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ORIGINAL ARTICLE

C-Reactive Protein and White Blood Cell Count as Biomarkers in the Diagnosis of Acute Appendicitis in Adults

C Odion[1], A E Dongo[1], J Kpolugbo[1], C Imoloamen[1], V Odigie[2], A A Okomayin[1], E Tagar[1]

ABSTRACT

Background: The diagnosis of acute appendicitis is largely clinical and once established, management ensues. However, diagnostic difficulties may arise, leading to negative appendicectomies of 15% – 30% if surgery is effected. Attempts are being made to reduce this high negative appendicectomy rate.

Aim: To analyse the roles of White Blood Cell (WBC) count and C-Reactive Protein (CRP) in improving the accuracy of diagnosing acute appendicitis.

Methods: This was a cross-sectional, prospective study on Sixty-six (66) patients who presented to the accident and emergency ward of Irrua Specialist Teaching Hospital (ISTH) and diagnosed clinically as acute appendicitis. WBC count and CRP were done for all recruited patients preoperatively. All recruited patients had appendicectomy and the appendixes sent for histology.

Results: The mean age was 30 years ± 14 SD and male: female ratio was 1:1.8. The negative appendicectomy rate in this study was 19.7%. The diagnostic accuracy, sensitivity, specificity and positive predictive value for WBC count were 73%, 72%, 77% and 93% respectively. The diagnostic accuracy, sensitivity, specificity and positive predictive value for CRP were 80%, 79%, 85% and 95% respectively. Combining both markers gave accuracy, sensitivity, specificity and positive predictive value of 91%, 91%, 90% and 97% respectively. With ROC curve construction, CRP was a slightly better biomarker than WBC (AUC CRP: 0.79, p=0.0012; AUC WBC: 0.76, p=0.028).

Conclusion: Combined WBC and CRP improved predictive ability for acute appendicitis. Overall, CRP is a slightly better biomarker than WBC in predicting acute appendicitis.

Key words: Acute appendicitis, appendicectomy, negative appendicectomy, white blood cell count, c-reactive protein

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[1] Department of Surgery, Irrua Specialist Teaching Hospital, Irrua.
[2] Department of Surgery, University of Benin Teaching Hospital, Benin City

Corresponding Author: Dr. Clement Odion, Department of Surgery, Irrua Specialist Teaching Hospital, Irrua. Edo State. Nigeria.

INTRODUCTION

Acute appendicitis remains one of the most common diseases treated by the general surgeon, with appendicectomy being the most commonly performed emergency surgery.[1]

The clinical diagnosis of acute appendicitis relies upon a detailed history, and thorough physical examination.[2] The diagnosis is largely clinical and once established, operative management ensues.[3]

Appendicitis is generally thought to have a low incidence rate in sub-Saharan Africa and in other developing countries in Asia and Latin America.[4] This may be explained by persons in these areas consuming a high fibre diet, creating a low transit time, and thus accounts for a low incidence of faecoliths as causative factor in acute appendicitis.[5] However, increasing incidence in some African countries have been reported by some authors in the last few decades.[6] Changing to a Western lifestyle, including diets, has accounted for this.[7] Contrary to the previously held belief, appendicitis is not rare in Africans.[8] In fact, in the 1970's, it was recognised as the most common cause of acute abdomen in the surgical service at the University College Hospital (UCH), Ibadan, Nigeria.[8]

The true population incidence of appendicitis in developing countries, like Nigeria, is unknown due to poor record keeping and unreliable population census.[9] Estimates of population incidence of appendicitis in countries like Ghana, Madagascar, Central African Republic and Ethiopia have relied on small population counts. However, these figures have shown a low incidence in comparison to countries in Western Europe and North America.[9] Ahmed *et a*l gave an incidence rate of 2.6 per 100,000 per annum in Northern Nigeria, over a ten-year period.[9]

Seasonal variations of acute appendicitis have also been reported widely, with paucity of information from Nigeria.[6] Higher incidences have been reported in the summer months by many authors.[6] Ashley reported an excess during spring, implicating viral infections as causative factor.[10] Oguntola *et al* found that appendicitis was more common during the rainy season in South-western Nigeria, a period of high humidity, high incidence of bacterial and viral infections and high prevalence of intestinal parasites.[6]

Despite appendicitis being a common disease, its presentation is not always typical and misdiagnosis is not uncommon.[11] Misdiagnoses have a major impact on healthcare systems, as well as important legal consequences.[12] Moreover, diagnostic difficulties may lead to negative appendicectomies,[13] or cases of missed appendicitis which might result in complications such as appendiceal perforation or abscess formation.[14] The rate of negative appendicectomy has been reported to be 15-30%,[15] with the reported postoperative morbidity associated with these negative explorations being 5-15%.[15]

To this end, diagnostic aids such as scoring systems,[16] ultrasonography, computed tomography (CT)[17] or even magnetic resonance imaging (MRI)[18] have been devised.

Some of these imaging modalities like CT scan and MRI are not readily available in our environment, and where present they tend to be very expensive. There's also concern for exposure to radiation as in the case of CT scan. Inflammatory markers such as white blood cell (WBC) count and C-reactive protein (CRP) are readily available and are commonly performed in patients with suspected appendicitis.

Thus, there's need to investigate these biomarkers with a view to improving the accuracy of diagnosis, and of course reduce the incidence of negative appendicectomies.

Therefore, the aim of this study was to provide local data on the roles of WBC count and CRP in

improving the accuracy of diagnosis of acute appendicitis and thus reducing the rate of negative appendicectomies.

MATERIALS AND METHODS

This was a cross-sectional, hospital based, prospective study carried out on 66 consenting patients who presented with right sided lower abdominal pain over a period of 12 months.

Inclusion criteria: Adult patients presenting with acute right iliac fossa pain in whom acute appendicitis was suspected, with duration of symptoms of at least 8 hours and who were 18 years and above, were included in the study.

Exclusion criteria: The following patients were excluded from the study:

1. Patients who are pregnant and patients with background diabetes mellitus, rhinosinusitis, cardiovascular diseases, gout and other cofounders that ordinarily could lead to elevation of CRP & WBC count.
2. Patients who opted for non-surgical treatment
3. Patients who declined to participate in the research.
4. Patients who had antibiotics/anti-inflammatory agents use for 5 days or more as this may affect the blood picture of the biomarkers CRP and WBC

Once consent was obtained, the patients were recruited into the study, taking into consideration the conditions for inclusion and exclusion.

At admission, blood samples for CRP and FBC (of which WBC count was studied) were obtained from all prospective patients for the purpose of this study. About 3mls of blood was collected in a plain bottle for the CRP and another 3mls of blood into Ethylenediamine tetraacetic acid (EDTA) bottle for FBC.

The 66 patients recruited into the study had appendicectomy. However, the decision to operate was based on clinical grounds and not influenced by the results of laboratory investigations.

Intraoperative Staging: A Lanz incision was used for all the appendicectomies. The position of the appendix was noted on entering the peritoneal cavity before delivery into the wound. Once the appendix was delivered, it was inspected macroscopically and staged as follows:

A. Normal appendix, if there was no evidence of inflammation, gangrene or perforation.
B. Inflamed appendix, if it was hyperaemic, oedematous, turgid.
C. Gangrenous appendix, if it had blackish discolouration or its surface had a fibrino-purulent coating.
D. Perforated appendix, if there was frank perforation, with visualization of the lumen.

The removed appendix was put in 10% neutral buffered formalin solution and fixed with paraffin for histology.

Patients were observed postoperatively till discharge and followed up in the outpatient clinic. The histopathology report was retrieved. Based on histopathology report, patients were postoperatively diagnosed either as positive or negative for appendicitis. The basis for histopathological diagnosis of acute appendicitis was the presence of neutrophil(s) in the muscularis propria of the vermiform appendix.[19]

Data Collection: Data was collected using a proforma designed for this study. All relevant information including biodata, clinical, laboratory, intraoperative and histological findings were entered into the proforma sheet at the time of presentation, and when subsequent data became available.

Statistical Analysis: Data were entered in a spread sheet and analysed using IBM SPSS (statistics package for social sciences) version 21.[20] The gender, level of education, occupation, ethnic groups, clinical features, intraoperative findings and histology report were measured as categorical variables. Age and laboratory reports were measured as numerical variable. Laboratory reports (WBC and CRP) were categorised into normal and high using cut-off values used by the laboratory. The normal cut off value for WBC was 8000 cells/mm^3 and for CRP was 6.5mg/L.

Receiver Operating Characteristics (ROC) Curve was constructed to compare WBC count and C-reactive protein. The construction of a Receiver Operating Characteristics (ROC) Curve is a method of comparing different tests by determining the area under the curve for each of the tests. A statistical test was then used to determine if the area under one curve differed significantly from the area under the other curve(s).[21]

RESULTS

A total of 66 patients who met the inclusion criteria were recruited into the study, and their data were analysed.

The age range of the participants was 18 – 90 years, with median age of 25 years and mean age of 30 years ± 14SD. The largest proportion of patients was in the age group 18 – 25 years, representing 50% of the participants.

There were 24 males and 42 females in this study, giving a male-female ratio of 1:1.8.

Table 1 shows the preoperative laboratory results (white blood cell count and C-reactive protein)

Table 1: Laboratory Reports of Study Participants

Variables	Frequency (n=66)	Percent (100%)
Preoperative laboratory findings		
WBC (Cells/mm^3)		
Normal	25	37.9
High	41	62.1
CRP (mg/L)		
Normal	22	33.3
High	44	66.7

WBC (white blood cells), Mean ± SD = 9746 ± 4531;
CRP (C-reactive protein), Mean ± SD = 6.8 ± 2.8

Table 2: Intraoperative findings

Variables	Frequency (n=66)	Percent (100%)
Position of appendix		
Rectroceacal	48	72.8
Pelvic	15	22.7
Preileal	2	3.0
Postileal	1	1.5

Of these 66 patients, 1(1.5%) had intraoperative macroscopic staging of normal appendix, 49 (74.2%) had inflamed appendix, 5 (7.6%) had gangrenous appendix and 11 (16.7%) had ruptured appendix.

All 66 patients had appendicectomy based on clinical diagnosis of acute appendicitis. Of these 66 patients, retrocaecal appendix was seen in 72.7%, pelvic 22.7%, pre-ileal 3.0% and post-ileal 1.5% (Table 2).

Of those with ruptured appendix, 5 (7.6%) had rupture at the tip, 3 (4.5%) at the body and 3 (4.5%) at the base.

In 13 of these 66 patients who had appendicectomy, normal appendix was found histopathologically, representing a negative appendicectomy rate of 19.7% (figure 1)

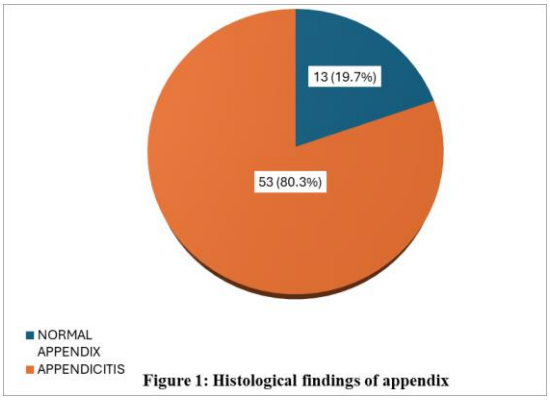

Figure 1: Biological findings of appendix

Table 3: Association between Sociodemographic Characteristics and Acute Appendicitis

Variables	k		Total
	Appendicitis	No Appendicitis	
Gender			
Male	22(91.7%)	2(8.3%)	24(100%)
Female	31(73.8%)	11(26.2%)	42(100%)
*p-value= 0.072			
Age in group (years)	37(74%)	13(26%)	50(100%)
16-35	12(100%)	0(0%)	12(100%)
36-45	4(100%)	0(0%)	4(100%)
≥ 46	p-value=0.075		
Chi value =5.18			

*Fishers Exact

The preoperative WBCs and CRPs were analysed to see their relationship to histology (Table 4). Out of 53 confirmed cases on histopathology, 38 positive cases of WBC were true positives yielding a sensitivity of 72.8%. Out of 13 confirmed negative cases on histopathology, 10 negative cases of WBC were true negatives, giving a specificity of 77%. Out of 41 positive cases of WBC, 38 were true positives, thus giving a positive predictive value of 93%. There were 25 negative cases of WBC with 10 being true negatives. This gave a negative predictive value of 40%. Thus, overall accuracy of WBC in the diagnosis of acute appendicitis was 73%. The LR+ and LR- were 3.1 and 0.36 respectively, thus giving odds ratio of 8.6.

All patients with negative appendicectomy were within the age group of 16 – 35 years age, with 84.6% of them being females (Table 3). There was no significant difference between the presence of acute appendicitis and gender, p=0.072; although 26.2% of females had negative appendicitis on histology compared to 8.3% of males. There was no significant difference between the presence of acute appendicitis and age in group, p=0.075; although 26% of study participants between the age group 16-35 years had no appendicitis compared to the other age groups (0%).

Table 4: Comparing White Blood Cell Count Values and Histology (True Disease Status) of Study Participants

	Histology (Gold Standard)		
Test Results	**Appendicitis**	**No Appendicitis**	**Total**
White blood cell (high)	38 (True Positive)	3 (False Positive)	41
White blood cell (normal)	15 (False Negative)	10 (True Negative)	25
Total	53	13	66

Out of 53 confirmed cases on histopathology, 42 positive cases of CRP were true positives yielding a sensitivity of 79% (Table 5). Out of 13 confirmed negative cases on histopathology, 11 negative cases of CRP were true negatives, giving a specificity of 85% (Table 5). Out of 44 positive cases of CRP, 42 were true positives, thus giving a positive predictive value of 95%. There were 22 negative cases of CRP with 11 being true negatives. This gave a negative predictive value of 50%. Thus, overall accuracy of CRP in the diagnosis of acute appendicitis was 80%. The LR+ and LR- were 5.13 and 0.24 respectively, thus giving odds ratio of 21.4.

Table 5: Comparing C - reactive protein Values and Histology (True Disease Status) of Study Participants

	Histology (Gold Standard)		
Test Results	**Appendicitis**	**No Appendicitis**	**Total**
C - reactive protein (high)	42 (True Positive)	2 (False Positive)	44
C - reactive protein (normal)	11 (False Negative)	11 (True Negative)	22
Total	53	13	66

Table 6: Predictive Values of both Tests (C-Reactive Protein and White Blood Cell Count) in the Diagnosis of Acute Appendicitis

	Histology (Gold Standard)		
Test Results	**Appendicitis**	**No Appendicitis**	**Total**
C - reactive protein and WBC (high)	30 (True Positive)	1 (False Positive)	31
C - reactive protein and WBC (normal)	3 (False Negative)	9 (True Negative)	12
Total	33	10	43

Table 6 shows the predictive values of combination of both tests (WBC & CRP) in the diagnosis of acute appendicitis. Combined WBC and CRP were elevated in 31 cases and normal in 12 cases. Out of the 33 confirmed cases on histopathology, 30 positive cases of both tests combined were true positives, yielding a sensitivity of 91%. Out of 10 confirmed negative cases on histopathology, 9 negative cases of both tests combined were true negatives, giving a specificity of 90%. Out of 31 positive cases of both tests combined, 30 were true positives, thus giving a positive predictive value of 97%. There were 12 negative cases of both tests combined, with 9 being true negatives. This gave a negative predictive value of 75%. Thus, overall accuracy of both tests combined in the diagnosis of acute appendicitis was 91%. The LR+ and LR- were 9.1 and 0.101 respectively, thus giving odds ratio of 90.

Table 7 shows a summary of the indices of diagnostic values for White Blood Cell count, C-reactive Protein, and combination of both White Blood Cell count, C-Reactive Protein.

Table 7: Summary of Diagnostic Accuracy, Sensitivity, Specificity, Positive Predictive Values of all the tests

	Indices of Diagnostic Values			
Diagnostic Method	**Accuracy (%)**	**Sensitivity (%)**	**Specificity (%)**	**Positive Predictive Value (%)**
White blood cell count (WBC)	73	72	77	93
C-reactive protein (CRP)	80	79	85	95
WBC+CRP	91	91	90	97

ROC (Receiver Operating Characteristics) curve analysis was performed to assess the diagnostic accuracy of CRP and WBC in predicting acute appendicitis (Figures 4 & 5). The area under the curve (AUC) for CRP, 0.79, P-value = 0.0012, was slightly higher than that of WBC count, 0.76, P-value =

0.0028. The p-value of both tests were statistically significant, being < 0.05. However, both tests showed a moderate predictive power.

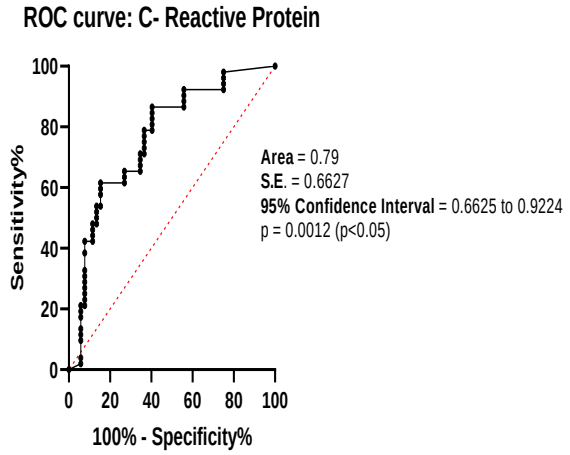

Figure 2: Receiver Operative Characteristic (ROC) curve with corresponding area under the curve (AUC) for C - reactive protein in predicting acute appendicitis

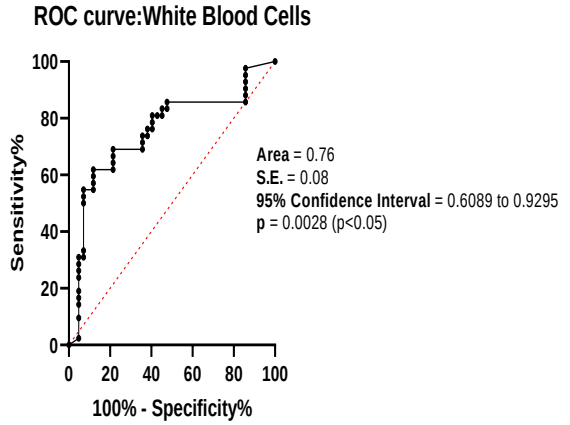

Figure 3: Receiver Operating Characteristics (ROC) curve with corresponding area under the curve (AUC) for white blood cell count in predicting acute appendicitis

DISCUSSION

The diagnosis of acute appendicitis is largely clinical. This implies a detailed history and thorough physical examination.[22] The most important step in the management of patients with suspected acute appendicitis is reaching the decision about operative intervention and its timing so that both appendicectomies and complicated appendicitis are kept to a minimum.[23] The burden of NA cannot be over emphasized. It is associated with appreciable degree of morbidity and mortality, including a significant increase in length of hospital stay, complications due to postoperative infection and death.[24] It is also a significant contributor to healthcare costs; Flum & Koepsell[24] estimated that NA accounted for nearly $750 million in healthcare costs in a single year in the United States of America (USA). Therefore, high rates of negative appendicectomy should no longer be considered acceptable.[25] Thus, there's no gainsaying the fact that reducing negative appendicectomy should become part of the considerations in the management of patients with suspected acute appendicitis.

In this study, the negative appendicectomy was 19.7%. This is in keeping with the overall negative appendicectomy of 15 – 30%.[15] This might be attributed to thorough history and examination of the patients before labelling them as cases of acute appendicitis. Several authors have reported varied rates. For example, Osime *et al* reported a NA rate of 16.1% at Chevron Hospital in Warri Nigeria, over a 5 year period.[26] Okobia *et al* in Benin City, Nigeria reported a NA rate of 32.2% with representation of both males and females.[27] Ogbonna *et al* reported a NA rate of 29.7% in males and 47% in females over a 5 year period in Jos, Nigeria.[28] Kpolugbo *et al* reported a NA rate of 47.2% over a 15 month period to assess the diagnostic accuracy of appendicitis.[29] In his study, Ajao reported a NA of 29.8%[8]. A low rate of 11.7% was reported by Ojo *et al*[30], while Edino *et al* reported a rate of 14.1%.[31]

Majority of the negative appendicectomies in this study were seen in women (26.2%), with males representing 8.3%. This is not unexpected as females have been reported to have a consistently higher incidence of negative appendicectomies.[26] The main reason for this is thought to be due to the high incidence of gynaecologic disorders in females, especially in the 2nd and 3rd decades of life.[26]

These patients who had negative appendicectomies were symptom free as at when the histology results became available. This may be due to antibiotics that was given to them while they were on admission. Thus, the actual cause of their right lower quadrant pain was not known. Not knowing the exact cause of this pain was a major limitation of this study.

The use of various diagnostic tools has been suggested as a means of improving the accuracy of diagnosis of acute appendicitis, thus reducing the rate of negative appendicectomy. Thus, this study examined the roles of WBC count and CRP in improving the accuracy of diagnosis of acute appendicitis. Table 7 shows a summary of the indices of diagnostic values for WBC count, CRP and combination of WBC count with CRP.

The overall accuracy of WBC count in diagnosing acute appendicitis was found to be 73%. Also, the sensitivity, specificity and positive predictive values were 72.8%, 77% and 93% respectively. These values are consistent with those of Nasir *et al*, who in their work found diagnostic accuracy, sensitivity, specificity and positive predictive values for WBC count to be 74%, 74.4%, 72.7% and 90.6% respectively.[32] But in the work done by Agrawal *et al* in Nepal, the positive predictive value was 81%[33], which is much lower than that obtained in the present study (93%). The reason for this difference may be due to the high cut-off for WBC count of > 11,000 cells/mm^3 used in their study as against > 8,000 cells/mm^3 used in the present study. Again, the odds ratio for WBC count in this study was 8.6, which is < 50. Thus, making the use of WBC count alone to be a weak test for the diagnosis of acute appendicitis. This is consistent with the work of Panagiotopoulou *et al*, where WBC count was shown to have a low discriminatory power for the diagnosis of acute appendicitis.[23] Therefore, when used alone, WBC count cannot be relied upon as a diagnostic tool for acute appendicitis.

The 2nd biomarker examined in this study, CRP, is actually a member of the class of acute phase reactants, as its level rises dramatically during inflammatory processes occurring in the body.[34] This rise is due to a corresponding rise in the plasma concentration of interleukin-6, which is produced predominantly by adipocytes.[34] In this study, the overall accuracy, sensitivity, specificity, positive and negative predictive values were found to be 80%, 79%, 85%, 95% and 50% respectively. These values are consistent with the values from the work of Nasir *et al*, who gave diagnostic accuracy, sensitivity, specificity and positive predictive values of 86%, 84.5%, 90.9% and 97.15 respectively.[32] Similarly, Shafi *et al* found positive predictive value for CRP to be 95.6%.[35] Amalesh *et al* found positive and negative predictive values for CRP of 88% and 48% respectively.[36] In the present study, also, the odds ratio was 21.4, which is < 50. Therefore, CRP, when used alone, is a weak test for diagnosing acute appendicitis. This is not surprising, as Amalesh *et al*, in their work, concluded that neither a raised nor normal CRP value was helpful in the diagnosis of acute appendicitis.[36] This is especially true owing partly to the non-specific nature of the test.

When CRP was combined with WBC count in this study, the diagnostic indices improved. The overall accuracy, sensitivity, specificity, positive and negative predictive values were found to be 91%, 91%, 90%, 97% and 75% respectively. This finding of improvement of these diagnostic indices when CRP was combined with WBC count is consistent with findings from previous studies. For example, Shafi *et al* found sensitivity, specificity and positive predictive values of 97.82%, 55.5% and 91.8% respectively for WBC count; 95%, 77.77% and 95.6% respectively for CRP. But with combination of WBC count and CRP, there was marked improvement in the specificity and positive predictive values of 88.88% and 97.46% respectively.[35] This finding has made several authors to conclude that a combination of WBC count and CRP would assist the surgeon in selecting patients that would need operative intervention, following a diagnosis of acute appendicitis. Again, from the present study, the odds ratio of a combination of WBC count with CRP was 90, which is > 50. This suggests that a combination of WBC count with CRP is a strong test. Thus, this test combination of WBC count and CRP can be relied upon in assisting the surgeon to make decision on operative intervention in cases of acute appendicitis. In fact, Sengupta *et al*, in their study, recommended that if WBC count and CRP are normal, then it is unlikely that the patient has acute appendicitis and as such, can be sent home.[37] But of course, that will be after confirming the cause of the right iliac fossa pain. Reliance on this test combination of WBC count and CRP in the diagnosis of acute appendicitis will prove helpful in a low resource setting like ours, where the cost of CT scan might not be affordable by most of the patients. Moreover, performance of these tests will not cause any delay in the management of these patients as test results can become available within 2 hours, or at most 3 hours of presentation.

Receiver operating characteristics (ROC) curves were constructed in this study to determine which of these two tests is a better biomarker for acute appendicitis, even though none of them is specific for the disease. The area under the curve was 0.79 for CRP and 0.76 for WBC count. Thus, CRP performed slightly better than WBC count. This is consistent with the findings of Asfar *et al*, who concluded that CRP was a more sensitive test than WBC count in the diagnosis of acute appendicitis.[38] However, some authors tend to disagree on this. For example, Grönroos and Grönroos in their retrospective study, concluded that WBC count was a better laboratory test than CRP in diagnosing acute appendicitis.[39] These differences may be due to non-uniformity in the timing of blood sampling for WBC count and CRP in relation to the onset of symptoms in these studies. This becomes very significant when considering the rise of these biomarkers in the disease trajectory of acute appendicitis. To this end, increase in WBC count has been indicated in the early stages of acute appendicitis, while increased CRP levels have been indicated in more advanced stages of the disease.[40] In this study, therefore, it is possible that majority of the patients presented in the course of the disease in favour of a rise in CRP than WBC count. This then becomes a major limitation of this study, as a one-off collection of samples was done each for WBC count and CRP. Serial measurements of these tests would likely have obviated this limitation by determining different cut-off points for different intervals from disease onset (e.g. collecting samples for these tests every 3 hours) and consequently increase the accuracy of the tests.

CONCLUSION

Acute appendicitis is one of the most frequent reasons for acute abdominal surgeries. Diagnosis is largely clinical. However, diagnostic difficulties may arise, leading to a high rate of negative appendicectomies. This study evaluated the value of White Blood Cell count and C-Reactive Protein in improving the accuracy of diagnosis of acute appendicitis, thus reducing negative appendicectomy. From this study, overall, preoperative CRP was shown to be a slightly better biomarker in predicting acute appendicitis than WBC. However, these tests were shown to have weak discriminatory power when used individually. When used in combination, the predictive ability for acute appendicitis was improved, accurately detecting 90% of patients with clinical presentation of acute appendicitis.

Therefore, all patients presenting with right sided lower abdominal pain, in whom acute appendicitis is suspected, should have WBC count and CRP done preoperatively. If both test results are normal, acute appendicitis is very unlikely. These patients should be investigated further, to search for other causes of right sided lower abdominal pain, especially in females who may require radiological investigations like ultrasound scan. Similarly, if both biomarkers are elevated, then acute appendicitis is likely, and patient may benefit from surgical intervention.

Conflict of interest

We declare no conflict of interest.

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