

Predictive Value of Serum C- Reactive Protein in Diagnosis of Acute Appendicitis and Comparison with Alvarado Score

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Abstract

Introduction: The morbidity and mortality rates associated with appendicitis are greatly increased when perforation ensues, wound infection rates increases, intraabdominal abscess formation increases 15 fold and mortality may be 50 times greater. Ruptured retro-cecal appendicitis can present as extremely fulminant form of a common disease such as extensive retroperitoneal and right thigh abscess.

Methodology: This study was performed on 114 consecutive patients who were operated on for clinically and/or radiologically suspected acute appendicitis. All these patients are subjected to diagnostic laparoscopy and appendicectomy. The presence of normal appendix, inflamed, perforated etc. are noted. The diagnosis was also confirmed histopathologically.

Results: Alvarado score and CRP in showed sensitivity of 85% and 81% respectively. But TLC showed highest specificity of 100%.CRP shows 73% specificity in our study. 62(54.4%) cases of positive Alvarado score patients showed positive c-reactive protein (CRP) in 53 (85.5%) cases, which shows a significant 'p' value of 0.0048. CRP showed positive predictive value of 97%, but it has a low negative predictive value of 29%.

Conclusion: Acute appendicitis remains a diagnosis

based primarily on history and clinical examination. Serum CRP estimation does not undercut the skill of an experienced surgeon, but compliments it.

Keywords:C-Reactive Protein; Acute Appendicitis; Alvarado Score.

Introduction

Acute appendicitis is a common surgical condition. Appendicectomy is the most common cause of acute surgical abdomen with a lifetime risk of 7%. Clinical assessment remains the most important first step in evaluating patients with an acute abdomen. However, clinical examination has been found to be accurate only in 47–76% of patients with acute abdominal pain. Even the most experienced surgeon will make correct diagnosis in 4 out of 5 cases. This drops to 50% with junior doctors and doctors working in the community. Delay in diagnosis may increase morbidity and mortality in these patients, many of them are elderly, and may have significant effects on hospital resources due to increased length of stay [1].

Despite intense research and discussion, the diagnosis of acute appendicitis is still difficult and remains perhaps the most common problem in clinical surgery. On the one hand normal appendix at appendicectomy represents misdiagnosis; on the other hand a diagnostic delay of appendicitis may lead to perforation, peritonitis and septicemia. In spite of careful clinical, laboratory and ultrasound examination, the rates of removing non diseased appendix remains at around 20% of all cases subjected to appendicectomy. No single sign, symptom or diagnostic test accurately makes the diagnosis of appendicular inflammation in all cases [2].

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Clinician will rely on history, clinical examination and blood tests to make a diagnosis and decide whether surgical intervention is warranted. This approach is the basis of the Alvarado score which has been shown to predict appendicitis with relatively high sensitivity and specificity [1].

The difficulty of diagnosing acute appendicitis in old age is reflected by the high incidence of perforation rather than by a high rate of negative appendectomy. Diagnosis is also difficult during pregnancy and may result in both maternal and fetal mortality. As the incidence of perforation is usually proportional to the duration of disease process, traditional teaching has encouraged surgeons to operate even when the diagnosis is probable rather than wait until it is certain. Appendicitis in infancy is a rare condition and associated with a high frequency of perforation and peritonitis. Diagnosis is often difficult because of variable and nonspecific clinical manifestations [3].

The morbidity and mortality rates associated with appendicitis are greatly increased when perforation ensues, wound infection rates increases, intraabdominal abscess formation increases 15 fold and mortality may be 50 times greater. Ruptured retrocecal appendicitis can present as extremely fulminant form of a common disease such as extensive retroperitoneal and right thigh abscess.

Equally distressing is the fact that perforation may occur in up to 35% of cases. So traditionally, surgeons have accepted a higher incidence of unnecessary appendectomies in order to decrease the incidence of perforation. This approach is being increasingly questioned in today's era of cost effective health care. The high rate of negative explorations for appendicitis are a burden faced not only by the surgeon, but also the patient and the society as a whole, since appendectomy, like any other operation, results in socio-economic impacts in the form of hospital expenses, lost working days, and declined productivity. The goal of surgical treatment is removal of an inflamed appendix before perforation with a minimal number of negative appendectomies [4].

Despite improvements in diagnostic methods, negative appendectomy rates still remain between 10 and 30% in acute appendicitis. Cost-effective and easily applicable diagnostic methods with prompt results are required to reduce negative appendectomy rates.

The role of inflammatory markers in diagnosing appendicitis has been extensively debated with the stated sensitivity and specificity of C-reactive protein

(CRP) range from 40-95%, with little consensus on white cell count (WCC) is a more sensitive or specific marker than CRP [5].

C - reactive protein (CRP) is an acute phase reactant, which rises rapidly in response to tissue injury and inflammation, and can be measured in serum 6-12 hours after the onset of inflammatory process. Many studies have investigated the role of CRP in improving the diagnosis of acute appendicitis, with promising results. Asfar S et al, have found that the specificity and sensitivity of serum CRP in the diagnosis of acute appendicitis was 86.6% and 93.6% respectively.

A meta-analysis by Andersson et al, incorporating 24 studies investigating the role of inflammatory markers in the diagnosis of appendicitis concluded that inflammatory markers themselves are weak discriminators for appendicitis unless combined with clinical findings. However recent paper by Sengupta et al, reviewed 98 patients presenting with lower abdominal pain and claims to be the first to demonstrate a negative predictive value and sensitivity of 100% when CRP and TLC are combined. They conclude that patients with a 'normal' TLC and CRP are unlikely to have appendicitis and can be safely sent home. If indeed it is the case that CRP and TLC combined are 100% sensitive, many unnecessary admissions, imaging procedures and surgical interventions may be prevented [1]. This study analyses the predictive value of CRP and TLC in patients undergoing appendectomy for clinically suspected appendicitis.

Methodology

This was a prospective study included all patients admitted with clinical diagnosis of acute appendicitis. Preoperative total leukocyte count (TLC) and C-reactive protein (CRP) was tested in patients undergoing surgery for suspected appendicitis. Surgery was indicated on the basis of clinical findings and/or ultrasound scan(USG) and/ or CT scan, but TLC and CRP values were ignored during the decision making process.

CRP estimation was done using diagnostic reagent kit for the in vitro detection of C-reactive protein in human serum by semi-quantitative rapid latex slide tests. In which serial dilutions of the test serum is prepared (e.g, 1:2, 1:4, 1:8, etc). One drop of each of these dilutions is tested with one drop of latex CRP reagent, observe agglutination for no longer than 2 minutes on glass slide provided in the kit. The highest

dilution which shows agglutination is taken as CRP titre of the test serum. CRP level calculated in terms of micrograms per ml by multiplying the highest dilution giving clear cut agglutination with a factor of 6 (sensitivity of antigen 6 mcq/ml).

This study was performed on 114 consecutive patients who were operated on for clinically and/ or radiologically suspected acute appendicitis. All these patients are subjected to diagnostic laparoscopy and appendectomy. The presence of normal appendix, inflamed, perforated etc. are noted. The diagnosis was also confirmed histopathologically.

Inclusion Criteria

1. All patients with clinically and radiologically suspected acute appendicitis.
2. Age 5 to 60 years.

Exclusion Criteria

1. Appendicular mass planned for conservative management.
2. Recurrent appendicitis / stump appendicitis.
3. Patients with co-existing inflammatory disorder.
4. Pregnancy.

Results

Before analysis of the collected data, few assumptions were made. Histopathological diagnosis was accepted as final confirmation of diagnosis. Though clinical examination and surgical decisions involved a large number of consultants in the Department of Surgery, no significance was attached to inter-observer variation, as all the consultants were well qualified and had good experience. Technical errors in serum CRP estimation were not assigned any significance, since all laboratory technicians were well experienced and the test kit was provided by standard manufacturers. Considering these assumptions were true, we have analyzed the data obtained, to seek the efficacy of serum C-reactive protein estimation in the diagnosis of acute appendicitis by evaluating the sensitivity, specificity, predictive values, diagnostic accuracy, error rates, and likelihood ratios of the same.

The prevalence of acute appendicitis is highest in the 10-19 and 20-29 yrs of age group. There is male predominance in total number of cases.

Table 1: Alvarado's score

Alvarado's score	Cases	
	No	%
3	3	2.6
4	13	11.4
5	15	13.2
6	21	18.4
7	14	12.3
8	25	21.9
9	18	15.8
10	5	4.4
Appendix unlikely (< 5)	16	14
Appendix possible (5&6)	36	31.6
Appendix likely (7&8)	39	34.2
Appendix highly likely (9&10)	23	20.2
Negative for appendix (4 or <)	16	14
Equivocal (5&6)	36	31.6
Positive for appendix (7 or >)	62	54.4

Table 2: CRP

CRP	Cases	
	No	%
<u>Negative</u>	28	24.6
<u>Positive</u>		
12	14	12.3
24	17	14.9
48	38	33.3
96	15	13.2
192	2	1.8
Positive total	86	75.4
Total	114	100

CRP was positive in 86 (75.4%) of 114 cases of which 83 (96.5%) cases shows histological positivity for acute appendicitis, only 3 (3.5%) cases of histologically positive appendicitis had negative CRP.

CRP was negative in 28 (24.6%) cases of which 20 (71.4%) cases are histologically positive for acute appendicitis. CRP has got the sensitivity of 81% and the specificity of 73% .

Table 3: Alvarado score and HPE results

Alvarado's score	Cases	
	No	%
3	3	2.6
4	13	11.4
5	15	13.2
6	21	18.4
7	14	12.3
8	25	21.9
9	18	15.8
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Appendix unlikely (< 5)	16	14
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Appendix likely (7&8)	39	34.2
Appendix highly likely (9&10)	23	20.2
Negative for appendix (4 or <)	16	14
Equivocal (5&6)	36	31.6
Positive for appendix (7 or >)	62	54.4

True positive	=	61	False positive	=	1
True negative	=	5	False negative	=	1
Sensitivity	=	$\frac{\text{True positive}}{\text{True positive} + \text{False negative}} \times 100 = 85$			
Specificity	=	$\frac{\text{True negative}}{\text{False positive} + \text{True negative}} \times 100 = 83$			
Accuracy	=	$\frac{\text{True positive} + \text{True negative}}{N} \times 100 = 85$			
Positive predictive value	=	$\frac{\text{True positive}}{\text{True positive} + \text{False positive}} \times 100 = 98$			
Negative predictive value	=	$\frac{\text{True negative}}{\text{True negative} + \text{False negative}} \times 100 = 31$			

Alvarado score of 7 or more is seen in 62 (54.4%) cases, of which 61(98.4%) cases are histologically positive for appendicitis. Only 1(1.6%) case of positive Alvarado score shows histologically negative appendicitis.

Negative Alvarado score (4or below) is seen in

16(14%) cases of which 11(68.8%) cases shows histologically positive appendicitis.

Alvarado score has the sensitivity of 85% and specificity of 83%, which has accuracy of 85% ,with positive predictive value of 98% and negative predictive value of 31%.

Table 4: CRP results and HPE results

CRP results	No. of Cases	HPE result			
		Positive		Negative	
		No	%	No	%
Positive	86	83	96.5	3	3.5
Negative	28	20	71.4	8	28.6

True positive	=	83	False positive	=	3
True negative	=	8	False negative	=	20
Sensitivity	=	$\frac{\text{True positive}}{\text{True positive} + \text{False negative}} \times 100$		=	81
Specificity	=	$\frac{\text{True negative}}{\text{False positive} + \text{True negative}} \times 100$		=	73
Accuracy	=	$\frac{\text{True positive} + \text{True negative}}{N} \times 100$		=	80
Positive predictive value	=	$\frac{\text{True positive}}{\text{True positive} + \text{False positive}} \times 100$		=	97
Negative predictive value	=	$\frac{\text{True negative}}{\text{True negative} + \text{False negative}} \times 100$		=	29

CRP was negative in 28 cases, out of which 20 (71.4%) cases showed histopathological positivity. only 8 (28.6%) cases of normal appendix Showed negative CRP.

Table 5: Alvarado score and CRP results

Alvarado score	No. of cases	CRP results			
		Positive		Negative	
		No	%	No	%
Appendix unlikely (< 5)	16	8	50	8	50
App. Possible (5&6)	36	25	69.4	11	30.6
App. Likely (7&8)	39	31	79.5	8	20.5
App. Highly likely (9&10)	23	22	95.7	1	4.3
Negative for app. (< 5)	16	8	50	8	50
Positive for app. (≥7)	62	53	85.5	9	14.5
'p'		0.0048 Significant			

Alvarado score and CRP in showed sensitivity of 85% and 81% respectively. But TLC showed highest specificity of 100%.CRP shows 73% specificity in our study.

62(54.4%) cases of positive Alvarado score patients showed positive c-reactive protein (CRP) in 53 (85.5%) cases, which shows a significant 'p' value of 0.0048.

CRP showed positive predictive value of 97%, but it has a low negative predictive value of 29%.

Positive predictive value for TLC reaches 100%, at the same time it showed a negative predictive value of only 22%.

Discussion

The Alvarado score is a 10-point scoring system based on clinical signs and symptoms and a differential leucocyte count. Alvarado recommended an operation for all patients with a score of 7 or more and observation for patients with scores of 5 or 6. A high score was found to be an easy and satisfactory

aid to early diagnosis of acute appendicitis in children and men, but had a high false-positive rate in women. But various studies have shown the scoring system to be not particularly advantageous. In our study, Alvarado score was suggestive of acute appendicitis in only in 62 cases out of which 61 cases histologically positive.

C-reactive protein has been a measure of acute phase reactions to inflammation for the last 15 years. CRP can be measured in the serum 6 - 12 hours after the onset of inflammatory process. Recently improved high sensitive and standardized quantitative assays in serum have allowed a re-evaluation of its potential as a diagnostic test. Many studies have investigated the role of CRP in improving the diagnosis of acute appendicitis.

In our study, serum CRP estimation in diagnosis of acute appendicitis yielded a sensitivity of 81% and specificity of 73%. Asfar S et al [1], have found that the specificity and sensitivity of serum CRP in the diagnosis of acute appendicitis was 86.6% and 93.6% respectively . It is shown that the sensitivity and specificity values are comparable with that of other

studies done in the past. This study proves the adjunct value of serum CRP estimation in suspected cases of acute appendicitis.

Serum CRP estimation because of its ease of applicability, availability even in rural settings and cost effectiveness is rapidly emerging as a diagnostic tool with proven use. Being an acute phase reactant, CRP may be elevated in other conditions as well, and hence the specificity of CRP is low.

CRP is the earliest to measure inflammatory marker because of its dramatic rise in response to inflammation and is always associated with pathological condition. CRP values have been found to rise on repeated testing, whereas WBC values decreased. CRP values when combined with other inflammatory markers like leucocytosis and neutrophilia and with clinical examination, provides high sensitivity and specificity rates.

Combination of leucocytosis and CRP values yielded a high sensitivity of 86% and specificity of 100% in our study.

Thus, at the end, it should be stressed that serum CRP estimation does not replace clinical diagnosis, but is useful adjunct in diagnosis of acute appendicitis. Clinical diagnosis is crucial in ruling out alternate diagnoses and other conditions which might give a false positive value on CRP estimation. Serum CRP value should be interpreted in combination with clinical findings and leucocyte count. Thus, serum CRP estimation does not undermine the importance of clinical diagnosis by a skilled surgeon, but compliments it.

Conclusion

Serum C-reactive protein (CRP) when elevated supports the clinical diagnosis of acute appendicitis.

CRP value in combination with Alvarado scoring system, which incorporates clinical signs and symptoms and leucocytosis, has the highest diagnostic accuracy.

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