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DIAGNOSTIC ACCURACY OF SERUM C-REACTIVE PROTEIN LEVELS IN ACUTE APPENDICITIS

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Abstract:
Introduction: Acute appendicitis is one of the most prevalent disease in Pakistan as well as worldwide. Patients who face the disease are very much miserable. Accurate and instant diagnosis is a big challenge faced by the surgeons in emergency departments of tertiary care hospitals, failure in these, results in further complications. Latest maximum diagnosis tools must be used deliberately to mitigate errors such that to palliate the patients. The study was designed to evaluate the correct diagnostic ability of CRP pertaining to acute appendicitis so that negative appendectomy rates are cut short.
Methodology: The study was executed in Surgical B Unit of Khyber Teaching Hospital at Peshawar, Khyber Pakhtunkhwa, Pakistan from 27th June to 26th December 2022 over 210 patients complaining of pain abdomen.
Results: Raised levels of inflammatory markers like C reactive protein (CRP) in a clinically suspected case of acute appendicitis suggest early exploration. It also has more diagnostic accuracy than ESR and leucocyte count in detecting inflammatory processes.
Conclusion: CRP is very important for the correct diagnosis of acute appendicitis along with other imaginary tools which must be used simultaneously.

Key Words: Surgeons, acute appendicitis, C- reactive protein, inflammatory markers

Introduction:

Acute inflammation of appendix which is termed as acute appendicitis is one of the most common cause of quick acute abdomen intervention in surgical emergency of tertiary care hospitals, that results in removal of appendix which is called as appendectomy (Bhangu et al., 2015)[1].
Prevalence of acute appendicitis in Pakistan is approximately 30% (Maistrenko et al., 2016)[2]. Worldwide data in 2020 showed the disease incidence in about 233 people per 100,000 (Jones et al., 2020)[3]. Despite the fact that in mid 20th century the appendicitis decreased in Western countries but newly industrialized countries in current century have shown increasing trend (Lee et al., 2010[4] , Sulu et al., 2010[5]). The disease has multiple etiology like lymphoid hyperplasia, fecolith impaction and ischemic compromise (Bhangu et al., 2015)[1].
Despite of modern modalities, the diagnosis of acute appendicitis is still enigmatical and in 15 to 30% of cases a normal appendix is removed unnecessarily (Demestrashvili et al. (2016), Wagner et al. (2018)) [6,7]

Researchers have tried different laboratory and imaging modalities as a tool for accurate diagnosis of acute appendicitis and were quite successful (Snyder et al., 2018)[8]. Now from the past few years interest has developed in one of inflammatory markers; C-reactive protein (CRP) levels to improve the diagnostic accuracy of the disease (Demetrashvili et al., 2019)[9]. Clinical diagnosis of acute appendicitis depends upon the acumen of the concerned surgeon.
Laboratory and imaging tests are measurements tools rather diagnostic. Lack of gold standard tools results in high rate of over diagnosis. This aim of this study was to evaluate the role of C-reactive protein levels in correctly diagnosing acute appendicitis.

Material and Methods:
This study was executed in Surgical B Unit of Khyber Teaching Hospital Peshawar, Khyber Pakhtunkhwa, Pakistan from 27th of June to 26th of December 2022 by Cross Sectional Design through non probability consecutive sampling technique.
Sample size of the study was **n = 210**: calculated by Buderer [10] sample size formula with following assumptions:
Prevalence of acute appendicitis= 30%
Anticipated sensitivity of CRP= 93%
Anticipated specificity of CRP= 78%
Margin of error= 6.7%
Confidence Level= 95%

Sample Selection:
Inclusion Criteria: Emergency patients (Both genders) with acute appendicitis: as per operational definition, between ages of 12-50 years.

Exclusion Criteria: Patients having raised CRP levels with no symptoms of acute appendicitis.

Data Collection Procedure:
After approval from the Ethics Review Board, patients meeting inclusion criteria from emergency department were brought under observation. Consent of no risk and ensuring confidentiality to the patients under study was taken. Baseline information such as age, gender, BMI (Kg/m^2) and pain duration (hours) were collected.
After being assessed by the consultant surgeon, patients with pain right iliac fossa and Alvarado score more than 06 were shifted for urgent appendectomy under general anesthesia. 05 cc blood samples were taken in yellow cap tube from all patients prior to appendectomy. The samples were tested in hospital's laboratory for determination of CRP level by consultant pathologist blinded to the clinical data. CRP level for acute appendicitis was noted as per operational definition. Patients underwent appendectomy by consultant surgeon and the researcher as assistant. Postoperatively specimen of the appendix was preserved in formalin and sent to the laboratory for histopathological analysis. Histopathology report was followed and compared with CRP levels.

Data Analysis:
Data, which was recorded on especially designed proforma (annexure 1) was analyzed using SPSS 22.0 Mean ± S.D was determined for continuous variables like age, weight and body mass index (BMI). Frequency and percentages were calculated for categorical variables like age, gender, BMI, pain duration, raised serum CRP level and histopathology. Effect modifiers like age, gender, BMI and duration of pain were controlled by stratification. Post-stratification 2 × 2 table was used to find sensitivity, specificity, positive predictive level (PPV), negative predictive value (NPV) and diagnostic accuracy.
Percent sensitivity, specificity, PPV, NPV and diagnostic accuracy of CRP were calculated using the following standard formulae: (Bolin and Lam, 2013[11], Parikh et al., 2008[12])
Sensitivity (%) = True Positive (TP) ÷ True Positive (TP) + False Negative (FN) X 100

Specificity (%) = True Negative (TN) ÷ True Negative (TN) + False Positive (FP) X 100
PPV (%) = True Positive (TP) ÷ True Positive (TP) + False Positive (FN) X 100
NPV (%) = True Negative (TN) ÷ False Negative (FN) + True Negative (TN) X 100
Diagnostic Accuracy (%) = TP + TN ÷ TP + FP + FN + TN X 100

Results:

The study included patients between 12 to 50 years of age. Mean age, weight and BMI of the patients under observation are given in Table 1. Sample size of the study was: n=210.

Table 1: Mean ± SD of patients age, weight and BMI N = 210

S. No.	Demographics and baseline characteristics	MEAN ± STD. DEVIATION
1.	Patient age (years)	27.80 ± 9.245
2.	Patient weight (Kg)	65.22 ± 7.101
3.	BMI (Kg/m^2)	21.40 ± 3.722

Out of 210, frequencies of the patients below or of and above 30 years of age were 117 and 93 respectively with percent values of 55.7 and 44.5 respectively (Table 2), 141 patients (67.1%) were male, while 69 patients (32.9%) were female (Table 3). The Table 4 represents that in total 210 patients, 120 were having BMI below than 21 kg/m^2 and 90 with BMI above 21 kg/m^2 with percent values of 57.1 and 42.9 respectively. Frequencies of the patients with pain duration less than or of and more than 06 hours were 123 and 87 respectively with percentages of 58.6 and 41.4 respectively as shown in Table 5. The Table 06 shows that frequency of the patients with raised serum CRP was 40, while frequency for low serum CRP was 170, with percent values of 19.0 and 81.0 respectively. Patient's frequency for yes and no histopathology was 65 and 145 respectively having percent digits of 21.4 and 78.6 respectively.

Table 2: Frequency and percentage according to age of the patients N = 210

S. No.	Age (years)	Frequency	Percent
1	≤30 years	117	55.7
2	>30 years	93	44.4
3	**Total**	**210**	**100.0**

Table 3:Frequency and percentage according to gender of the patients N = 210

S. No.	Gender	Frequency	Percent
1	Male	141	67.1
2	Female	69	32.9
3	**Total**	**210**	**100.0**

Table 4: Frequency and percentage according to BMI of the patients N = 210

S. No.	BMI (kg/m^2)	Frequency	Percent
1	<21kg/m^2	120	57.1
2	≥21kg/m^2	90	42.9
3	**Total**	**210**	**100.0**

Table 5: Frequency and percentage of the patients according to pain duration N =210

S. No.	Pain Duration (hours)	Frequency	Percent
1	≤6 hours	123	58.6
2	>6 hours	87	41.4
3	**Total**	**210**	**100.0**

Table 6: Frequency and percentage of acute appendicitis according raised serum CRP level N =210

S. No.	Raised Serum CRP	Frequency	Percent
1	Yes	40	19.0
2	No	170	81.0
3	**Total**	**210**	**100.0**

Table 7: Frequency and percentage of acute appendicitis on histopathology N =210

S. No.	Histopathology	Frequency	Percent
1	Yes	45	21.4
2	No	165	78.6
3	**Total**	**210**	**100.0**

The Table 8 shows histopathological results of serum CRP of the studied patients. In total 45 patients with true acute appendicitis, 35 were having +ive, while 10 were having –ive lab. results. The table further reveals that in 165 patients with only symptoms of the disease (false acute appendicitis), 5 have +ive and 160 have –ive lab. results. Percentage of patients who were actually diseased and have evidence on histopathology as well was 77.7% (Sensitivity). Patients who were not diseased, with evidence on histopathology also, were 96.9% (specificity). Out of 40 patients, who have +ive histopathology, 87.5% were actually diseased (positive predictive value (PPV)), while out of 170 patients with –ive histopathology, 94.1% were un diseased (negative predictive value (NPV)). The ability of correct diagnosis of the test was 92.8%.

Table 8: Diagnostic Accuracy of Serum CRP w.r.t histopathology N = 210

CRP * HISTOPATHOLOGY					
		HISTOPATHOLOGY		Total	**Sensitivity = 77.7%** **Specificity = 96.9%** **PPV= 87.5%** **NPV= 94.1%** **Accuracy = 92.8%**
		POSITIVE	**NEGATIVE**		
CRP	**POSITIVE**	35 (87.5%)	5 (12.5%)	40 (100.0%)	
	NEGATIVE	10 (5.9%)	160 (94.1%)	170 (100.0%)	
Total		45 (21.4%)	165 (78.6%)	210 (100.0%)	

The Table 9 below manifest that in 117 patients under or of the age 30 years 17 were having true appendicitis, but 13 have +ive and 04 have -ive histopathology. In the rest 100 patients who were having false appendicitis, only 2 have +ive histopathology while 98 have –ive histopathology. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy were 76.5%, 98.0%, 86.7%, 96.1% and 94.5% respectively. The table further reveals that in 93 patients who were above the age of 30 years 28 were with true appendicitis, bifurcating them in 22 and 6 with +ive and –ve histopathology respectively. In 65 patients with false appendicitis, 3 were having +ive histopathology and 62 were having –ive histopathology. Sensitivity, specificity, PPV, NPV and accuracy were 78.6%, 95.4%, 88.0%, 91.2% and 90.3% respectively.

Table 9:Stratification of Diagnostic accuracy w.r.t to age of the patient N = 210

PATIENT AGE (years)	**CRP * HISTOPATHOLOGY**				
≤30 years		**HISTOPATHOLOGY**		Total	**Sensitivity = 76.5%** **Specificity = 98.0%**
		POSITIVE	**NEGATIVE**		

	CRP	**POSITIVE**	13 (86.7%)	2 (13.3%)	15 (100.0%)	**PPV= 86.7% NPV= 96.1% Accuracy = 94.5%**
		NEGATIVE	4 (3.9%)	98 (96.1%)	102 (100.0%)	
	Total		17 (14.5%)	100 (85.5%)	117 (100.0%)	
>30 years	**CRP**	**POSITIVE**	22 (88.0%)	3 (12.0%)	25 (100.0%)	**Sensitivity = 78.6% Specificity = 95.4% PPV= 88.0% NPV= 91.2% Accuracy = 90.3%**
		NEGATIVE	6 (8.8%)	62 (91.1)	68 (100.0%)	
	Total		28 (30.1%)	65 (69.9%)	93 (100.0%)	

Stratification of the total 210 studied sample patients pertaining to BMI, CRP histopathology (+ive and –ive) and appendicitis (true and false) shows that in 120 patients who have BMI below 21.0 kg/m^2 24 were actually diseased (true appendicitis), in whom 21 have +ive while the remaining have –ive histopathology. Out of 96 patients who are un diseased (false appendicitis) 3 have +ive and 93 have –ive histopathology. Sensitivity, specificity, PPV, NPV of the patients were 87.5%, 96.9%, 87.5% and 96.9% respectively with accuracy of the test of 95.0%. Out of 90 patients with BMI of or above 21.0 kg/m^2 21 patients have true appendicitis, who were divided in 14 and 7 i.e. +ive and –ive histopathology respectively.

The table further indicates that 69 patients were having only the symptom of the disease (false appendicitis), in which 2 have +ive while 67 have –ive histopathology. Patient's sensitivity, specificity, PPV, NPV were 66.7%, 97.1%, 87.5% and 90.5% respectively with accuracy of 90.0% (Table 10).

Table 10: Stratification of diagnostic accuracy w.r.t BMI of the patient N = 210

PATIENT BMI (kg/m^2)	**CRP * HISTOPATHOLOGY**					
<21.0 kg/m^2			**HISTOPATHOLOGY**		Total	**Sensitivity = 87.5% Specificity = 96.9% PPV= 87.5% NPV= 96.9% Accuracy = 95.0%**
			POSITIVE	**NEGATIVE**		
	CRP	**POSITIVE**	21 (87.5%)	3 (12.5%)	24 (100.0%)	
		NEGATIVE	3 (3.1%)	93 (96.9%)	96 (100.0%)	
	Total		24 (20.0%)	96 (80.0%)	120 (100.0%)	
≥ 21.0 kg/m^2	**CRP**	**POSITIVE**	14 (87.5%)	2 (12.5%)	16 (100.0%)	**Sensitivity = 66.7% Specificity = 97.1% PPV= 87.5% NPV= 90.5% Accuracy = 90.0%**
		NEGATIVE	7 (9.5%)	67 (90.5%)	74 (100.0%)	
	Total		21 (23.3%)	69 (76.7%)	90 (100.0%)	

The Table 11 outlines relation of number of patients with pain duration of or less and more than 06 hours with CRP histopathology; +ive and –ive. Number of patients with less than 06 hours pain duration was 123. Patients with true appendicitis were 22, in which 17 have +ive while 5 have –ive lab. results. Furthermore, patients with false appendicitis were 101 in number, with +ive lab. results of only 1 while –ive lab. results of 101. 77.2%, 99.0%, 94.4%, 95.2% and 95.1% were sensitivity, specificity, PPV, NPV and accuracy respectively.

The table further shows that in 210 studied patients 87 were having pain of more than 06 hours, in whom 23 respondents were having acute appendicitis actually (true acute appendicitis), 18 have evidence on histopathology while 5 have not. However 64 were the patients with the disease symptom only (false acute appendicitis), 60 with histopathological evidence, and 04 with no evidence. Values of sensitivity, specificity, PPV, NPV and accuracy, which were derived through the above mentioned formulae are 78.3%, 93.8%, 81.8%, 92.3% and 90.0% respectively.

Table 11: Stratification of diagnostic accuracy w.r.t pain duration N = 210

PAIN DURATION	**CRP * HISTOPATHOLOGY**					
≤ 06 hours			**HISTOPATHOLOGY**		Total	**Sensitivity = 77.2%** **Specificity = 99.0%** **PPV= 94.4%** **NPV= 95.2%** **Accuracy = 95.1%**
			POSITIVE	**NEGATIVE**		
	CRP	**POSITIVE**	17 (94.4%)	1 (5.6%)	18 (100.0%)	
		NEGATIVE	5 (4.8%)	100 (95.2%)	105 (100.0%)	
	Total		22 (17.9%)	101 (82.1%)	123 (100.0%)	
> 06 hours	**CRP**	**POSITIVE**	18 (81.8%)	4 (18.2%)	22 (100.0%)	**Sensitivity = 78.3%** **Specificity = 93.8%** **PPV= 81.8%** **NPV= 92.3%** **Accuracy = 90.0%**
		NEGATIVE	5 (7.7%)	60 (92.3)	65 (100.0%)	
	Total		23 (26.4%)	64 (73.6%)	87 (100.0%)	

The Table 12 indicates that out of 210 observed patients for acute appendicitis 141 were male and 69 were female. In 141 male patients 31 were truly diseased (true acute appendicitis) with 23 having +ive lab. results and 08 having –ive lab. results. The number of male patients who were not diseased (false acute appendicitis) was 110, with 03 patients having no evidence on histopathology and 107 have evidence for not having the disease. Sensitivity, specificity, PPV, NPV and accuracy were 74.1%, 97.3%, 88.5%, 93.0% and 92.2% respectively as shown in the table.

In 69 female tested patients 14 were having true appendicitis; 12 were with +ve and 02 were with –ive lab. results. 55 patients were having false appendicitis, in which 02 have +ive and 53 have –ive results. Sensitivity, specificity, PPV, NPV and accuracy were 85.7%, 96.4%, 85.7%, 96.4% and 94.2% respectively (Table 12).

Table 12: Stratification of diagnostic accuracy w.r.t gender N = 210

GENDER	**CRP * HISTOPATHOLOGY**					
MALE			**HISTOPATHOLOGY**		Total	**Sensitivity = 74.1%** **Specificity = 97.3%** **PPV= 88.5%** **NPV= 93.0%** **Accuracy = 92.2%**
			POSITIVE	**NEGATIVE**		
	CRP	**POSITIVE**	23 (88.5%)	3 (11.5%)	26 (100.0%)	
		NEGATIVE	08 (6.9%)	107 (93.1%)	115 (100.0%)	
	Total		31 (21.9%)	110 (78.1%)	141 (100.0%)	
FEMALE	**CRP**	**POSITIVE**	12 (85.7%)	2 (14.3%)	14 (100.0%)	**Sensitivity = 85.7%** **Specificity = 96.4%**
		NEGATIVE	02 (3.6%)	53 (96.4)	55 (100.0%)	

	Total	14 (20.3%)	55 (79.7%)	69 (100.0%)	**PPV= 85.7% NPV= 96.4% Accuracy = 94.2%**

Discussion:

Ion et al., 2019[13] reported 93% sensitivity, 78% specificity, 93% positive predictive value and 78% negative predictive value of CRP for the detection of acute appendicitis and thus shows concurrence with the our findings. Results of the study of Bahram, 2011[14] is at par with ours, who suggested that C-reactive protein (CRP) is an important detective tool for early diagnosis of acute appendicitis, the combination of the three i.e. history, clinical examination and CRP have high diagnostic abilities for the detection of acute appendicitis. Findings of wen et al., 2005[15] confirm our results, who observed extremely rare cases of inflamed appendix among the children with normal level of CRP although highly suspected for acute appendicitis clinically. Kollar et al., 2015[16] determined that CRP is very necessary before appendectomy of the suspected patients because it can also diagnose the severity of the disease, they found that patients with high level of CRP have more chance to the complications of acute appendicitis, they further suggested that if a person has raised level of CRP followed by diagnosed acute appendicitis through clinical assessment and imaging modalities then he/she would have no other choice except for urgent appendectomy, their results are in accordance with ours.

Hanson et al., 2014[17] from their research work concluded that patient's history, clinical examinations and laboratory investigation often over looks acute appendicitis, but its combined diagnosis with CRP leads to the accurate detection of the disease, hence the study proved our results. Ohle et al., 2011[18] sketched that inflammatory parameters alone or combined helps a lot to depict acute appendicitis, but these parameters do not have more importance than clinical examination. Thus the results are in conformity with ours. Di Saverio et al., 2015[19] and Ohene and Togbe, 2006[20], observed that using routine imaging modules didn't overcome negative appendectomy.

Conclusions:

All the categorical parameters for CRP of the patients have sensitivity more than 70% except for BMI $\geq$ 21.0 kg/m^2, specificity is > 95% and PPV is > 85% except of the patients with pain duration > 06 hours. NPV of the patients and accuracy of the test for all parameters is $\geq$ 90.0%.

CRP has a great importance in the diagnosis of acute appendicitis. Presence of other inflammatory disease processes simultaneously decreases its correct diagnostic ability, due to which careful clinical checkup with imaging tools is crucial in atypical cases.

Recommendations:

The study recommends that substantial importance must be given to CRP as routine laboratory test in order to eliminate the chances of negative appendectomy which may significantly reduce the patients suffering: physically, morally and financially etc.

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