



Role Of Raised C-Reactive Protein (CRP) As the Indicator for Surgical Intervention in Clinically Diagnosed Acute Appendicitis

Mohammad Monjur Hasan Mamun^{1*}, Arun Kumar Pal², Md. Rajibul Hoque³, Sharmila Mondol⁴, Syed Abdul Adil⁵, Mahboob Hasan⁶, Kaniz Fatima Khan⁷

¹Assistant Professor, Department of Surgery, Dhaka Medical College & Hospital, Dhaka, Bangladesh.

Email: sajalmmm@gmail.com

Orcid ID: 0000-0003-2234-1482,

²Assistant Professor, Department of Surgery, Dhaka Medical College & Hospital, Dhaka, Bangladesh.

Email: arunlopa93952002@gmail.com

Orcid ID: 0000-0001-9879-4029,

³Phase B resident, Department of Hepatobiliary and Liver Transplant Surgery, BSMMU, Dhaka, Bangladesh.

Email: rhronyk53@gmail.com

Orcid ID: 0000-0002-303x

⁴Medical Officer, Department of Radiology & Imaging, Dhaka Medical College & Hospital, Dhaka, Bangladesh.

Email: mondolsharmila47@gmail.com

Orcid ID: 0000-0003-4819-8936,

⁵Assistant Professor, Department of Pediatric Surgery, Dhaka Medical College & Hospital, Dhaka, Bangladesh.

Email: adilrupsha@gmail.com

Orcid ID: 0000-0003-0576-3151,

⁶Professor and Head, Department of Surgery, Army Medical College, Chattogram, Bangladesh.

Email: drmhasanhbp@gmail.com

Orcid ID: 0000-0002-9829-4646

⁷Medical Officer, Border Guard Hospital, Dhaka, Bangladesh.

Email: drkaniz75@gmail.com

Orcid ID: 0000-0003-3199-5226

*Corresponding author

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Abstract

Background: The diagnosis of acute appendicitis relies more on the clinical acumen of the surgeon than on the investigations. As the condition is associated with an acute-phase reaction the analysis of WBC, neutrophil percentage and serum level of CRP has been demonstrated to be important diagnostic tools. Surprisingly the level of CRP becomes proportionately raised with increasing severity of the histopathological variety of the appendix. Aim of the study: The aim of this study was to compare the preoperative CRP level with postoperative histological findings and find out a predictive value of CRP as an indicator for surgical intervention in acute appendicitis. **Material & Methods:** It was a prospective, cross-sectional, observational study executed in the Department of Surgery, Dhaka Medical College Hospital from January to December of 2015 where 107 patients were included in this study. Preoperative level of CRP and WBC count was done in all selected patients. Histopathological severity of the resected specimen of the appendix was determined postoperatively. The correlation between preoperative clinical factors and the actual histological severity and identification of surgical indication markers was assessed to determine whether only the CRP level significantly differs between the surgical treatment necessary group and the possible non-surgical treatment group. **Results:** 54% (58) of the patients were female out of a total of 107. Peak incidence (25.2%) was in the 16-20 years age group. Neither age nor gender had any significance with the type of appendicitis. Among the patients 28.1% (30) had gangrenous appendicitis. In patients with histopathologically proven acute appendicitis, both the WBC count and serum CRP level were raised. But only the CRP level significantly differs between gangrenous appendicitis and uncomplicated appendicitis (p-value<0.0001). The specificity and sensitivity of serum CRP for gangrenous appendicitis were 97% and 71% respectively. The ROC curve indicated that the cutoff value of CRP for gangrenous appendicitis is 6.2 mg/dl. **Conclusions:** A normal pre-operative serum CRP measurement in patients with suspected acute appendicitis is most likely associated with a normal or uncomplicated inflammation of the appendix. The rate of unnecessary appendectomies would probably reduce in this patient group by deferring surgery. Only the CRP level is consistent with the severity of appendicitis and can be considered to be a surgical indication marker for acute appendicitis.



Keywords:- Acute appendicitis, C-Reactive protein (CRP), WBC count, Pre-operative, Histopathology, Receiver-operating characteristic (ROC), ALVARADO.

INTRODUCTION

By most to be a vestigial organ, the vermiform appendix is considered. Its importance in surgery results only from its propensity for inflammation, which results in the clinical syndrome known as acute appendicitis.^[1] The dominant aetiological factor is obstruction of the lumen of the appendix, faecoliths being the most common cause of appendiceal obstruction. Hypertrophy of lymphoid tissue, tumors, and intestinal parasites constitutes a less common cause. The traditional concept has been that there is a predictable sequence of events that ultimately lead to eventual appendiceal rupture. Obstruction at the proximal part of the appendiceal lumen produces a closed-loop obstruction. But rapid distention occurs owing to continuous normal selection by appendiceal mucosa with the rapid multiplication of the resident bacteria of the appendix. With a progressive increase in the pressure in the organ, venous pressure is exceeded. In engorgement and vascular congestion, capillaries and venules are occluded, but arteriolar inflow continues, resulting. Soon serosa of the appendix followed by parietal peritoneum in the region is involved in the inflammatory process, which produced the characteristic shift in pain to the right lower quadrant. With progressive distention compromising the venous return and subsequently the arteriolar inflow, the area with the poorest blood supply, the antimesenteric border develops ellipsoidal infarcts. As distention, bacterial invasion, compromise of the vascular supply, and infarction progress,

perforation occurs, usually through one of the infarcted areas on the antimesenteric border.^[2] The classical clinical features patients with acute appendicitis present with a history of vague central abdominal pain. Nausea or vomiting and anorexia usually coexist with mildly elevated temperatures. After up to 24 hours pain shifts to the right iliac fossa. When the pain has moved there may be localized tenderness, guarding, rebound, and percussion tenderness in the right iliac fossa, the maximal site being one-third of the way from the anterior superior iliac spine to the umbilicus. This classical picture may vary owing to different positions in the appendix.^[3] Inflammation of the appendix ranges from minor, simple, acute inflammation with a spontaneous resolution to suppurative necrosis, gangrene, and perforation.³ Still then appendectomy primarily has been the treatment for acute appendicitis for over 120 years irrespective of its type of presentation.^[4] However Only 20% of patients present with complicated appendicitis, and non-operative management with antibiotics and supportive treatment has been explored as a therapeutic option for patients with early uncomplicated appendicitis, with resolution in most of them.^[5] A recent prospective multi-center randomized controlled trial has demonstrated that simple acute appendicitis can be initially treated successfully by non-surgical management with antibiotics and percutaneous drainage if necessary.^[6,7,8] Furthermore this initial non-surgical management has been shown to be safe and effective; though the risk of recurrent appendicitis after non-surgical treatment is 5% to 37%.^[6,9] On the other hand, acute complicated

appendicitis should be treated with emergency surgery.^[10] Traditionally the diagnosis of acute appendicitis relies more on clinical suspicion and physical findings. Laboratory and imaging studies are done to mere exclude other pathologies. However, the focus has always been to establish the preoperative diagnosis of acute appendicitis rather than determining its pathological varieties which are actually done by per-operative findings and postoperative histopathology. With the possible non-operative management of uncomplicated acute appendicitis, the question arises regarding the preoperative determination of a pathological variety of acute appendicitis so as to avoid unnecessary surgery. In this context, any novel diagnostic tool that can foretell the type of pathological variety of appendix might help the surgeon to establish a firm indication for the possible surgical intervention.

OBJECTIVES

General objective:

To correlate preoperative raised serum CRP level with histopathological findings of surgically treated appendicitis.

Specific objective:

1. To measure serum CRP level and total and differential WBC count in all clinically diagnosed acute appendicitis.
2. To find out the histological findings of the resected appendix.
3. To correlate the actual histological severity of the resected appendix with the level of CRP.
4. To compare serum CRP levels between gangrenous and non-gangrenous appendicitis.

5. To determine the exact cutoff value of CRP for gangrenous appendicitis.
6. To find out the sensitivity and specificity of CRP for the gangrenous appendix.
7. To compare the positive predictive value of CRP and the total count of WBC.

MATERIAL AND METHODS

It was a prospective, cross-sectional observational study, conducted in the Department of Surgery, Dhaka Medical College & Hospital, Dhaka from the period in January 2012. A total of 107 patients were selected as the study sample based on inclusion and exclusion criteria.

Inclusion criteria:

Clinically diagnosed patients with acute appendicitis who underwent appendicectomy

Exclusion criteria:

- Patients with co-existing chronic or acute diseases; i.e., cardiovascular, arthritis diseases
- Immunocompromised patients (DM, corticosteroid therapy)
- Pregnant patients
- Patients with pre-operative findings suggested diseases other than appendicitis

A convenient sampling technique was followed for sample selection. Ethical clearance was taken from the ethical research committee of Dhaka Medical College. Informed written consent was taken from all of the study participants or legal guardians after adequately explaining to them, the purpose of the study. After getting written consent from the patients or legal guardians in a preformed consent form,

in each case, information about the patient was collected in a prescribed questionnaire. All data gathered from the data collection sheet was transferred to Microsoft Excel version Office 2010. After compilation, these data were shifted to statistical analysis software for further

analysis. Then the results were taken in the bar chart, pie chart, ROC curve, and table format. Data were compiled in Microsoft Excel version Office 2010. Later on, it was transferred to SPSS (Statistical Package for Social Science) version 14.0.0 for statistical analysis.^[11]

RESULTS

Table 1: Gender wise pathological types of acute appendicitis (N=107)

Gender	Pathological type of acute appendicitis			P-value
	Uncomplicated (n=74)	Gangrenous (n=30)	Normal (n=3)	
Male	32 (65.3%)	15 (30.6%)	2 (4.1%)	0.634
Female	42 (72.4%)	15 (25.9%)	1 (1.7%)	

Table 2: Pathological types of appendicitis (N=107)

Pathological types	n (%)
Normal Appendix	3 (2.8%)
Uncomplicated	74 (69.2%)
Gangrenous	30 (28.0%)

After postoperative histopathology of appendicitis, out of 107 patients, 3(2.8%) were normal types, 74 (69.2%) were uncomplicated, and the rest 30(28%) were gangrenous types of appendicitis.

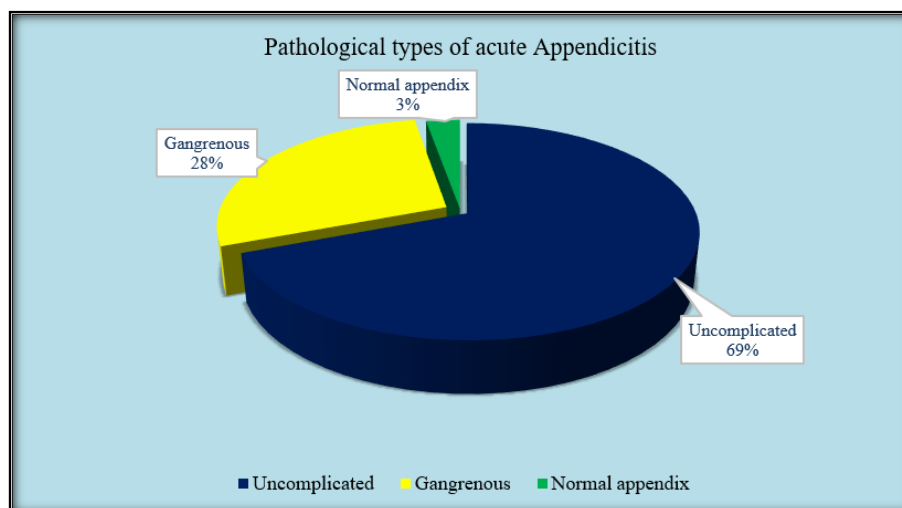


Figure 1: Pathological types of acute Appendicitis

Table 2: ALVARADO score in patients with uncomplicated appendicitis and gangrenous appendicitis

ALVARADO score*	Pathological type of acute appendicitis			P-value
	Uncomplicated (n=74)	Gangrenous (n=30)	Normal (n=3)	



>8	12 (52.2%)	11 (47.8%)	0	0.005* ^s
8	25 (83.3%)	5 (16.7%)	0	
7	15 (51.8%)	13 (44.8%)	1 (3.4%)	
6	15 (93.8%)	1 (6.2%)	0	
5	5 (83.3%)	0	1 (16.7%)	
<5	2 (66.7%)	0	1 (33.3%)	

*ALVARADO score- Based on 8 different parameters for the diagnosis of acute appendicitis

Table 3: Per-operative and postoperative evaluation of the condition of the Vermiform Appendix (N=107)

	Normal Appendix (n=3)	Uncomplicated Appendicitis (n=74)	Gangrenous Appendicitis (n=30)
Per-operative naked-eye evaluation*	4 (3.7%)	71 (66.3%)	32 (30%)
Histological evaluation#	3 (2.8%)	74 (69.2%)	30 (28%)

*Operation notes

#Histo pathology report

Table 4: Preoperative laboratory findings and histological severity of Acute Appendicitis (N=107)

	CRP		Total Count of WBC		Neutrophil Percentage	
	Normal	Raised	Normal	Raised	Normal	Raised
Normal Appendix (n=3)	2(66.7%)	1(33.3%)	2(66.7%)	1(33.3%)	2(66.7%)	1(33.3%)
Uncomplicated Appendicitis (n=74)	6(8.1%)	68(91.9%)	11(14.9%)	63(85.1%)	21(28.4%)	53(71.6)
Gangrenous Appendicitis (n=30)	0(0.0%)	30(100%)	2(6.7%)	28(93.3%)	4(13.3%)	26(86.7%)

Table 5: Comparison between the histological severities and Laboratory Findings (N=107)

	Uncomplicated (n=74)	Gangrenous (n=30)	Normal (n=3)	P-value
CRP level (mg/dl) (mean ± SD)	4.48±2.36	11.84±3.82	0.5±0.26	0.0001* ^s
WBC count (x100/mm ³) (mean ± SD)	129.62±18.04	134.27±18.04	106.67±24.67	0.077* ^{ns}
Neutrophil percentage (%) (mean ± SD)	82.70±7.04	85.43±6.02	71.33±10.97	0.081* ^{ns}

Table 6: Diagnostic accuracy, sensitivity, and specificity of WBC count and CRP in uncomplicated and gangrenous acute appendicitis (N=107)

Diagnostic test		Pathological type of acute appendicitis	
		Acute Appendicitis	Gangrenous Appendicitis
CRP	Sensitivity	94%	97%
	Specificity	67%	71%
	PPV*	94%	57%
	NPV**	25%	98%

	Diagnostic accuracy	93%	80%
WBC	Sensitivity	87%	63%
	Specificity	67%	51%
	PPV*	98%	33%
	NPV**	13%	78%
	Diagnostic accuracy	87%	55%

*OPP: Positive predictive value

**NNV: Negative predictive value

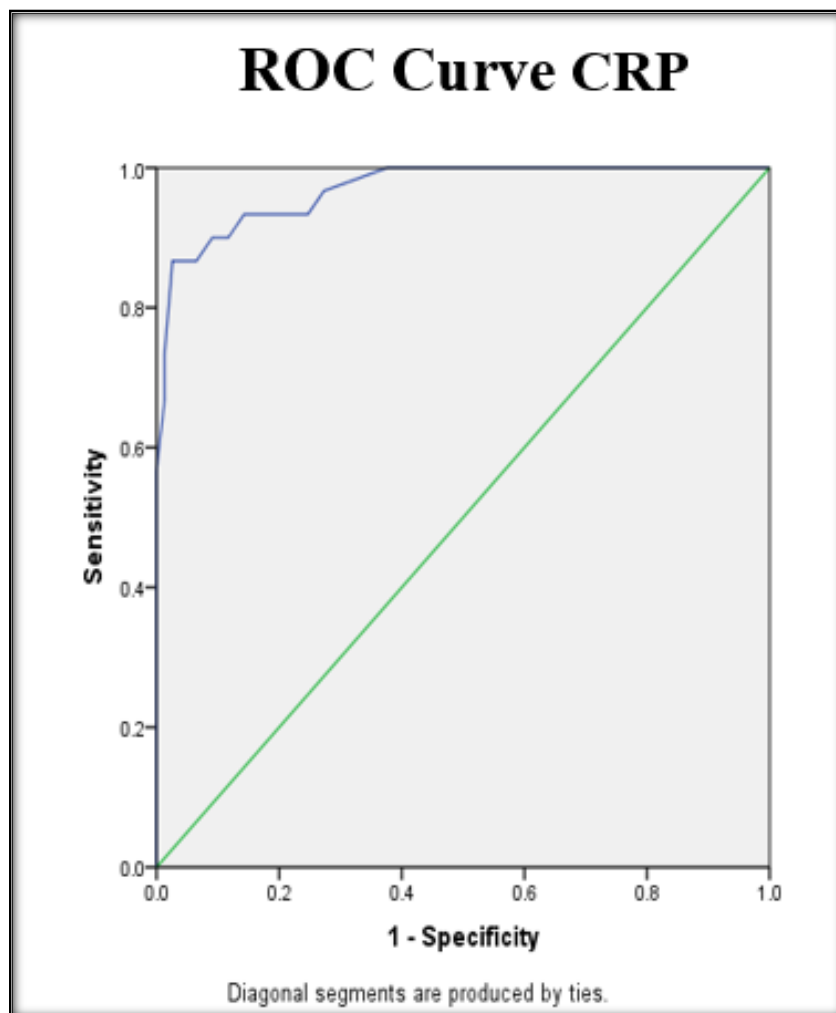


Figure 2: Receiver-operating characteristic (ROC) curve for serum C-reactive protein (CRP) levels of gangrenous appendicitis.

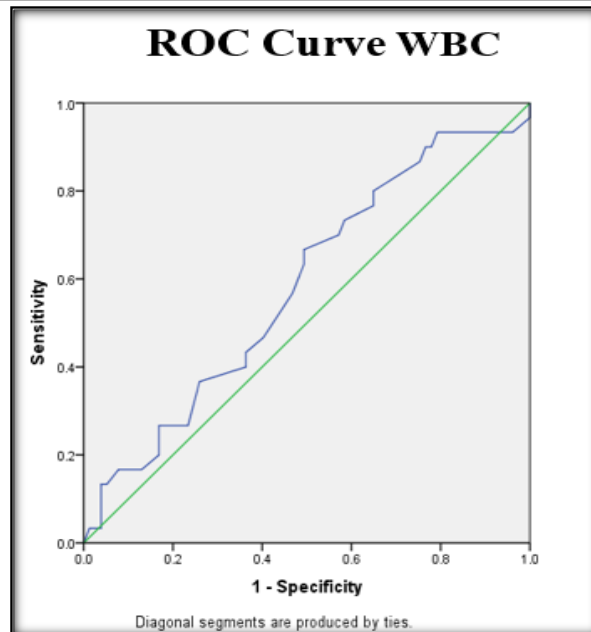
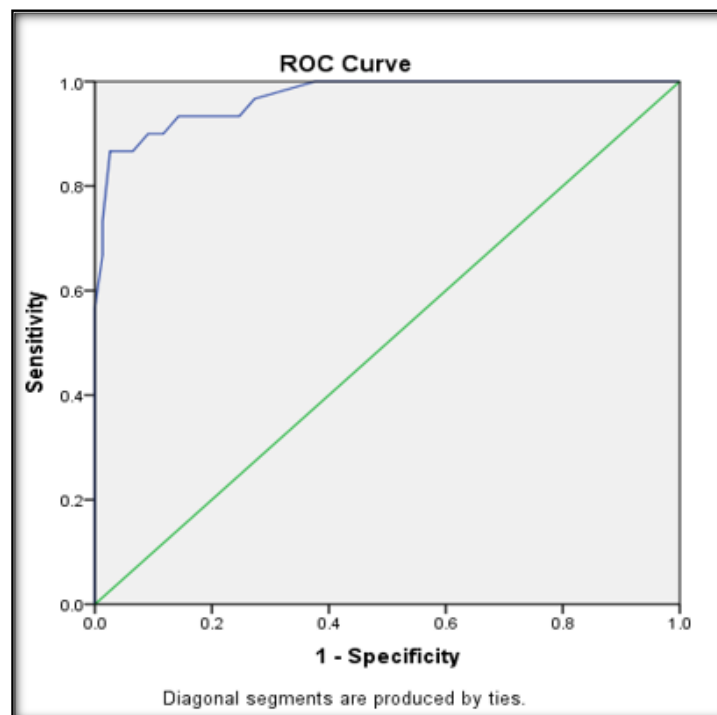


Figure 3: Receiver-operating characteristic (ROC) curve for WBC count of gangrenous appendicitis.



DISCUSSION

In this study, the sampling method was followed purposively so, the gender difference

was not properly represented. However, still, the current report hardly makes a difference in the male-female ratio in the incidence of acute



appendicitis.^[1,2] Gender differences had no significance in the progression of gangrenous appendicitis. Inflammatory markers should not be considered specific for any medical or surgical disease. However, when applied to patients with suspected acute appendicitis they could be a helpful diagnostic tool. To date, many inflammatory markers have been used for the diagnosis of acute appendicitis. CRP and WBC counts are the most common and widely used laboratory tests.^[12] In addition to finding more novel inflammatory parameters research on D-dimer, procalcitonin, IL-6 and IL-10 has also been tried by various studies.^[13,14,15] Both WBC count and CRP were not so accurate laboratory data for the diagnosis of uncomplicated appendicitis in the current study. Accuracy, sensitivity, and specificity were 93, 94, and 67 percent for CRP and 87, 87, and 67 percent for WBC count in uncomplicated appendicitis. However predictive values of CRP for appendicitis have been very heterogeneous in the medical literature (sensitivity ranging from 40 percent to 99 percent and specificity from 27 percent to 90 percent).^[16,17,18] Sensitivity in the current study was consistent with values obtained by other authors but specificity was higher.^[12] Any laboratory test for appendicitis should have a high sensitivity to avoid a late diagnosis, but also a high specificity to avoid unnecessary further studies or negative appendectomies.^[19] The dynamic usefulness of inflammatory parameters has been pointed out by some authors which performed repeated laboratory examinations in patients with equivocal signs.^[20] It has been suggested that CRP could accurately predict perforated appendicitis in children and adults.^[21] Results from the present study confirm a close correlation between CRP and the severity of

appendicitis, which is consistent with the results reported by Grönroos et al.^[20] The current study showed that the WBC counts and neutrophil percentage are not useful for a surgical indication. However univariate analysis indicated that only CRP was significantly different between gangrenous appendicitis and uncomplicated appendicitis. Multivariate analysis showed that only CRP was an independent marker for the gangrenous appendix. The optimal cutoff value of CRP derived from the ROC curve was around 6.2 mg/dl. Distinguishing between perforated or gangrenous and uncomplicated appendicitis becomes more important as an increasing number of authors claim that these are different entities.^[9] Gangrenous or perforated appendicitis requires emergent surgery whereas non-perforated appendicitis can be accurately delayed. Even some authors suggest that medical treatment could be suitable for uncomplicated appendicitis.³⁻⁵ Findings in the current study give additional information for the surgical indication for appendicitis. Numerous previous studies have shown that retrospective study has documented that the sensitivity of CRP in these patients is greater than 90%.^[22] Furthermore, the negative appendectomy rate is reduced by approximately 8% if surgery is canceled in patients with CRP levels and white blood cell counts within the reference range.^[23] Another prospective study has shown that it is important to measure serial CRP levels and white blood cell counts in patients with suspected appendicitis.^[17] The sensitivity of CRP levels in predicting appendicitis was 60% on admission and increased to 100% by the fourth blood specimen. Conversely, white blood cell counts exhibited a sensitivity of 95% on admission but

dropped to 75% by the fourth specimen. The limitation of this study was the single serum CRP level done during admission only. Other studies confirm that an elevated CRP serves as a systemic marker of focal inflammation and infection.^[23,24] The current study clearly suggested that CRP leads to precise prediction of the severity of acute appendicitis for treatment. However, CRP is not specific to appendicitis, and one should consider the presence of other diseases such as a diverticulum, inflammation of the ileum, or urogenital and gynecological disorders. Therefore, before using our system for surgical indication, clinicians interpreting clinical information must depend on their subjective experience and modalities.

CONCLUSIONS

In conclusion, it can be said that serum CRP level is the most useful laboratory parameter in the evaluation of acute appendicitis and is strongly correlated to the severity of the inflammation and accurately detect gangrenous appendicitis. Patient with acute appendicitis with serum CRP level below the cut-off value (6.2 mg/dl) has a very low chance of gangrenous appendicitis; emergent surgery is not indicated and clinical observation or further imaging is the best choice of management in this

setting. A multicenter randomized double-blinded prospective study with a larger sample size would be beneficial to evaluate the role of current as well as newer inflammatory markers like PCT, D-dimer, IL-6, and IL-10. Newer technologically advanced diagnostic modalities like computed tomography and diagnostic laparoscopy should be evaluated in the settings of our country. The role of CRP in the atypical presentation of acute appendicitis needs to be clarified to avoid negative laparotomies. A re-evaluation of the clinical findings should be done to explore the possibility of diagnosing gangrenous appendix by the clinical impression of the clinician.

Limitation of the Study

This study was conducted with small sample size, so the findings may not represent the whole scenario. No randomization or blinding method was followed in the study. This might probably raise the sampling error & biasness. The role of CRP in the negative laparotomy has not been clarified with the incidences of negative laparotomies in the study setting. The possibility of the gangrenous appendix by the clinical impression of the clinician and preoperative visual impression has not been correlated with the level of CRP.

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