VOLUME - 11, ISSUE	- 11, NOVEMBER - 2022 •	<ul> <li>PRINT ISSN No. 2277 - 816</li> </ul>	0 • DOI : 10.36106/gjra

State FOR RESERACE	Original Research Paper	General Surgery		
International	EVALUATION OF CRP (C-REACTIVE PROTEIN) AND PROCALCITONIN AS DIAGNOSTIC MARKERS IN ACUTE APPENDICITIS			
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## ABSTRACT

Background: One of the most prevalent abdominal crises is acute appendicitis. Many efforts have been directed towards early diagnosis and intervention. Delay in diagnosis leads to increase morbidity and costs. Present study was aimed to evaluate the correlation of CRP and PCT with perioperative findings in suspected cases of acute appendicitis and to find whether they can aid in the diagnosis of acute appendicitis. Material and Methods: Present study was hospital based screening test study, conducted patients of age > 18 years, either gender, who presented with right iliac fossa pain lasting < 48 hours and were tentatively diagnosed with acute appendicitis, underwent surgery. Results: Among 115 patients with acute appendicitis, most of patients belong to age group of 21 to 30 years (45.2%) followed by 31 to 40 and 10 to 20 years (18.3 %). Out of 115 patients 40 (34.8%) patients were females and 75 (65.2%) patients were males. CRP was positive in 84 (73.04%) and procalcitonin was positive in 66 (57.39%) patients with acute appendicitis. CRP had a sensitivity of 72.82%, a specificity of 25%, a positive predictive value of 89.29%, and a negative predictive value of 9.68 %. Procalcitonin had a sensitivity of 57.28 %, a specificity of 41.67 %, a positive predictive value of 89.39 %, and a negative predictive value of 10.20%. Conclusion: Elevation in CRP as well as procalcitonin levels only cannot be used for final diagnosis of acute appendicitis, but it can act as an adjunct when evaluating the available clinical and laboratory

## **KEYWORDS** : CRP, procalcitonin, acute appendicitis, sensitivity, specificity

### INTRODUCTION

Acute abdominal pain is a common complaint among emergency department patients. Diagnosis of one of the common pathologies behind acute abdominal pain, acute appendicitis has radically changed over the last decades. One of the most prevalent abdominal crises is acute appendicitis. Appendicitis affects around 7% of the population at some point in their lives.<sup>1,2</sup> Most commonly acute appendicitis occurs between the ages of 5 and 45, with a mean age of 28.<sup>2</sup>

Many efforts have been directed towards early diagnosis and intervention. Delay in diagnosis leads to increase morbidity and costs.3 Because mild appendicitis can progress to perforation, which has a significantly higher morbidity and mortality rate, surgeons are more inclined to operate when the diagnosis is suspected rather than waiting until it is proven. But there are number of major and minor complications following appendectomy.<sup>4</sup>

The diagnosis of appendicitis can be difficult, occasionally challenging the diagnostic skills of even the most experienced surgeon. Attempts to increase the diagnostic accuracy of acute appendicitis have included computer aided diagnosis, imaging by ultrasonography, laparoscopy and even radioactive isotope imaging.<sup>5</sup>

To enhance the clinical diagnosis of acute appendicitis, many biochemical measures such as white blood cell (WBC) count, C- reactive protein (CRP), Interleukin-6 (IL6), and Procalcitonin (PCT) have been utilized.<sup>6</sup>

Leukocyte count and C-responsive protein (CRP) are the most commonly utilized tests. Procalcitonin (PCT) has been read up as a biomarker for severity of appendiceal inflammation. Present study was aimed to evaluate the correlation of CRP and PCT with perioperative findings in suspected cases of acute appendicitis and to find whether they can aid in the diagnosis of acute appendicitis.

### MATERIAL AND METHODS

Present study was hospital based screening test study, conducted in department of general surgery, at Bharati hospital, Pune, India. Study duration was of 2 years (September 2019 to August 2021). Ethical clearance was obtained from Ethical Clearance Committee of the institution for the study.

### Inclusion criteria

Patients age > 18 years either gender, who presented with right iliac fossa pain lasting < 48 hours and were tentatively diagnosed with acute appendicitis, underwent surgery

### Exclusion criteria

- Complicated Cases of Appendicitis, Chronic Appendicitis
- Chronic Inflammatory or Auto-immune disorders like TB, RA, gout, etc.

The eligible patients were briefed about the nature of the study and a written informed consent was obtained from the consenting patients. Patient's demographic profile, duration of symptoms and blood samples were collected for WBC count, differential leucocyte count and preoperative Creactive protein. Blood samples were stored at -20°C for procalcitonin estimation.

CRP was quantitated by autoanalyzer by 'randox – imola'. The value of  $\geq$  5 mg/dL is taken as positive for CRP. Procalcitonin was quantitated by autoanalyzer 'Abbott' and the value taken into consideration was  $\geq l ng/dL$ .

Confirmation of acute appendicitis as the final diagnosis was obtained from histopathological analysis of the appendix specimen.

The collected data was coded and entered in Microsoft Excel sheet. The data was analysed using SPSS (Statistical Package for social sciences) version 25.0 software. Chi-square test / Fisher's exact test was used to find the association between 2 or more attributes for qualitative data variables.

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#### RESULTS

In present study, 115 patients with acute appendicitis were included. Most of patients belong to age group of 21 to 30 years (45.2%) followed by 31 to 40 and 10 to 20 years (18.3%). Out of 115 patients 40 (34.8%) patients were females and 75 (65.2%) patients were males.

#### Table 1: General characteristics

Characteristics	Number of cases	Percentage
Age group (in years)		
10-20	21	18.3
21-30	52	45.2
31-40	21	18.3
41-50	10	8.7
>50	11	9.57
Gender		
Females	40	34.8
Males	75	65.2

Mean values of Haematological parameters were total leukocyte count (TLC) 13065  $\pm$  3904, neutrophil count 81.11  $\pm$  6.89 and biochemical parameters viz. C reactive protein (CRP) 16.08  $\pm$  18.97 and procalcitonin 0.80  $\pm$  0.92.

## Table 2: Levels of haematological and biochemical parameters

Parameters	Mean $\pm$ SD
TLC	$13065 \pm 3904$
Neutrophils	81.11 ± 6.89
CRP	$16.08 \pm 18.97$
Procalcitonin	$0.80 \pm 0.92$

As per their respective cut off values, CRP was positive in 84 (73.04%) and procalcitonin was positive in 66 (57.39%) patients with acute appendicitis.

## Table 3: The distribution of patients as per normal values of CRP and procalcitonin

	CRP (n=115) Procalcitonin (n=11	
Positive	84 (73.04 %)	66 (57.39 %)
Negative	31 (26.96 %)	49 (42.61 %)



## Chart 1- distribution of patients as per normal values of CRP and procalcitonin

The diagnostic efficacy of C reactive protein against the gold standard histopathology was compared for the diagnosis of acute appendicitis. There were 75 (true positive) and 28 (false negative) patients who were positive and negative by CRP which were also shown to be positive and negative respectively for diagnosis of acute appendicitis by histopathology. The sensitivity, specificity, positive predictive and negative predictive values were calculated. CRP had a sensitivity of 72.82%, a specificity of 25%, a positive predictive value of 89.29%, and a negative predictive value of 9.68%.

Table 4: Cross table for CRP against a gold standard histopathology

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	CRP	Histopathology	Total		
		Positive	Negative		
	Positive	75 (89.29 %)	9 (10.71 %)	84 (%)	
	Negative	28 (90.32 %)	3 (9.68 %)	31 (%)	
	Total	103 (%)	12 (%)		

CRP and histopathology



#### Chart 2-Association of CRP and histopathology

# Table 5: Efficacy parameters for CRP against histopathology

Statistic	Value	Standard	95% Confi	dence
		Error	Limits	
Sensitivity	72.82	4.38	64.22	81.41
Specificity	25	12.50	5	49.50
Positive Predictive Value	89.29	3.37	82.67	95.90
Negative Predictive	9.68	5.31	0	20.08
Value				

The diagnostic efficacy of procalcitonin against the gold standard histopathology was compared for the diagnosis of acute appendicitis. There were 59 (true positive) and 44 (false negative) patients who were positive and negative by cut off value of procalcitonin which were also shown to be positive and negative for acute appendicitis by histopathology respectively. Procalcitonin had a sensitivity of 57.28 %, a specificity of 41.67 %, a positive predictive value of 89.39 %, and a negative predictive value of 10.20 %.

# Table 6: Cross table for procalcitonin against a gold standard histopathology

Procalcitonin	Histopathology report		Total
	Positive	Negative	
Positive	59 (89.39 %)	7 (10.61 %)	66 (%)
Negative	44 (89.8 %)	5 (10.2 %)	49 (%)
Total	59 (89.39 %)	7 (10.61 %)	

Procalcitonin and histopathology



#### Chart 3-Association of procalcitonin and histopathology

## Table 7: Efficacy parameters for procalcitonin against histopathology

Statistic	Value	Standard Error	95% Confidence Limits	
Sensitivity	57.28	4.87	47.73	66.83
Specificity	41.67	14.23	13.77	69.56
Positive Predictive Value	89.39	3.79	81.97	96.82
Negative Predictive Value	10.20	4.32	1.73	18.68

### DISCUSSION

Delay in diagnosis and treatment increases the risk of perforation, surgical morbidity, death, and hospital stay. Despite the development of sophisticated laboratory and imaging diagnostic modalities, in-hospital observation and

#### VOLUME - 11, ISSUE - 11, NOVEMBER - 2022 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

repeated clinical examination remain the most common methods of diagnosing acute appendicitis. But this may result in an increase in the number of patients operated on with a false positive diagnosis of acute appendicitis.

Acute abdominal pain occurs for 7–10% of all emergency room visits. Acute appendicitis (AA) is one of the most prevalent causes of lower abdominal pain that leads patients to the emergency room, and it is the most common diagnosis made in young patients admitted to the hospital with an acute abdomen.<sup>8</sup>

Clinical diagnosis of AA is frequently difficult and requires a synthesis of clinical, laboratory, and radiographic evidence. In recent years, the diagnostic utility of laboratory inflammatory markers has been explored, with varying and contradicting results, most notably in a diverse sample of adults and children.<sup>9</sup>

Appendicitis is most frequent in children aged 10 to 20, however no age group is immune. Perforation occurs at a rate ranging from 16% to 40%, with a larger frequency appearing in younger age groups (40–57%) and in people over the age of 50 (55–70%).<sup>10</sup> Xharra, S et al.,<sup>11</sup> there were 90 males and 83 females out of 173 patients. The mean age of patients was 19.7  $\pm$  10.5 years ranging between 5 to 59years and (83.5%) of patients were under 30years old.

As per the normal cut off values of C reactive protein and procalcitonin the patients were divided as positive and negative for respective tests. As per their respective cut off values, CRP was positive in 84 (73.04%) and procalcitonin was positive among 66 (57.39%) patients with acute appendicitis.

The values of CRP in a study by Shakhatreh HS et al.,<sup>12</sup> were ranging between 6 to 93.4 mg/l with mean level of 36.2 mg/l in patients with acute appendicitis. Kaya B et al.,<sup>13</sup> noted that among patients with perforated appendicitis reported that the levels of PCT, D-dimer and CRP were higher than the upper normal limit in 25.6%, 28.2% and 69.2% of patients.

A wide variation in level of CRP was reported by Xharra S et al.,<sup>11</sup> among the study groups of acute appendicitis. Menka K et al.,<sup>14</sup> reported abnormal levels of CRP and procalcitonin in sepsis too. Similarly, in patients with septic arthritis and osteomyelitis the PCT values were found to be elevated as per study by Greeff E.<sup>15</sup>

Significantly high levels of CRP were seen with gangrenous and perforated appendix as reported by Paltola H et al.,<sup>16</sup> High levels of CRP can even predict post-operative complications in appendicitis. It has been shown that the predictive value CRP is higher in appendicitis than in other causes of acute abdomen.<sup>17</sup> It is a better indicator of complicated appendix than WBC count.<sup>18</sup> The sensitivity for CRP in this investigation was determined to be 72.82 %, the specificity was 25 %, the positive predictive value was 89.29 %, and the negative predictive value was 9.68 %. The ROC curve analysis for CRP gave the non-significant cut-off value of 9.2 with AUC of 0.538, sensitivity was 57.28% and specificity was 63.64%.

Shakhatreh  $HS^{12}$  evaluated the efficacy of CRP against clinical diagnosis of acute appendicitis. CRP level predicted total 11% cases to be false positive 4% cases as false negative, while the prediction was false in 9 patients by clinical diagnosis. Mohammed AA et al.,<sup>19</sup> reported the sensitivity, specificity, positive and negative predictive values for CRP were 87.7%, 84.8%, 89.7%, 82%, which were higher than the present study except for positive predictive value similar to present study.

detected lowest sensitivity, specificity, positive and negative predictive values. Similar to present study Xharra, S et al.,<sup>10</sup> compared CRP with histopathology, with 12.71% and 4.05% rates of false-negativity and false positivity respectively. Further, based on the surgeons' clinical impression, the diagnosis was correct among 87.28% and false in 12.72% patients. The positive predictive value of the CRP was 94.7%, specificity 72%, sensitivity 85.1%, and accuracy 83.2%.

Jaiswal AK et al.,<sup>21</sup> Among 48 HPE proves cases of acute appendicitis found correlation of CRP and histopathology, a sensitivity of 91.6%, specificity of 81.8% for CRP was reported, which was much higher than the present study. In a meta-analysis conducted by Hallan S et al.,<sup>22</sup> the mean sensitivity of CRP for the diagnosis of appendicitis was 70%, and mean specificity was 62%. After pooling all the data, the authors found the sensitivity of 62% and specificity of 66%. The authors conclude in favor of CRP as an aid in diagnosis of acute appendicitis.

In healthy individuals, the normal plasma PCT levels are < 0.5 ng/ml. In recent decades, scientific evidence has gathered in favour of utilizing plasma PCT level as a biomarker for acute appendicitis. This concept is based on the hypothesis that faecolith that carry a high load of gram-negative bacteria play a predominant role in pathophysiology of acute appendicitis by causing obstruction of appendiceal lumen.<sup>20</sup>

PCT levels, unlike CRP, do not rise in individuals with sterile inflammation or viral infection. For this reason, it is a good biomarker in many inflammatory conditions, such as acute appendicitis, sepsis, and meningitis.<sup>23</sup> Cui W et al.,<sup>24</sup> confirmed positive role of Procalcitonin in accurate in diagnosing complicated acute appendicitis, with higher a pooled sensitivity of 89%, specificity of 90% compared to present study.

Kaya B et al., <sup>13</sup> reported very low i.e., 26% diagnostic value of PCT for detecting acute appendicitis. A low cut off value as compared to present study was reported by Yamashita H et al., <sup>23</sup> using ROC curve analysis and found the optimal cut-off value of 0.07ng/ml, with AUC of 0.777. In an experimental acute appendicitis Destek S et al., <sup>25</sup> in an ROC curve analysis reported the cutoff value of 21.24 with sensitivity of 90.47% and specificity of 85.71%.

The efficacy of procalcitonin is also evaluated in diagnosis of septic arthritis and osteomyelitis by Greeff E,<sup>15</sup> the sensitivity of 75% and specificity of 90% was calculated for procalcitonin in diagnosis of arthritis and osteomyelitis above the cut- off value of 0.5ng/ml. Therefore, aiding in the diagnosis of septic arthritis or acute osteomyelitis. The area under the ROC curve (AUC) for CRP and procalcitonin were non-significant, which were 0.538 and 0.573 respectively. The cut off values calculated were 9.2 and 1.75 for CRP and procalcitonin with sensitivity and specificity of 57.28% & 63.64% and 82.52% & 41.67% respectively.

Delay in diagnosis and treatment increases the risk of perforation, surgical morbidity, death, and hospital stay. Accurate and cost-effective diagnostic test is highly desirable to further aid the clinical assessment of patients and to be lifesaving and reassuring to patients and physicians respectively.

### CONCLUSION

The cut-off values of 9.2 and 1.75 were calculated for CRP and procalcitonin in diagnosis of acute appendicitis. The CRP though sensitive, but was not specific, while procalcitonin has low sensitivity as well as specificity for the diagnosis of acute appendicitis.

Comparable to present study for CRP, Mishra DS et al.,20 Therefore, the elevation in CRP as well as procalcitonin levels

only cannot be used for final diagnosis of acute appendicitis, but it can act as an adjunct when evaluating the available clinical and laboratory

#### Conflict of Interest: None to declare Source of funding: Nil

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