



Role of Serum C-Reactive Protein Levels in Diagnosis of Acute Appendicitis

Authors

**Dr Bhagwan.C. Balagopal¹, Dr Shilpy Gangawala², Dr Lohith Shetty Raju³
Dr Rewanth R Katamreddy⁴, Dr Hemanth Vupputuri⁴**

Kempegowda Institute of Medical Sciences and Research Centre K.R Road, VV Puram Bangalore
PIN:560004

Corresponding Author

Dr Hemanth Vupputuri

Senior Resident in Dept of Surgery, Kempegowda Institute of Medical Sciences and Research Centre
K.R Road, VV Puram Bangalore Pin:560004

Email:hemumbbs@gmail.com, Ph:+919739966876

Abstract

Background: Appendectomy is one of the most common surgical emergencies. Despite of many advances in biochemical and radiological investigations, rate of negative appendectomy [histopathology negative] is considerably high.

Aims: Is to emphasize the impact of a normal (rather than raised) serum C - reactive protein (CRP) in reducing the rate of negative explorations. The chief objective of the present study is to correlate pre-operative serum levels of C-reactive protein and elevated WBC counts with the histopathology of the removed appendix to reduce the rate of negative appendectomies.

Methods and Material: The present study included 100 patients over a period of one year from January 2013 to January 2014. Pre-Operative investigations were done which included WBC count and CRP levels. Postoperative histopathological report was correlated with WBC count and CRP levels. We tried to evaluate the efficacy of CRP and WBC count in the diagnosis of appendicitis and to see whether negative appendectomies could be avoided.

Results: In 100 cases of appendectomy, 85 patients (85%) had histologically proved appendicitis. 15% underwent negative appendectomy. TLC >10,000 cells/mm³ was seen in 42(42%) patients, out of which 40 had HPE proved appendicitis (P=0.015). CRP was positive in 76.5% of HPE proved appendicitis patients. Of the 15 patients who had HPE negative appendix, 14 (93%) had negative CRP (P<0.01).

Conclusions: CRP levels combined with Total Leukocyte Count can play a significant role in diagnosis of acute appendicitis. Whenever CRP and TLC are normal diagnosis other than appendicitis should be considered.

Keywords: Acute Appendicitis, CRP, TLC, Histopathology, Negative Appendectomy.

INTRODUCTION

Acute Appendicitis is a common surgical emergency the diagnosis of which usually depends on

clinical history, physical examination, radiological and lab investigations (chiefly leukocytosis) Atypical presentation are not uncommon and

more over many inflammatory and non-inflammatory conditions may mimic the presentation of acute appendicitis thus making the diagnosis a very difficult task.^(1,2,3,4) The classic triad of history compatible with acute appendicitis, pain at Mc Burney's point and leukocytosis has a diagnostic accuracy rate of less than 80 percent, and even when radiological technique such as ultrasonography, computed tomography are included, the accuracy does not reach 90 percent.^(5,6,7,8,9,10) This is especially true in females and in the extremes of age.^(1,2,3,4)

The accurate diagnosis is very important as a diagnosis of acute appendicitis needs immediate surgery while other diagnosis may not require surgery⁽¹¹⁾. While overcautious approach and delay of diagnosis may adversely affect the outcome in acute appendicitis.

Hence the ideal scenario is to achieve a diagnostic sensitivity of 100% in patients with Right Iliac Fossa pain so as to prevent negative appendectomies. Currently there is relatively high rate (15-30%) of negative explorations for acute appendicitis.^(1,2,3,4) The reported post operative morbidity associated with the negative explorations is 5-15%^(1,2,4,12,13,14). Negative appendectomies also results in socio- economic impacts in form of lost working days and declined productivity⁽¹⁵⁾. Hence the need of the hour are additional tests that would improve the diagnostic accuracy and reduce the number of unnecessary surgery.

C-Reactive Protein (CRP) is the prototypical acute phase protein (20,21) in humans and is an important mediator of host defense. In healthy young adult volunteer blood donors, the median concentration of CRP is 0.8 mg/l, the 90th centile is 3.0 mg/l, and the 99thcentile is 10 mg/l⁽¹⁶⁾, but following an acute-phase stimulus, values may increase from less than 50 µg/l to more than 500 mg/l, that is, 10,000-fold. De novo hepatic synthesis starts very rapidly after a single stimulus, serum concentrations rising above 5 mg/l by about 6 hours and peaking around 48 hours. The plasma half-life of CRP is about 19

hours and is constant under all conditions of health and disease, so that the sole determinant of circulating CRP concentration is the synthesis rate⁽¹⁶⁾, which thus directly reflects the intensity of the pathological process stimulating CRP production. When the stimulus for increased production completely ceases, the circulating CRP concentration falls rapidly, at almost the rate of plasma CRP clearance. CRP has a significant role in complement activation and opsonization. Measuring and charting C-reactive protein values can prove useful in determining disease progress or the effectiveness of treatments.

The main aim of this study is to emphasize the impact of a normal (rather than raised) serum C - reactive protein in reducing the rate of negative explorations. The chief objective of the present study is to correlate pre-operative serum levels of C-reactive protein and elevated WBC counts with the histopathology of the removed appendix to reduce the rate of negative appendectomies.

MATERIALS AND METHODS

The present study included 100 patients admitted to Department of Surgery, Kempegowda Institute of Medical Sciences and Research Centre, Bangalore over a period of one year from January 2013 to January 2014.

The type of Sampling was Purposive Sampling. These patients were diagnosed to have acute appendicitis. Written informed consent was obtained from all patients and the study design was approved by the ethics committee of our hospital. Criteria for the patients to be included in the study were:

Those patients presenting with:

1. Periumbilical abdominal pain associated with nausea and vomiting and/or
2. Localized pain in right iliac fossa and/or
3. Tenderness (usually rebound over Mc.burney's point) and/or
4. Right sided pelvic tenderness on per rectal examination (pelvic appendicitis)

While exclusion criteria included Patients with right iliac fossa pain other than acute appendicitis

like urinary tract infection (diagnosed by H/o burning micturition and urine examination), pelvic diseases in females (pelvic inflammatory diseases diagnosed by h/o white discharge per vagina and USG abdomen), patients with other known condition which is likely to elevate CRP like Crohn's disease, acute pancreatitis etc.

Pre-Operative investigations were done which included WBC count and CRP levels. WBC count of $>10,000$ cells/mm³ was considered positive and neutrophil count of $>75\%$ was considered positive. 3 ml blood for CRP was collected in a plain test tube and serum was used for the study. No special preparation of the patient is required prior to sample collection by approved techniques. Only serum was used for testing. The materials provided with the CRP kit are reagent pack and accessories pack. The reagent pack comprised of Rhelax CRP latex reagent, positive control and negative control. The accessories pack comprised of glass slide with six reaction circles, sample dispensing pipettes, mixing sticks and rubber teats. Reagent contains 0.1% Sodium Azide as preservative. Rhelax CRP slide test for detection of CRP is based on agglutination. The test serum was mixed with rhelax CRP latex reagent and allowed to react. When serum concentration was greater than 0.6 mg/dl, a visible agglutination was observed. When serum concentration was less than 0.6mg/dl, then no agglutination was observed⁽¹⁷⁾. All the samples were tested in the same lab by the same technician.

Postoperative histopathology specimens were reported by the same pathologist for all cases. The histological diagnosis of acute appendicitis required involvement of the muscularis of the appendix. Postoperative histopathological report was correlated with WBC count and CRP levels. We tried to evaluate the efficacy of CRP and WBC count in the diagnosis of appendicitis and to see whether negative appendectomies could be avoided.

Statistical Methods: Sensitivity, specificity, positive predictive value of the test, negative predictive value of the test and accuracy were calculated. Chi-Square and Fischer Exact test have been used to find the significance of association of study parameters with HPE findings.

RESULTS

The study shows that maximum numbers of cases were in the age group of 20-24 years accounting for 33%. A major part of the study was males (63%) whereas females accounted for 37% cases with a Male: Female: 1.7:1. While pain abdomen was the presenting symptom in all cases under study it was followed by vomiting (56%), fever (44%) and urinary and bowel complaints in only 21% cases. In the present study majority of cases had tenderness at presentation (98%), rebound tenderness (49%), guarding (34%), per rectal tenderness (46%) whereas other signs as Rovsing sign, Psoas test and Obturator test were present in 17%, 22% and 9% cases respectively. In 100 cases of appendectomy, 85 patients (85%) had histologically proved appendicitis. 15% underwent negative appendectomy. USG was done in 48 patient- 47 (55.3%) was picked up by USG. TLC $>10,000$ cells/mm³ was seen in 42(42%) patients, out of which 40 had HPE proved appendicitis. (P=0.015) Neutrophil $>75\%$ in 39 (39%) patients, out of which 38 (44.75%) had HPE proved appendicitis. CRP was positive in 76.5% of HPE proved appendicitis patients. Of the 15 patients who had HPE negative appendix, 14 (93%) had negative CRP.

Table 1: Association of Study parameters with CRP

Study parameters	HPE results (Appendicitis)		Total (n=100)	P value	OR (Positive)
	Negative (n=15)	Positive (n=85)			
USG +	1 (6.7%)	47 (55.3%)	48	0.001**	17.32
TLC >1100	2 (13.3%)	40 (47.1%)	42	0.015*	5.78
Neutrophil >75%	1 (6.7%)	38 (44.7%)	39	0.005**	11.32
CRP +	1 (6.7%)	65 (76.5%)	66	P<0.001	45.5
Inference	Patients presented with CRP+ are 45.5 times more likely to have HPE findings appendicitis with P<0.001				

The sensitivity, specificity of TLC is 47% and 86.67% respectively. In the present study normal TLC value excludes acute appendicitis with predictive values of 95.23%.

Table 2: The sensitivity, specificity and the predictive values of TLC in the diagnosis of acute appendicitis

TLC	Histopathology Negative	Histopathology Positive	Total
>10,000	2 (FP)	40(TP)	42
<10,000	13(TN)	45(FN)	58
TOTAL	15	85	

Sensitivity= $TP/TP+FN=40/40+45= 47\%$

Specificity= $TN/TN+FP=13/13+2= 86.67\%$

Positive predictive value= $TP/TP+FP= 40/40+2= 95.23\%$

Negative predictive value= $TN/TN+FN=13/13+45= 22.48\%$

The sensitivity, specificity of serum CRP is 76.47% and 93.33% respectively. In the present study normal CRP value excludes acute appendicitis with predictive values of 98.48%.

Table 3: The sensitivity, specificity and the predictive values of serum CRP measurement in the diagnosis of acute appendicitis

CRP	Histopathology Negative	Histopathology Positive	Total
HIGH	1(FP)	65(TP)	66
NORMAL	14(TN)	20(FN)	34
TOTAL	15	85	

Sensitivity= $TP/TP+FN= 65/65+20= 76.47\%$

Specificity= $TN/TN+FP=14/14+1=93.33\%$

Positive predictive value= $TP/TP+FP= 65/65+1= 98.48\%$

Negative predictive value= $TN/TN+FN=14/14+1= 93.33\%$

In the present study positive predictive value for leukocyte count and CRP value are 95.24% and 98.48% respectively.

Table 4: Diagnostic value of study parameters in diagnosing the Appendicitis

Study parameters	Diagnostic value in respect of Appendicitis					
	Sensitivity	Specificity	PPV	NPV	Accuracy	Kappa
USG +	82.46	83.33	97.92	33.33	82.54	0.39
TLC >1100	47.06	86.67	95.24	22.41	53.00	0.15
Neutrophil >75	44.71	93.33	97.44	22.95	52.00	0.17
CRP +	76.00	93.33	98.48	41.18	79.30	0.46

DISCUSSION

The present study conducted at our institute gave an insight into the utility of CRP as a diagnostic tool in itself and some interesting fact about appendicitis in general. It showed that the maximum numbers of cases were in the age group of 20-24 years accounting for 33%. Male: Female ratio was 1.7:1. Majority of the patients with acute appendicitis present with right sided lower abdominal pain, nausea, vomiting and fever.

In our study normal CRP value excluded acute appendicitis with a predictive value of 98.48% On correlating CRP levels with histopathologically positive and negative cases, we found that the sensitivity and specificity of CRP were 70% and 93.3% respectively. While normal leukocyte count

excluded acute appendicitis with a predictive value of 95.24%, Neutrophilia>75% was seen in 44.7% patients . Involvement of muscularis layer of appendix was considered on histopathological examination for diagnosis of acute appendicitis. 85 (85%) patients had histologically proven acute appendicitis. In all patients pre operative leukocyte count and serum CRP were significantly high (P= 0.015 and P= <0.001) respectively.

To improve the diagnostic accuracy both the inflammatory markers that is- TLC and CRP were helpful, when measured together as this increases their positive predictive value. This fact proved in our study was comparable to the results in other studies.

Table 5: The sensitivity, specificity and the predictive values of serum CRP measurement in the diagnosis of acute appendicitis

	Sensitivity	Specificity	PPV	NPV	Accuracy
Asfar et al(1)	93.6%	86.6%	96.7%	76.5%	-
Sanjuan et al(18)	58%	80%	-	-	83.8%
Gurleyik et al(19)	93.5%	80%	-	-	91%
Our Study	70%	93.3%	98.48%	41.18%	79.3%

If in a patient presenting with right iliac fossa pain, both TLC and CRP are normal, the diagnosis of appendicitis is very unlikely. The rate of negative explorations for appendicitis was 15% in our study. In this group of patients the pre operative CRP levels were found to be normal in all but one patient, showing specificity 93.33%. These findings suggest that a normal pre operative leukocyte count and CRP level is not likely to be associated with acute appendicitis. Deferring surgery in this group of patients would probably reduce the high rate of unnecessary appendectomies.

Thus in a time where there is ample clinical dilemma owing to interoperable variability in Ultrasonography which is the work horse diagnostic tool in diagnosing acute abdomen and variable clinical presentation of the patients in acute appendicitis, CRP levels combined with Total Leukocyte Count can play a significant role in diagnosis of Acute appendicitis ^(20,21). It can

reduce need for costlier radiological investigations such as Computed Tomography and also prevent Negative appendectomy. Since it is a biochemical investigation the scope for inter-operator variability is also less and various studies along with the present one proves the reliability of the test beyond doubt.

Hence CRP level can be combined with TLC levels and used routinely in the diagnosis of Acute Appendicitis ^(20,21). It decreases the dilemma of the surgeon and gives him the accurate diagnosis so that the fear of negative appendectomy is reduced and that too can be achieved with low cost and without need for higher radiological investigations. Moreover the complications and psychological stress of negative appendectomies can also be reduced. Thus CRP is an invaluable tool and the authors press for the need to include this investigation in the diagnostic routine for Acute appendicitis.

REFERENCES

1. Asfar S et al Would measurement of C-reactive protein reduce the rate of negative exploration for acute appendicitis? J R Coll Surg Edinb. 2000 Feb; 45(1): 21-4.
2. Jess P et al. Acute appendicitis: prospective trial concerning diagnostic accuracy & complications. Am J Surg 1981;141:232-4
3. Pieper R, Kager L, Nasman P. Acute appendicitis: a clinical study of 1018 cases of emergency appendectomies. Acta Chir Scand 1982; 148:51-62.
4. Hoffmann J., Rasmussen O. Aids in the diagnosis of acute appendicitis. Br J Surg 1989; 76: 774-9.
5. Gronroos JM et al Phospholipase A2, C-reactive protein, and white blood cell count in the diagnosis of acute appendicitis. ClinChem 1994; 40: 1757-60.
6. Delany HM. Appendicitis: trends and risks, 1996. J Assoc Acad Minor Phys 1996; 7: 70-7.
7. Van Dieijen-Visser MP, Go PMNYH, Brombacher PJ. The value of laboratory tests in patients suspected of acute appendicitis. Eur J ClinChemClinBiochem 1991; 29: 749-52.
8. Andersson RE, Hugander A, Thulin AJ. Diagnostic accuracy and perforation rate in appendicitis: association with age and sex of the patient and with appendectomy rate. Eur J Surg 1992; 158: 37-41.
9. Gronroos JM, Forsstrom JJ, Irjala K, Nevalainen TJ. Phospholipase A2, C-reactive protein, and white blood cell count in the diagnosis of acute appendicitis. ClinChem 1994; 40: 1757-60.
10. Balthazar EJ et al. Acute appendicitis: CT and US correlation in 100 patients. Radiology 1994; 190: 31-5.
11. Mason LB, Deyden WE. Primary appendectomy. Am J Surg 1976; 42: 239-43.
12. Lewis FR, Holcroft JW, Boey J, Dunphy JE. Appendicitis: a critical review of diagnosis and treatment in 1000 cases. Arch Surg 1975; 110: 667-84
13. Chang FC, Hogle HH, Welling DR. The fate of the negative appendix. Am J Surg 1973; 126: 752-5.
14. Webster DP, Schneider CN, Cheche S, et al: Differentiating acute appendicitis from pelvic inflammatory disease in women of childbearing age. Am J Emerg Med 1993 Nov; 11(6): 569-72.
15. Shakhathreh HS. The accuracy of C-reactive protein in the diagnosis of acute appendicitis compared with that of clinical diagnosis. Med Arh. 2000; 54(2): 109-10.
16. Wilcox RT, Traverso LW. Have the evaluation and treatment of acute appendicitis changed with new technology? SurgClin North Am 1997; 77:1355-70.
17. Shine, B., de Beer, F.C., and Pepys, M.B. 1981. Solid phase radioimmunoassays for C-reactive protein. Clin. Chim. Acta. 117:13-23.
18. Rodriguez-Sanjuan JC et al. C-reactive protein and leukocyte count in the diagnosis of acute appendicitis in children. Dis Colon Rectum. 1999 Oct; 42(10): 1325-9.
19. Gurleyik E, Gurleyik G, Unalmiser S. Accuracy of serum C-reactive protein measurements in diagnosis of acute appendicitis compared with surgeon's clinical impression. Dis Colon Rectum 1995; 38: 1270-4.
20. Ceren Şen Tanrikulu, Mehmet Akif Karamercan. The predictive value of Alvarado score, inflammatory parameters and ultrasound imaging in the diagnosis of acute appendicitis .UlusCerrahiDerg 2016; 32: 115-121.
21. Maru Kim, Sung-Jeep Kim and Hang Joo Cho. International normalized ratio and serum C-reactive protein are feasible markers to predict complicated appendicitis. Kim et al. World Journal of Emergency Surgery (2016) 11:31.