into 2 groups according to appendix histology result. Group 1 includes patients with negative appendicectomy, i.e. normal appendix on histology ($n = 10$) and group 2 includes patients with appendicitis on histology ($n = 55$).

Patients' demographic profile was recorded. A detailed history, abdominal examination, and signs and symptoms were also recorded.

All these data were statistically analyzed using SPSS 16.0 software Windows version (Inc., Chicago, USA). Continuous variables were expressed as mean and standard deviation or range. Student's t-test was used to analyze the difference between means of variables two groups. Receiver operating characteristic (ROC) curve of TLC, CRP, and D-dimer was analyzed. P value < 0.05 was considered as statistically significant.

Results

Of 65 patients, 46 (70.8%) were male and 19 (29.2%) were female, and the mean age was 31.18 ± 14.59 years (range: 15 to 65 years). The most common symptom was pain in right iliac fossa which was present in all patients (100%) followed by nausea/vomiting in 45 (69.2%). Rovsing's sign was present in 45 (69.2%) patients and other common sign was Obturator sign which was present in 35 (53.8%) cases. Ten (15.4%) patients were having Modified Alvarado scoring (MAS) between 1 and 4 (Appendicitis unlikely), 27 (41.6%) were having MAS between 5 and 6 (Appendicitis possible), and 28 (43.0%) patients were having MAS between 7 and 9 (Appendicitis definitive). Elevated leucocyte count was present in 53 (81.5%) patients while elevated CRP level was present in 59 (90.8%) and raised D-Dimer level was present in 47 (72.3%) patients. The General characteristics of patients are shown in [Table 1].

On ultrasonography, 54 (83%) patients were diagnosed as acute appendicitis. CECT abdomen was done in only 12 patients, of these 10 (83.3%) had the diagnosis of acute appendicitis. On histopathology, 13 patients (20.0%) were acute appendicitis, 7 (10.8%) patients were acute on chronic appendicitis, 35 (53.8%) patients were chronic appendicitis, and 10 (15.4%) patients were normal appendix. According to histopathology findings, patients were divided into 2 groups: Group 1 includes patients with negative appendicectomy, i.e. normal appendix on histology ($n = 10$) and group 2 includes patients with appendicitis on histology ($n = 55$).

Table 2 describes the comparison of mean leucocyte count, CRP, and D-dimer levels between negative appendicectomy and histologically confirmed appendicitis group. The mean leucocyte count, CRP, and D-dimer levels were significantly raised in appendicitis group as compared to negative appendicectomy group ($P = 0.025$, $P = 0.036$, and $P = 0.025$, respectively).

The receiver operating characteristic (ROC) curve for TLC was not helpful for differentiating between appendicitis and negative appendicitis ($P = 0.073$). In addition, D-dimer was helpful for differentiating between appendicitis and negative appendicitis ($P = 0.002$). However, CRP was also found to be helpful for differentiating between appendicitis and negative appendicitis ($P = 0.030$). The area under the curve (AUC), cut off value, and sensitivity and specificity of inflammatory markers are shown in Table 3 and Figure 1.

Discussion

Nowadays even with the use of novel diagnostic markers, the diagnosis of appendicitis is still a major problem worldwide. It may be related with the perforation and complications. Misdiagnosis of acute appendicitis can lead to unnecessary surgery. Studies published in the literature reported a 9%–20% negative appendectomy rate.[6-8]

Table 1: General characteristics of patients

Characteristics	Number (%)
Age (Years)	31.18±14.59
Sex (Male/Female)	46 (70.8) / 19 (29.2)
Pain in right iliac fossa	65 (100)
Nausea/Vomiting	45 (69.2)
Fever	24 (36.9)
Anorexia	36 (55.4)
Rovsing's sign	45 (69.2)
Obturator sign	35 (53.8)
Psoas sign	13 (20.0)
Modified Alvarado scoring	
1-4 (Appendicitis unlikely)	10 (15.4)
5-6 (Appendicitis possible)	27 (41.6)
7-9 (Appendicitis definitive)	28 (43.0)
Raised Leucocyte count (>7000)	53 (81.5%) [mean±SD] 10300.00±3728.33
CRP (>3 mg/l)	59 (90.8%) [mean±SD] 115.24±77.01
D-dimer (>5 mg/l)	47 (72.3%) [mean±SD] 2.57±2.27

Table 2: Comparison of inflammatory markers between negative appendicectomy and histologically confirmed appendicitis group

Inflammatory markers	negative appendicectomy group (n=10)	Histologically confirmed appendicitis group (n=55)	P
Total leukocyte count	7485.80±912.660	10300.00±3894.069	0.025
CRP	75.03±55.094	127.42±73.576	0.036
D-dimer	1.10±.761	2.84±2.354	0.025

Table 3: Receiver operating characteristic (ROC) curve analysis of TLC, CRP, and D-dimer

Test Result Variable(s)	Area	Cut-off value	*P*	Sensitivity	Specificity
TLC	0.679	8569.00	0.073	63.6	50.0
CRP	0.716	87.63	0.030	61.8	60.0
D-dimer	0.817	1.15	0.002	72.7	70.0

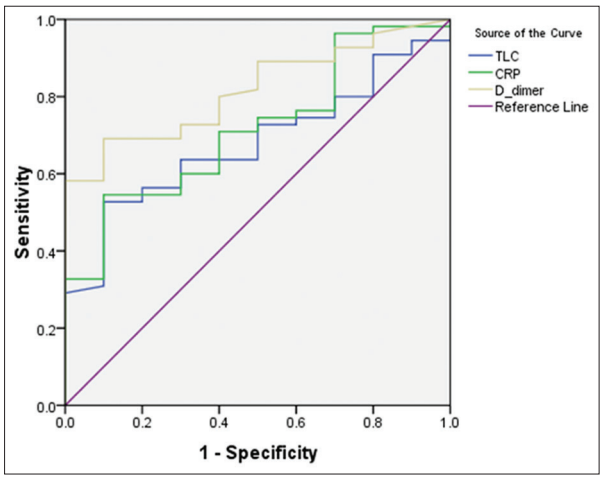

Figure 1: Receiver operating characteristic (ROC) curve

Leukocyte count is the most commonly used laboratory test for the diagnosis of acute appendicitis. It is simply implemented in routine practice and has an advantage of cost-effectiveness, but has partial sensitivity and specificity.[9] Although it is not the main objective of this study, the sensitivity and specificity of leukocyte count were found to be 63.6% and 50.0%, respectively. But leukocyte level was significantly higher in histologically confirmed appendicitis group when compared to negative appendicectomy group ($P = 0.025$). The low specificity of leukocyte count seems to be a not useful diagnostic marker of acute appendicitis. Various inflammatory markers, including CRP, D-dimer, phospholipase A2, and serum amyloid A have been used to increase diagnostic accurateness in acute appendicitis.[10-12] CRP and D-dimer are inflammatory markers, which are raised in infective and septic conditions but also used for diagnosis of acute appendicitis.

CRP is frequently used to guide the clinical assessment of acute appendicitis. It is an acute-phase reactant that synthesized in liver in response to the tissue injury. The measurement of CRP is practical, easily applicable, and cost-effective. The previous studies have demonstrated a sensitivity of 40% to 94% and a specificity of 38% to 87% for CRP measurement.[13-15] In our study, the sensitivity and specificity of CRP were 61.8%, and 60.0%, respectively. These results showed that CRP was a useful marker for the diagnosis of acute appendicitis. On the other hand, this study also showed that CRP was significantly increased in patients with acute appendicitis. CRP level was significantly higher in histologically confirmed appendicitis group when compared to negative appendicectomy group ($P = 0.036$). Meta-analytic study of Hallan and Asberg showed that CRP had moderate accuracy in diagnosing acute appendicitis.[16] When compared to PCT and D-dimer, CRP was found to have higher sensitivity and diagnostic accuracy for acute appendicitis. Some authors have reported that CRP can predict the severity of appendicitis.[17,18] However, PCT and CRP levels are also important in differentiating between uncomplicated acute appendicitis with complicated acute appendicitis.[19] Therefore, the precise differential of acute appendicitis is essential for avoiding unnecessary risks of anesthesia and surgical intervention, and also lower hospitalization costs.[19]

It has been suggested that the obstruction of the appendix, subsequent ischemia, and the inflammatory response that accompanies these events could increase D-dimer level in blood. D-Dimer in normal ranges has proven to have high specificity in excluding important conditions such as disseminated intravascular coagulopathy, pulmonary embolism, or thromboembolism.[20]

In our study, the sensitivity and specificity of D-dimer were 72.7% and 70%, respectively. These results showed that D-dimer was also a useful marker for the diagnosis of acute appendicitis. On the other hand, this study also showed that D-dimer was significantly increased in patients with acute appendicitis. D-dimer level was significantly higher in histologically confirmed appendicitis group when compared to negative appendicectomy group ($P = 0.025$). Kaya *et al.* in their study found that the sensitivity and specificity of D-dimer were 67.4% and 75.0%, respectively.[21] This is consistent with the hypothesis that prolonged appendicitis presenting with parietal peritoneal irritation and irreversible ischemia of the walls lead to fibrinolysis and an increase in D-Dimer levels. High D-Dimer levels are suggestive of ongoing appendicitis; however, this is not a useful marker for diagnosis. D-Dimer has a high positive predictive value and could then be a good indicator of a risk of gangrenous or perforated appendicitis, which has more clinical significance. However, this is an unspecific marker which is also elevated in other causes of abdominal pain; therefore, this is not shown to be useful in the diagnosis of appendicitis.[21]

Conclusion

At present, the biomarkers commonly used in the evaluation for acute appendicitis are lacking in specificity. The overall proportion of conservative treatment in acute appendicitis is still low. These have led to continued efforts to explore the optimal diagnostic methods with ideal sensitivity and specificity for acute appendicitis to reduce the morbidity and also treatment costs. Although this study has some limitations, such as having a small sample size for negative appendicitis, we can conclude that CRP and D-dimer seem to be useful markers in the evaluation of acute appendicitis. Future studies with larger sample size would be beneficial to justify the role of D-dimer and CRP in acute appendicitis.

Ethical clearance

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Conflicts of interest

There are no conflicts of interest.

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