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Original Research Article

Diagnostic value of C-reactive protein as a predictor of complicated appendicitis like perforated/gangrenous appendicitis

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ABSTRACT

Background: Appendicitis is inflammation of appendix. Appendicitis remains the most common abdominal surgical emergency. There is no reliable specific marker for acute appendicitis and its complications. C- reactive protein is an acute phase reactant produced by the liver during the acute inflammation, which rises rapidly in presence of inflammation. CRP is a more sensitive and reliable indicator of inflammatory processes than ESR and leucocyte count. The aim of this study was to evaluate whether CRP predict the severity of appendicitis.
Methods: This study was hospital based, observational study. After history and clinical examination, patient underwent USG whole abdomen. Diagnosis of appendicitis was established. After that patient underwent routine blood investigations including, CRP. After confirming diagnosis of appendicitis, patients underwent appendectomy and biopsy of appendix was sent for histopathological examination.
Results: In our study, CRP value > 6.15mg/L has a sensitivity of 100.0% and a specificity of 54% in predicting complicated perforated or gangrenous appendicitis. The positive predictive value and negative predictive value of CRP were 100% and 61.54% respectively. The cut off level at around 6mg/dL needs to be handled carefully and a person with high CRP should undergo surgery immediately.
Conclusions: This study clearly suggested that CRP leads to precise prediction of the severity of acute appendicitis for treatment. A person with high CRP should undergo surgery immediately ures.

Keywords: C- reactive protein, Inflammation, Perforated/gangrenous appendicitis

INTRODUCTION

Appendicitis is a condition characterized by inflammation of appendix. The crude incidence of acute appendicitis was 86 per 100,000 per year. Although the incidence of nonperforated appendicitis was highest among adolescents and young adults (13-40 years of age), perforated appendicitis occurred at almost the same incidence in all sex and age groups. Acute abdominal pain is one of most common surgical emergencies. Appendicitis remains the most common abdominal surgical emergency with a life time prevalence of one in seven.[1] There is no reliable specific marker for acute appendicitis and is a reminder for the art of surgical diagnosis. It has been shown that appendicular abscess occurs in 2-6% and appendicular perforation in 25.8% of untreated patients.[2] In the continued absence of a 100% accurate test for appendicitis, any investigation that can contribute to its diagnosis is valuable.

C- reactive protein is an acute phase reactant, which rises rapidly in response to tissue injury and can be measured in serum 6-12hours after the onset of inflammation. Many studies have investigated the role of CRP in

improving the diagnosis of acute appendicitis, with promising results.[3-5] Tillet and Francis in 1930 first described C-reactive protein. They demonstrated that CRP could bind to C-polysaccharide of streptococcus in acute phase sera. CRP was discovered in the Avery laboratory of Rockefeller institute. C-reactive protein has been a measure of the acute phase reaction to inflammation for the last 20 years recently improved highly sensitive and standardized quantitative assay in serum and CSF have allowed a reevaluation of its potential as a diagnostic laboratory test.[4]

C-reactive protein is an abnormal serum glycoprotein produced by the liver during the acute inflammation. Because it disappears rapidly when the inflammation subsides its detection signifies the presence of a current inflammatory process. CRP production is a non-specific response to disease and it can never on its own be used as a diagnostic test. However if CRP results are interpreted in the light of full clinical information on the patient, then it can provide exceptionally useful information. CRP is a cyclic pentameric protein composed of five non-covalently bound, identical 23.5 kDa subunits, arranged in a doughnut-shaped polymer. The main function of this pentamer is related to the ability to bind biologically significant ligands in vivo. Tillet and Francis first described protein in 1930. They concluded that sera of patients suffering from acute and reactive infection precipitated with a non-proteic pneumococcus extract called C polysaccharide in the presence of calcium ions. The protein that caused this reaction was therefore called C reactive protein. The function of CRP is related to its role in the innate immune system. Similar to immunoglobulin IgG, it activates complement, binds to Fc receptors and acts as an opsonin for various pathogens. Interaction of CRP with Fe receptors leads to the generation of pro inflammatory cytokines that enhance inflammatory response. Unlike IgG, which specifically recognizes distinct antigenic epitopes, CRP recognizes altered self and foreign molecules based on pattern recognition.

Thus, CRP is thought to act as a surveillance molecule for altered self and certain pathogens. This recognition provides an early defence and leads to a pro inflammatory signal and activation of the humoral, adaptive immune system. CRP binds to molecular groups found on a wide variety of bacteria and act as an opsonin. CRP may also be important in the recognition of necrotic tissues. CRP binds to apoptotie cells, protects the cells from assembly of the terminal complement components, and sustains an anti-inflammatory innate immune response. In man, the only CRP gene coding sequence is found on Chromosome 1. The liver synthesizes CRP. Synthesis of CRP and other acute phase proteins by hepatocytes is modulated by cytokines. Interleukins l b and 6 and tumour necrosis factor are the most important regulators of CRP synthesis. After stimulation with IL-6, IL-l b, TNF and INF, the hepatocytes receive signals to start transcription of DNA coding for CRP. CRP begins to rise in bacterial infections within 4-6hours, peaks at 36-50hours, closely parallels acute response with 4-7 hour half-life, allowing to normal 3-7 days after the stimulus is withdrawn.

Why measure CRP?

Levels of CRP increase very rapidly in response to trauma, inflammation and infection and decrease rapidly with the resolution of the condition. Since an elevated CRP level is always associated with pathological changes, determination of CRP is of great value in diagnosis, treatment and monitoring of inflammatory conditions.

CRP is a more sensitive and reliable indicator of inflammatory processes than ESR and leucocyte count.

The serum CRP concentrations increase faster than that of ESR and falls very quickly when the condition subsides.

Rises in CRP are only one part of a number of intricate changes in serum proteins and enzymes but it happens to be one that is earliest to measure because it increases so dramatically.

- Normal values
- Adult serum: 0.07 to 8ug/ml
- Neonatal serum: 0.01 to 0.35ug/ml
- CRP in acute appendicitis.

Many studies have illustrated the role of CRP in improving the diagnosis of acute appendicitis.[3-5] CRP is a more sensitive and reliable indicator of inflammatory processes than ESR and leucocyte count. The serum CRP concentrations increase faster than that of ESR and falls very quickly when the condition subsides. False negative results generally only occur early in infective episodes. The aim of this study was to evaluate whether blood inflammatory markers predict the severity of appendicitis and to identify an independent marker for the surgical indication of acute appendicitis.

METHODS

This study was at the Department of General Surgery, SMS Medical College, Jaipur from 1 March 2017 to 30 November 2018. It was hospital based, observational study. Every eligible case of appendicitis admitting in department of surgery of SMS hospital were enrolled on first cum first basis. All the cases of appendicitis admitting in department of surgery of SMS medical college in the given period which meet the inclusion and exclusion criteria.

Inclusion criteria

- Admission to the emergency department with possibility of acute appendicitis.

- Informed consent.

Exclusion criteria

- HIV seropositivity,
- Patients on cortico steroid therapy,
- Patient with inflammatory bowel diseases or sickle cell disease.
- Waiting interval appendectomy.

Data collection method/methodology

Informed consent was taken from the patient in the pre designed format. Approval of the institutional ethical committee was taken to conduct the above study. Secrecy and confidentiality was maintained.

After history and clinical examination, patient underwent USG whole abdomen. Diagnosis of appendicitis was established. After that patient underwent routine blood investigations including, CRP.

After confirming diagnosis of appendicitis, patients underwent appendectomy and biopsy of appendix was sent for histopathological examination.

Statistical analysis

Continuous variables are presented as mean ±SD, and categorical variables are presented as absolute numbers and percentage. Data will checked for normality before statistical analysis. Normally distributed continuous variables will compared using the unpaired t test, whereas the MannWhitney U test will used for those variables that are not normally distributed. Categorical variables will be analyzed using either the chi square test or Fisher's exact test. For all statistical tests, a P value less than 0.05 will be considered statistically significant.

RESULTS

In the results, following three groups were categorized:

- Group A= Acute appendicitis
- Group G= Gangrenous appendicitis
- Group P= Perforated appendicitis

Total no. of cases was 120 in this study. Out of these 120 cases, 64 (54.33%), 12 (10.00%) and 44 (36.67%) cases were diagnosed acute, gangrenous and perforated appendicitis respectively on the basis of histopathological examination. Mean age of all patients was 25.88±10.13 years (range, 15-73) (Table 1). Male and female were 61(49.17%) and 59 (50.83%) cases respectively (Table 2).

Mean duration of symptoms was 3.85±2.51 days (range, 1-10). Mean of TLC was 12.18±5.08cu.mm. (range 3.8-26.0). Of the 120 patients, mean of hospital Stay was 3.38±1.1895 days (range, 2.0-6.0).

Table 1: Age statistics among the groups.

Total number of patients (n=120)	Mean age±SD (years)	P value	A vs. G	A vs. P	G vs. P
Group A (n=64)	24.25±8.61(range 15-48)				
Group G (n=12)	28.50±15.51(range 15-73)	0.162	0.375	0.220	0.954
Group P (n=44)	27.55±10.26 (range 15-50)				
Mean age of all patients (n=120) = 25.88 ±10.13 years (range 15-73)					

Table 2: Gender wise distribution of the cases.

Total number of patients (n=120)	Group A (n=64)	Group G (n=12)	Group P (n=44)
Female (n=59) (49.17%)	36 (56.25%)	5 (41.67%)	18 (40.91%)
Male (n=61) (50.83%)	28 (43.75%)	7 (58.33%)	26 (59.09%)

Table 3: Alvarado score.

Total number of patients (n=120)	Mean Alvarado score	P value	A vs. G	A vs. P	G vs. P
Group A (n=64)	6.86±2.21 (range 2.0-10.0)				
Group G (n=12)	8.75±0.97 (range 8.0-10.0)	0.000	0.002	0.000	0.842
Group P (n=44)	9.07±0.95 (range 6.0-10.0)				
Mean Alvarado score in all patients (n=120) =7.86±2.04 (range 2.0-10.0)					

Of the 120 patients, mean of Alvarado score was 7.86±2.04 (range, 2.0-10.0). 6.86±2.21 (range, 2.0-10.0), 8.75±0.97 (range, 8.0-10.0) and 9.07±0.95 (range, 6.0-10.0) were mean of Alvarado score of group A, group G and group P respectively. Significant difference was observed according to Alvarado score on ANOVA test (P=.000). On applying post Hoc Analysis to find the mean difference in two group separately, mean of Alvarado score was significantly higher in group G (P=.002) and P (P=.000) as compared to group A (Table 3).

Diagnostic performance of CRP for the differential diagnosis of complicated appendicitis (perforated and gangrenous) vs acute appendicitis without complication at the optimal cut-off points of the ROC analysis curves.

Receiver operating characteristic ROC for CRP showing (1-specificty) on the X axis and sensitivity on Y Axis exercising different cut off value to land at the choice the most apposite cut off point and which provide the greatest sum of sensitivity and specificity.

Table 4: ROC curve analysis (CRP).

Area under the curve				
Test result variable(s): CRP				
Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% confidence interval	
			Lower bound	Upper bound
0.802	0.039	0.000	0.726	0.878
The test result variable (s): CRP has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.				
a. Under the nonparametric assumption				
b. Null hypothesis: true area = 0.5				

Table 5: Sensitivity, specificity, 1-specificity of CRP.

Positive if greater than or equal To[a]	Sensitivity	1 - Specificity	Specificity	Youdon index
6.150	1.000	0.461	0.539	0.539

The optimum cut off value was obtained by points of test values that grants the highest Youden index that is (SN+SP)-1.

ROC curve analysis was performed to determine the optimal cut-off values of significant variables (CRP) detected between the two groups. A 6.15 UNIT area under the curve (AUC = 0.802) optimal cut-off value of CRP, with a sensitivity of 100.0% and a specificity of 54%, was determined with SE 0.039. This level is excellent to use as a screening test (Table 4) (Figure 1).

Table 5 illustrate sensitivity, specificity, 1-specificity (false positivity rate) of CRP at diverse level appropriate for perforated appendicitis. As the level of CRP increases, sensitivity lessens and specificity enhances.

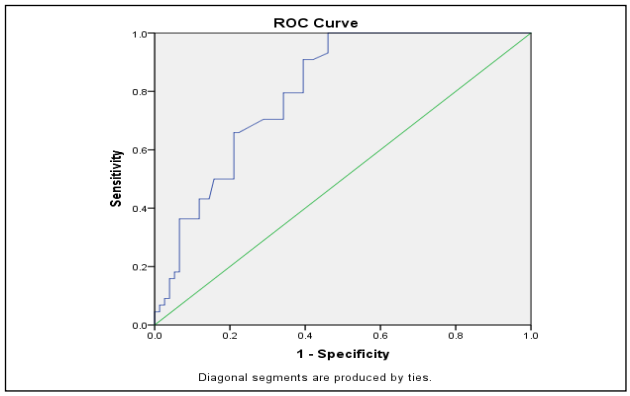

Figure 1: ROC curve analysis (CRP).

ROC plot of CRP in complicated appendicitis (perforated and gangrenous) vs acute appendicitis without complication.

DISCUSSION

The prospective, observational study was conducted in Department of Surgery, SMS Medical College and Hospital, Jaipur from 1 March 2017 to 30 November 2018. After inclusion and exclusion criteria, total 120 patients of appendicitis were included in this study. All the patients underwent emergency open appendectomy by grid-iron incision.

Of the 120 cases, 64 (54.33%) patients, 12 (10.00%) patients and 44 (36.67%) patients were diagnosed acute, gangrenous and perforated appendicitis respectively on the basis of histopathological examination.

In our study, mean age of all patients was 25.88±10.13 years (range, 15-73). Mean duration of symptoms was 3.85±2.51 days (range, 1-10). Mean TLC of all patients was 12.18±5.08 cu.mm. (range 3.8-26.0). Mean neutrophils count (%) was 75.94±12.27 (range, 40.0-95.0).

Of the 120 patients, mean of Alvarado score was 7.86±2.04 (range, 2.0-10.0). 6.86±2.21 (range, 2.0-10.0), 8.75±0.97 (range, 8.0-10.0) and 9.07±0.95 (range, 6.0-10.0) were mean of Alvarado score of Group A, Group G and Group P respectively. Significant difference was observed according to Alvarado score on ANOVA test (p=0.000). On applying post Hoc Analysis to find the mean difference in two group separately, Mean Of Alvarado Score was significantly higher in Group G (p=0.002) and P (p=0.000) as compared to Group A. Ghag GS et al, concluded in their study that 40% of the patients have the score 6 or 7. This represents high likelihood for appendicitis. 56.66% of patients had the Alvarado score as 8 or 9. A high Alvarado score amongst

the study group indicates complicated, perforated appendicitis. The difference in the number of subjects having higher Alvarado score between patients having perforated and non-perforated appendicitis was found to be statistically significant (p value 0.038). That implies that patients with perforated appendicitis always has significantly high Alvarado score. Alvarado score is best preoperative determinant of appendicitis and can predict the likelihood of perforation in select cases.[6] This findings regarding to Alvarado score are similar to this study. These results are also comparable to those reported by Dey S Jawaid A, Baidya N, Chan MY, and Khan I.[7-11]

Of the 120 patients, mean of hospital Stay was 3.38±1.1895 days (range, 2.0-6.0). We can infer that higher Alvarado score are observed in cases of acute appendicitis with complications like perforated or gangrenous appendix.

ROC curve analysis was performed to determine the optimal cut-off values of significant variables (CRP) detected between the two groups. A 6.15mg/L area under the curve (AUC = 0.802) optimal cut-off value of CRP, with a sensitivity of 100.0 % and a specificity of 54 %, was determined with SE 0.039. This level is excellent to use as a screening test. The positive predictive value and negative predictive value of CRP were 100% and 61.54% respectively.

Gurleyik et al, noted a CRP sensitivity of 96.6% in 87 of 90 patients with histologically proven disease.[12] Similarly, Shakhatreh (2000) found a CRP sensitivity of 95.5% in 85 of 89 patients with histologically proven appendicitis.[3] Asfar et al, reported a CRP sensitivity of 93.6% in 78 patients undergoing appendectomy.[4]

Kyriakidis AV, in their study concluded that in acute appendicitis the values of CRP could be normal or slightly elevated at the beginning of the disease (first hours) and in cases of gangrenous or perforated appendicitis CRP values are almost always significantly elevated. When WBC and CRP values are normal, acute appendicitis is rarely the diagnosis for right lower quadrant pain.[13]

Lai CY, studied that high CRP levels could possibly predict the diagnosis of complicated appendicitis and facilitate more appropriate surgical care.[14]

Tarleker S et al, studied that elevated CRP has a higher sensitivity (100%) for complications of acute appendicitis than specificity. The cut off level at around 6mg/dL needs to be handled carefully and may need much higher patient number to reach the confidant level.[15] Cut-off value of CRP in our study is near to this study.

Ahmed N concluded in his study that C reactive protein greater than 48mg/lit is an indication of perforated appendix and when the surgeon is in fix whether to go conservatively or apply some intervention; CRP can be a good diagnostic aid.[16] In this study of 120 case, there was no mortality.

CONCLUSION

Our study concluded that CRP value >6.15mg/L has a sensitivity of 100.0% and a specificity of 54% in predicting complicated perforated or gangrenous appendicitis.

This study clearly suggested that CRP leads to precise prediction of the severity of acute appendicitis for treatment. Elevated CRP has a higher sensitivity for complications of acute appendicitis than specificity. The cut off level at around 6mg/dL needs to be handled carefully and may need much higher patient number to reach the confidant level. If clinical symptoms and image examinations indicate that a person has appendicitis, a person with high CRP should undergo surgery immediately.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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