

## Original Research Article

# Evaluation of procalcitonin as a predictor of severity of acute appendicitis

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## ABSTRACT

**Background:** Acute appendicitis is the most common surgical emergency worldwide. The treatment of choice is emergency appendectomy. A delayed diagnosis and hence a delayed treatment increases the complication rate. Despite the best efforts negative appendectomy rate is still high since there is no single best test available to reach the diagnosis.

**Methods:** This was an institutional study conducted at DRPGMC Tanda, comprising of 28 patients and 7 healthy controls. The patients with clinical diagnosis of acute appendicitis were subjected to appendectomy after taking a blood sample for serum procalcitonin and performing an ultrasonogram of abdomen.

**Results:** We observed that mean levels of procalcitonin (PCT) were significantly higher in patients of acute appendicitis in comparison to healthy controls. The range of PCT levels in group 2 i.e., patients with uncomplicated acute appendicitis were from 0.54 to 0.74 ng/ml with mean value of 0.61 ng/ml, whereas in group 3 i.e. patients with complicated acute appendicitis, the range were from 1.14 to 2.56 ng/ml with mean value of 1.62 ng/ml. PCT levels were significantly higher in group 3 as compared to group 1 and group 2 ( $p < 0.0001$ ). In group 2, mean PCT levels were significantly higher in comparison to group 1 ( $p < 0.0001$ ). Statistical analysis of our data shows a cut-off value of procalcitonin to be 0.203 ng/ml. We observed sensitivity and specificity of PCT to be 96% and 100% respectively.

**Conclusions:** This study concludes that levels of serum PCT can be used as a laboratory marker for making a diagnosis of acute appendicitis and also for predicting its severity.

**Keywords:** Acute appendicitis, Alvarado score, Appendectomy, Procalcitonin

## INTRODUCTION

Acute appendicitis is the most common cause of acute abdomen worldwide making emergency appendectomy the most commonly performed surgery.<sup>1</sup> It is a disease of the young affecting the patients between the second to fourth decades of life. Nearly 25% people suffering from acute appendicitis present with perforated appendix. This

incidence is higher in children less than 5 years and elderly more than 65 years of age.<sup>2</sup> Mortality rate of acute appendicitis (AA) is 0.3%, which rises considerably to the tune of 5.5% in older patients, 6.5% in case of perforated appendix and 80% in neonates.<sup>3</sup> Although numerous abdominal conditions may mimic it but clinical examination is still the most common method of diagnosing acute appendicitis. This makes it difficult to

rule out such conditions on the basis of clinical examination alone. Thus laboratory investigations, imaging techniques and various scoring systems have been used to confirm the diagnosis of acute appendicitis, But despite all these modalities being used, the negative appendectomy rate (NAR) has been reported from 9% to 44%.<sup>4</sup> Because of this high NAR the efforts are on to find new diagnostic methods with high sensitivity and specificity. Many inflammatory markers like C-reactive protein (CRP), a raised total leukocyte count (TLC) have been used for the diagnosis of acute abdominal conditions including acute appendicitis. Procalcitonin (PCT) is an established lab marker for disease severity in patients with infection and sepsis. Concentration of PCT selectively increases in case of bacterial infections, while in case of viral infections its concentration remains normal.<sup>5</sup> It has been seen that the level of Procalcitonin correlates with severity of inflammation.<sup>6</sup> It is a better marker than C-reactive protein which also rise in inflammatory states.<sup>7</sup> PCT can help in making the diagnosis of acute appendicitis and can also prevent unnecessary appendectomies being performed. The purpose of this study was therefore to assess the value of serum PCT in making a diagnosis and predicting the severity of acute appendicitis, in order to improve the clinical decision making.

**METHODS**

The present study was a hospital-based prospective observational study conducted between August 2017 to August 2018, in the Department of Surgery, Dr. Rajendra Prasad Government Medical College, Tanda after being approved by the institutional ethics committee and taking informed consents from the study participants. A total number of 35 participants, 28 of whom were patients with clinical diagnosis of acute appendicitis and 07 healthy controls who gave informed consent, were included in the study. Pregnant females, patients in whom diagnosis other than acute appendicitis was made, patients of age <10 years, patients with pneumonia, COPD, and arthritis were excluded. Study group was examined for signs and symptoms of disease on admission. A detailed history was taken and examination done. Blood samples were collected for hematological and biochemical analysis. The diagnosis of acute appendicitis was made on the basis of clinical findings, lab investigations, imaging (USG, CT Abdomen if needed) as per the protocol defined. Serum PCT were sent preoperatively and measured using the immuno luminometric method (LUMI- test procalcitonin). Patients were subjected to appendectomy and operative findings were recorded whether appendix was normal looking, inflamed, perforated or gangrenous. After surgery, the specimen was sent for histopathological examination (HPE). Based on the operative findings and HPE reports, the study group was subdivided into following four subgroups.

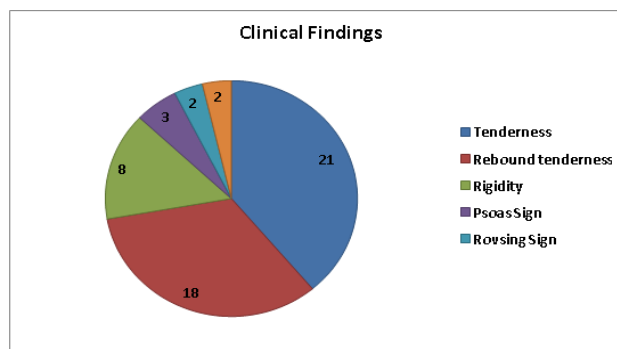
- Group 1 contains patient whose appendix were normal after appendectomy.

- Group 2 consist of patients of acute uncomplicated (inflamed) appendicitis.
- Group 3 had patients of acute complicated appendicitis (perforated appendix, gangrenous appendix).
- Group 4 was healthy controls.

Data was expressed as frequency, percentage, mean, and standard deviation wherever applicable. quantitative variables between 2 groups and more than 2 groups were compared using Student t-test and one way ANOVA followed by Bonferroni Correcion Analysis. Diagnostic values were assessed by calculating sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). Receiver operating characteristic (ROC) analysis was performed and the area under the ROC curve (AUC) was calculated to assess the diagnostic value of PCT for each category of acute appendicitis. P value<0.05 was considered significant. Stastical analysis was performed using SPSS v21.

**RESULTS**

The age of the patients with acute appendicitis in present study, ranged from 10 years to 65 years, with a mean age of 29.4 years. Out of the 28 patients of acute appendicitis, 5 (28%) were females and 23 (72%) were males. Males outnumbered females with a ratio of 4.6:1. All the patients presented with typical symptoms of acute appendicitis viz. migratory pain, nausea and/or vomiting, fever and anorexia (Figure 1). Duration of symptoms was within 24 to 48 hours in 15 (53%) patients. Mean duration of symptoms was 44.64 hours.



**Figure 1: Clinical findings.**

The TLC levels, in present study, ranged from 4300/mm<sup>3</sup> to 20760/mm<sup>3</sup> with a mean of 10800/mm<sup>3</sup>. Out of the 28 patients of acute appendicitis, leukocytosis was observed in 21 (75%) patients. Shift to left was also observed in 20 (71%) patients. In present study Alvarado score ranged from 4 to 10 with a mean of 7.57. Alvarado score was more than seven in 22 (78%) patients, 5 to 6 in 5 (18%) patients and less than five in 1 (4%) patient. Out of 28 patients with acute appendicitis in present study, ultrasonogram (USG) abdomen was suggestive of acute

appendicitis in 14 (50%) patients, acute appendicitis with phlegmon formation in 2 (7%) patients, and appendicolith with free fluid in right iliac fossa in 2 (7%) patients (Table 1). The appendix was not visualized in 10 (36%) patients. Out of these 10 patients probe tenderness was positive in 7 (25%) patients and absent in 3 (11%) patients.

Thus USG abdomen was positive for appendicitis in 25 (89%) patients and negative in 3 (11%) patients. Out of these 25 patients diagnosed as acute appendicitis, 24 (85%) patients turned out to be acute appendicitis after surgery on histopathological examination (HPE), while one patient had normal appendix. This patient gave history of passing stone in urine after 04 days of appendectomy. Out of 3 (11%) patients with negative sonological findings for acute appendicitis, one patient revealed right nephrolithiasis with cholelithiasis but other 2 patients were confirmed as acute appendicitis on HPE. Diagnosis of acute appendicitis was made on the basis of Alvarado Score and USG abdomen. 28 patients thus diagnosed as acute appendicitis were subjected to

appendectomy. Intraoperatively, inflamed appendix were seen in 21 (75%) patients, perforated appendix in 04 (14%) patients and gangrenous appendix in 1 (4%) patient. In 2 (7%) patients appendix was grossly normal and did not appear inflamed. We also found that out of the 28 patients of acute appendicitis who were operated, position of appendix was retrocaecal in 17 (60%) patients, pelvic in 7 (25%) patients, paracaecal in 2 (7%) patients, postileal and preileal in 1 (4%) patient each. In 28 patients operated for acute appendicitis, histopathological examination showed acute appendicitis in 14 (50%) patients, acute suppurative appendicitis in 9 (31%) patients, acute appendicitis with peri appendicitis in 1 (4%) patients, acute-on- chronic appendicitis in 1 (4%) patient, chronic appendicitis in 1 (4%) patient, and normal appendix in 2 (7%) patients. In these two patients appendix had appeared normal during surgery too. Out of these two patients with normal appendix, one had right nephrolithiasis with cholelithiasis and the other patient gave history of passing stone in urine after 04 days of appendectomy. However, clinically both these patients mimicked acute appendicitis at the time of presentation.

**Table 1: USG findings.**

		No. of patients (n=28)	Percentage
<b>USG positive for appendicitis</b>	Acute appendicitis	14	50
	Acute appendicitis with phlegmon formation	02	7
	Appendicolith with free fluid in RIF	02	7
	Probe tenderness suggestive of acute appendicitis	07	25
<b>USG negative for appendicitis</b>	Normal appendix	03	11

**Table 2: Sensitivity and specificity of USG.**

USG findings	Histopathology positive (n=26)	Histopathology negative (n=2)
<b>Positive for acute appendicitis (n=25)</b>	24	1
<b>Negative for acute appendicitis (n=3)</b>	2	1
<b>Sensitivity</b>	92.30%	
<b>Specificity</b>	50.0%	
<b>Positive predictive value</b>	96%	
<b>Negative predictive value</b>	33.33%	

**Table 3: Procalcitonin values in study group and control group.**

PCT (ng/ml)	Group 1 (n=2)	Group 2 (n=21)	Group 3 (n=5)	Group 4 (n=7)
<b>Mean</b>	0.03	0.61	1.62	0.04
<b>SD</b>	0.014	0.055	0.15	0.008
<b>Range</b>	0.02-0.04	0.54-0.74	1.14-2.56	0.03-0.05
<b>F value</b>	393.27			
<b>P value between the groups</b>	<0.0001			
<b>P value</b>	<0.0001 (Group 1 vs. 2); <0.0001 (Group 1 vs. 3); 1.000 (Group 1 vs. 4); <0.0001 (Group 2 vs. 3) <0.0001 (Group 2 vs. 4); <0.0001 (Group 3 vs. 4)			

**Table 4: Diagnostic value of procalcitonin.**

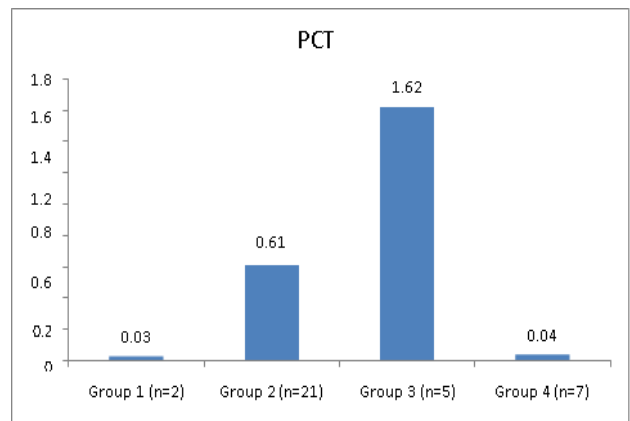
		Histopathological findings	
		Acute appendicitis (n=26)	Normal appendix (n=2)
PCT levels	Elevated	25	0
	Normal	1	2
Sensitivity		96%	
Specificity		100%	
Positive predictive value		100%	
Negative predictive value		66.66%	

Out of these 25 patients diagnosed as acute appendicitis on USG abdomen, 24 patients were found to have acute appendicitis at the time of surgery which was confirmed by histopathological examination of appendix. One patient had normal appendix on HPE. Among 3 patients having negative USG abdomen for appendicitis and being subjected to surgery on clinical basis, one patient had normal appendix on HPE and other 2 patients had acute appendicitis confirmed histopathologically. Hence, the sensitivity and specificity of ultrasound for diagnosis of acute appendicitis was 92.30% and 50% respectively (Table 2). On further analysis based upon the operative findings and histopathological reports the study group (patients with acute appendicitis) was subdivided into 3 groups; group 1, 2 (7%) patients with normal appendix; group 2, 21 (75%) patients with acute uncomplicated appendicitis; group 3, 5 (18%) patients with acute complicated appendix.

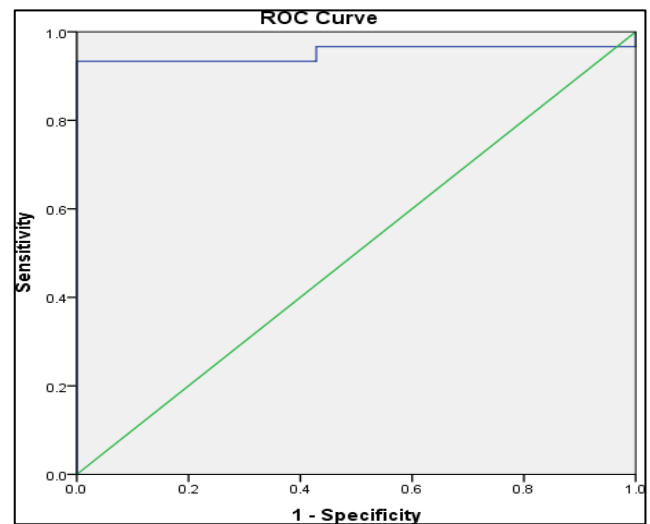
The serum PCT levels in healthy controls (group 4) ranged from 0.03 to 0.05 ng/ml with a mean of 0.04 ng/ml (Table 3). PCT levels in the patients (study group) ranged from 0.02 to 2.56 ng/ml with a mean of 1.29 ng/ml. The mean levels of PCT were higher in the study group (acute appendicitis) as compared to the healthy controls, with statistical significance ( $p < 0.00001$ ). The PCT levels of 2 (7%) patients with normal appendix on HPE were 0.02 and 0.04 ng/ml respectively which were comparable to healthy controls. On further analyzing PCT levels in different groups, i.e. in group 1, group 2, and group 3 patients, it was observed that mean PCT levels were 0.03 ng/ml, 0.61 ng/ml, and 1.62 ng/ml respectively (Figure 2). PCT levels were significantly higher in group 3 as compared to group 1 and group 2 ( $P < 0.0001$ ). In group 2, mean PCT levels were significantly higher in comparison to group 1 ( $P < 0.0001$ ). The value of PCT levels increased with severity of appendicitis. PCT levels were significantly higher in complicated appendicitis as compared to uncomplicated appendicitis.

Out of 26 (93%) of patients with acute appendicitis after operative and histopathological confirmation 1 (4%) patient had normal value of procalcitonin (Table 4). The cause of appendicitis in this patient may be attributed to viral etiology. However, PCT levels were normal in 2 (7%) patients having normal appendix. Thus, sensitivity, specificity, positive predictive value, and negative

predictive value of procalcitonin came out to be 96%, 100%, 100%, and 66.66% respectively.



**Figure 2: Procalcitonin values in study group and control group.**



**Figure 3: ROC curve.**

**Cut off value of procalcitonin**

Statistical analysis of our data shows a ROC (receiver operating characteristic) curve analysis for cut-off value of procalcitonin to be 0.203 ng/ml. We observed sensitivity and specificity of 96% and 100% respectively (area under the curve=0.952; CI: 0.88-1.00).

## DISCUSSION

Acute appendicitis is the most common cause of acute abdomen and emergency appendectomy is the most commonly performed emergency surgery worldwide. Delay in diagnosis and treatment results in an increased rate of perforation, postoperative morbidity, mortality and increased length of hospital stay.<sup>8</sup> Despite all the available sophisticated laboratory and imaging diagnostic modalities, in-hospital observation and repeated clinical examination remains the most common way of diagnosis of acute appendicitis but all these efforts still couldn't lower the NAR which has been reported upto 44%.<sup>4</sup> Several biochemical parameters including white blood cell (WBC) count, C-reactive protein (CRP), interleukin-6 (IL6) and Procalcitonin have been used to further improve the clinical diagnosis of AA.<sup>9</sup> Acute appendicitis can occur in all age groups ranging from infants to geriatrics but 40% of cases are reported in young people ranging from 10 to 29 years of age.<sup>1</sup> In present study also majority of patients (54%) were in age-group of 11-30 years. The age of the patients in our study ranged from 10 to 65 years with a mean age of 29.4 years, which was comparable to observations of Vaziri et al who reported the mean age of 28.57 years in their study.<sup>10</sup> Male predominance of acute appendicitis has been shown by various authors.<sup>1,4,11</sup> Santoso et al reported that 64% of the patients were males in their study.<sup>12</sup> In a study by Khan et al, 77% of the patients of acute appendicitis were males.<sup>13</sup> Likewise, 72% of the patients with acute appendicitis in present study were males. All the patients presented with predominant symptoms of appendicitis viz. migratory pain, nausea and/or vomiting, fever and anorexia. The mean duration of symptoms in our study was 44.64 hours (1.86 days). In a study by Vaziri et al, mean duration of symptoms from onset to presentation to hospital was 33 hours (1.35 day).<sup>10</sup> Nshuti et al has reported that 63% of patients presented within 48 hours of symptoms.<sup>14</sup> Similarly, 53% patients in present study presented within a period of 24 to 48 hours. TLC count was found significantly higher in 75% of patients which is in accordance to findings of Anwar et al where elevated TLC count was reported in 76% of patients.<sup>15</sup> We observed shift to left of leucocytes in 71.42% of patients which was similar to study by Anwar et al where they have observed that 75% of patients with AA had shift to left.<sup>15</sup> Elevated serum bilirubin levels in acute appendicitis can either appear as a result of bacteraemia or endotoxaemia, both possible in the catarrhal and phlegmonous forms as well as in the gangrenous or perforated appendicitis. Hyperbilirubinemia is found to be associated with appendicitis and might be a useful laboratory test for identifying patients with appendiceal perforation and gangrene preoperatively.<sup>16</sup> Total bilirubin levels in present study ranged from 0.44 to 3.30 mg/dl with a mean value of 1.03 mg/dl which was comparable to a study by Thakur et al where mean value of total bilirubin was 1.04 mg/dl.<sup>17</sup> Elevated bilirubin was observed in 36% of our patients which is comparable to the study by Estrada et al where elevated total bilirubin

was reported in 37.55% of patients.<sup>18</sup> In present study 50% of the patients who had gangrenous or perforated appendix had elevated total bilirubin which is similar to findings of Thakur et al where hyperbilirubinemia was found in 69.23% of patients with perforated/gangrenous appendicitis.<sup>17</sup> The sensitivity and specificity of ultrasound for diagnosis of acute appendicitis was 92.30% and 50% respectively. Likewise, Giljaca et al reported sensitivity and specificity were 71% to 92% and 83% to 96%.<sup>19</sup> Position of appendix in present study was retrocaecal in 60% patients, pelvic in 25% patients, paracaecal in 7% patients, postileal and preileal in 4% patient each. Present findings are consistent with findings of Patel et al where they found retrocaecal appendix in 63% patients, pelvic in 18% patients, paracaecal in 5% patients, postileal in 7% patients.<sup>20</sup>

Histopathologically appendix was normal in 2(7%) patients in present study. The negative appendectomy rate was 7%. Anwar et al have reported a negative appendectomy rate of 5.4% to 30%.<sup>15</sup> In present study, out of 26(93%) patients with acute appendicitis after operative and histopathological confirmation, 25 (89%) had elevated levels of serum PCT and 1 (4%) patient had normal value of parocalcitonin. The cause of appendicitis in this patient may be attributed to viral etiology. Various authors have also reported significantly higher levels of PCT in acute appendicitis than healthy individuals.<sup>21-23</sup> Similarly, Assicot et al observed that the PCT levels do not increase in patients with sterile inflammation or viral infection.<sup>24</sup> In present study the sensitivity and specificity of serum PCT measurement for acute appendicitis was 96% and 100%. These findings were similar to a study by Chandel et al where sensitivity and specificity of procalcitonin for diagnosing acute appendicitis was 95.67% and 100% respectively.<sup>25</sup> Kaya et al observed positive and negative predictive value of procalcitonin as 90% and 30% for diagnosing AA, however we found a positive and negative predictive value of 100% and 66.66% respectively.<sup>26</sup> We observed that the patients with acute complicated appendicitis had significantly higher levels of procalcitonin in comparison to the patients with acute uncomplicated appendicitis. The levels of Procalcitonin increased with severity of appendicitis. Yu et al has reported that PCT has little value in diagnosing acute appendicitis.<sup>27</sup> However at the same time it has greater diagnostic value in identifying complicated appendicitis. Kaya et al stated that due to their low sensitivity and diagnostic value, PCT and D-dimer are not better markers than CRP for the diagnosis of acute appendicitis.<sup>26</sup> Wu et al concluded that determination of the PCT level may be useful for risk assessment of Emergency Department patients with suspected complicated appendicitis.<sup>28</sup> Chandel et al have reported that in India the serum PCT was found to be a better indicator for diagnosing the acute appendicitis than the serum CRP and other tests.<sup>25</sup> They concluded that the serum PCT levels when combined with reliable clinical signs and symptoms is an excellent diagnostic marker of

the disease and should be done in appendicitis patients to prevent unnecessary appendectomies.

### Limitations

The limitation of present study was the small sample size. The reason for this was the extremely high price of serum procalcitonin levels, which consumed the allotted grant by the college in a few patients only.

### CONCLUSION

From the results of this study we can extrapolate that serum PCT levels in association with Alvarado score can be used as an excellent diagnostic marker of acute appendicitis including prediction of complicated appendicitis. More randomized controlled trials with large number of patients are required to further validate the use of serum procalcitonin in the diagnosis of acute appendicitis.

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*Conflict of interest: None declared*

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

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