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Evaluating the Role of C-reactive Protein in Reducing the Rate of Negative Appendicectomies

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Acute appendicitis is a common surgical condition of the abdomen. However, diagnostic difficulties may arise, resulting in high rate of negative appendicectomies.
This study aimed to assess the role of C-reactive protein (CRP) in improving the accuracy of diagnosis of acute appendicitis and thus reducing the rate of negative appendicectomies.
Materials and Method: The study was a cross-sectional, hospital-based study carried out on 66 patients who had appendicectomy following a clinical diagnosis of acute appendicitis. Samples for CRP were collected from all recruited patients preoperatively. Following appendicectomy, the appendix was sent for histology. A proforma was used to collect data. All the statistical analyses

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were performed using IBM statistics package for social sciences (SPSS) version 21. At 95% confidence level, p-values less than 0.05 were considered significant.
Results: Thirteen (13) of the appendices removed had normal histopathologic examination, giving a negative appendicectomy rate of 19.7%. The diagnostic accuracy, sensitivity, specificity and positive predictive value for preoperative CRP were 80%, 79%, 85% and 95% respectively.
Conclusion: An elevated level of CRP is a useful aid for the diagnosis of acute appendicitis. Deferring surgery in patients with normal CRP would likely decrease the incidence of negative appendicectomies.

Keywords: Acute appendicitis; appendicectomy; negative appendicectomy; C-reactive protein.

1. INTRODUCTION

Acute appendicitis is one of the commonest abdominal surgical emergencies [1-3]. It is most frequently seen in the second to fourth decade of life [3-4]. The lifetime risk of acute appendicitis in males is 8.6% and in females 6.7% in the US [4]. Appendicitis is generally thought to have a low incidence rate in sub-Saharan Africa and in other developing countries in Asia and Latin America [5-6]. However, increasing incidence in some African countries have been reported by some authors in the last few decades [7-9]. Changing to a western lifestyle, including diets, has accounted for this increase [5,8,9].

The diagnosis of acute appendicitis is predominantly clinical. This, however, can be challenging even in the most experienced of clinical hands because of the many different conditions that manifest with acute abdominal pain as well as the occasional non-specific initial presentation of the disease [5]. No single sign, symptom, or diagnostic test confirms the diagnosis of appendiceal inflammation in all cases [5-6]. In patients with questionable clinical findings, the aggressive surgical approach has been "when in doubt, take it out", and the price paid has been the frequent removal of normal appendixes [10-12]. Therefore, misdiagnosis is not uncommon [5-6].

Some authors admonished that it is far better to subject a moderate number of patients to a theoretically unnecessary operation, than to let one patient suffer perforation [13]. This, therefore, provides the background for negative appendicectomy, which is a term used to describe surgery done for suspected appendicitis, in which the appendix is found to be normal on histological evaluation [14].

Based on unaided clinical diagnosis, the NA rate is about 15-30%, and reaches up to 30-50% in women of childbearing age because of the prevalence of gynaecological diseases [15]. Osime et al reported a NA rate of 16.1% at Chevron Hospital in Warri Nigeria, over a 5 year period [16]. Okobia et al in Benin City, Nigeria reported a NA rate of 32.2% with representation of both males and females [17]. Kpolugbo *et al* reported a NA rate of 47.2% over a 15month period to assess the diagnostic accuracy of appendicitis [18]. Kakande and colleagues in Uganda reported a NA rate of 29.5% over a five year period [19]. Gilmore in England reported a negative appendicectomy rate of 22% [20].

The burden of NA cannot be overemphasized. 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 [16,19]. It is also a significant contributor to healthcare costs. Flum & Koepsell [4] estimated that NA accounted for nearly $750 million in healthcare costs in a single year in the United States of America (USA). Thus, reducing negative appendicectomy rate should be part of the considerations in the management of patients with suspected acute appendicitis.

Several methods or strategies are available for improving the accuracy of diagnosis of acute appendicitis and reducing the incidence of negative appendicectomy, without necessarily increasing the rate of complicated appendicitis. These strategies include scoring systems, inflammatory markers, imaging techniques and laparoscopy among others [10,13,15].

The judicious use of simple urine and blood tests, particularly inflammatory response biomarkers, should allow exclusion of other pathologies and provide additional evidence to support a clinical diagnosis of appendicitis [14,15]. The most commonly used serological markers of inflammation in the diagnosis of acute appendicitis are the leucocyte count and CRP [21]. Neither of these, however, is diagnostic of

acute appendicitis and studies have attempted to define potential diagnostic threshold values which are predictive of a diagnosis and disease severity [22,23]. In the presence of normal inflammatory markers like CRP, the diagnosis of acute appendicitis is unlikely [17,23]. Studies of inflammatory markers, notably of CRP, have concluded that evaluation of CRP can support the diagnosis of acute appendicitis [21-23].

Many reports have investigated the value of CRP in improving the diagnostic accuracy of acute appendicitis with conflicting results. Shafi et al, in their study of 200 selected patients, sensitivity and specificity were 93% and 85% respectively [10]. Gurleyik and Unalmiser, in their study, calculated the sensitivity, specificity and accuracy of serum CRP measurements as 93.5%, 80% and 91% respectively [24]. Nasir et al gave overall accuracy of CRP in diagnosis of acute appendicitis as 86% [21]. Afser et al found positive and negative predictive values of CRP as 96.7% and 76.5% respectively, and suggested that normal CRP level is not associated with acute appendicitis [21]. Amalesh *et al* found positive and negative predictive values of CRP as 88% and 48% respectively, and concluded that neither raised nor normal CRP values are helpful in the diagnosis of acute appendicitis [24].

The diagnostic and discriminatory values of CRP in acute appendicitis have been studied extensively, but the results remain controversial [10,21-23]. This study aimed to evaluate the role of CRP in improving the diagnosis of and predicting the severity of acute appendicitis.

2. MATERIALS AND METHODS

This was a cross-sectional, hospital-based study carried out over a period of 20 months. All patients with acute right iliac fossa pain who on clinical examination had features in keeping with acute appendicitis, with duration of symptoms being at least 8 hours and who are 18 years and above, were included in the study. Patients who were pregnant, had background diabetes mellitus, and other cofounders that could lead to elevation of CRP were excluded from the study.

The Fischer's formula [25] for calculating the minimum size for a cross sectional study was employed and a sensitivity of 96% from Erkassap's study [24] was used. The calculated sample size after adding the 10% attrition rate was 66.

Patients who fulfilled the inclusion criteria were enrolled into the study as they presented to the accident and emergency room. The objectives of the study were explained to each patient at the time of enrolment. Informed consent was obtained.

At admission, blood samples for CRP were obtained from all prospective patients for the purpose of this study. Samples were collected into plain bottles, separated into serum after spinning at 3000 revolutions/minute for 2 minutes and were analysed using Enzyme linked Immunosorbent assay (ELISA) technique and read with the ELISA reader.

All 66 patients recruited into the study were operated. However, the decision to operate was based on clinical grounds and not influenced by the results of laboratory investigations. The patients were then worked up for surgery. All the procedures were performed as emergencies under general anaesthesia with muscle relaxation.

Appendicectomy was done for all patients and the removed appendixes were sent for a histopathological examination. The intra-operative findings were compared with histopathology results and then correlated with CRP values. Patients were followed up till eventual discharge from clinic.

Data collection was done 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. Data were entered in a spread sheet and analysed using Statistical Package for Social Sciences(IBM SPSS) version 21. Laboratory reports for CRP were categorized into normal and high using cut-off values used by the laboratory. The normal cut off value for CRP was 6.5mg/L. The sensitivity, specificity, and predictive values for CRP were calculated using the appropriate formulas.

3. RESULTS

The age range of the participants was 18 – 90 years, with median age of 25 years and mean age of 31 years ±14SD. The largest proportion of patients was in the age group 18– 25 years, representing 50% of the participants. The social

demographic characteristics of the patients are shown in Table 1. There were 24 males and 42 females in this study, giving a male-female ratio of 1:1.8.

Right iliac fossa pain was the chief complaint, present in all the patients. This was followed by anorexia (81.8%) and nausea/vomiting (74.2%). Urinary symptoms were present in 10.6% of the patients while 7.8% had comorbidities. The clinical examination findings are as shown in Table 2.

Table 3 shows the preoperative laboratory results of C-reactive protein.

Table 1. Sociodemographic characteristics of study participants

Variables	Frequency, n = 66	Percent (100%)
Gender		
Male	24	36.4
Female	42	63.6
Age in groups (years)		
18-25	33	50.0
26-35	17	25.8
36-45	10	15.2
46-55	02	3.0
56-65	02	3.0
≥66	02	3.0

Median ± Range = 25±74 years, Minimum (16 years), Maximum (90 years)

Table 2. Clinical presentations of study participants

Variables	Frequency (n =66)	Percent (100%)
Temperature		
Normal (36.0-37.4^{0}C)	43	65.2
High (≥37.5^{0}C)	23	34.8
Right Iliac Fossa Tenderness		
Yes	66	100
Rebound Tenderness		
Yes	62	93.9
No	04	6.1
Pointing Sign		
Yes	65	98.5
No	01	1.5
Rovsing Sign		
Yes	29	43.9
No	37	56.1
Psoas Sign		
Yes	30	45.5
No	36	54.5
Obturator sign		
Yes	13	19.7
No	53	80.3
Digital Rectal Examination		
Yes	12	18.2
No	54	81.8

Table 3. Preoperative laboratory CRP reports of study participants

Variables	Frequency (n=66)	Percent (100%)
C-reactive protein (mg/L)		
Normal	22	33.3
High	44	66.7

CRP, Mean ± SD = 6.8 ± 2.8

Table 4. Intraoperative findings

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

Table 5. Association between sociodemographic characteristics and acute appendicitis

Variables	Histology Findings		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)			
16-35	37(74%)	13(26%)	50(100%)
36-45	12(100%)	0(0%)	12(100%)
≥ 46	4(100%)	0(0%)	4(100%)
Chi value =5.18	p-value=0.075		

**Fishers exact*

All patients with negative appendicectomies were within the age group of 18 – 35 years age, with 84.6% of them being females. 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 18-35 years had no appendicitis compared to the other age groups (0%).

The preoperative CRPs were analysed to see their relationship to histology (Table 6).

Out of 53 confirmed cases on histopathology, 42 positive cases of CRP were true positives yielding a sensitivity of 79%. Out of 13 confirmed negative cases on histopathology, 11 negative cases of CRP were true negatives, giving a specificity of 85%. 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 7 shows the relationship between histopathological diagnosis and macroscopic findings of acute appendicitis. Out of 13 confirmed negative cases on histopathology, 1 case was staged macroscopically as true negative, giving a specificity of 77%. Out of the 53 patients macroscopically staged as having appendicitis, all of them were confirmed histopathologically as true appendicitis, giving a sensitivity of 100%. Out of 65 positive cases on macroscopy, 53 were true positives, thus giving a positive predictive value of 81.5%. There was 1 negative case on macroscopy with it being true negative. This gave a negative predictive value of 100%. The overall accuracy of macroscopy in the diagnosis of acute appendicitis was 81.8%.

Attempts were also made to find out how this inflammatory marker predicted the severity of acute appendicitis. Table 8 shows a comparison of the mean values of CRP with all stages of acute appendicitis. It was observed that there was a progressive rise in the mean values of this biomarker from normal appendix to uncomplicated appendicitis and to complicated appendicitis. There was statistically significant difference for CRP between those with normal appendix and those with uncomplicated appendicitis (p value = 0.001). However, there was no statistically significant difference for CRP between those with uncomplicated appendicitis and those with complicated appendicitis (p value = 0.568).

Table 6. 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 7. Relationship between macroscopic findings and histological findings

	Histology (Gold Standard)		
Macroscopic Findings	**Appendicitis**	**No Appendicitis**	**Total**
Appendicitis	53 (True Positive)	12 (False Positive)	65
Normal Appendix	0 (False Negative)	1 (True Negative)	1
Total	53	13	66

Table 8. Mean C-Reactive protein values

Variables	**Patients**	**C-reactive protein (mg/l)**
Normal Appendix	13	4.32±2.44
Acute appendicitis	37	7.23±2.50
Complicated appendicitis	16	7.66±2.48
Normal Appendix vs Acute appendicitis		p= 0.001
Acute appendix (uncomplicated) vs Complicated appendicitis		P= 0.568

4. DISCUSSION

The diagnosis of acute appendicitis is largely clinical requiring a detailed history and thorough physical examination [5] 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 [2]. The burden of NA cannot be overemphasized. It is associated with appreciable degree of morbidity and mortality, including an appreciable increase in the duration of hospital stay and postoperative complications [2-5]. It is also a significant contributor to healthcare costs. Flum & Koepsell [4] 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 [13]. 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% [8]. 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 [16] Okobia et al in Benin City, Nigeria reported a NA rate of 32.2% with representation of both males and females [17]. Kpolugbo et al reported a NA rate of 47.2% over a 15 month period to assess the diagnostic accuracy of appendicitis [18]. A low rate of 11.7% was reported by Ojo et al [26], while Edino et al reported a rate of 14.1%. [2].

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 [16-18]. 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 [16]. 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 CRP in improving the accuracy of diagnosis of acute appendicitis.

The 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 [27]. This rise is due to a corresponding rise in the plasma concentration of interleukin-6, which is produced predominantly by adipocytes [27]. 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 [21]. Similarly, Shafi *et al* found positive predictive value for CRP to be 95.6% [10]. 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 is helpful in the diagnosis of acute appendicitis [24]. This is especially true owing partly to the non-specific nature of the test.

These differences may be due to non-uniformity in the timing of blood sampling for 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, increases in CRP levels have been indicated in more advanced stages of the disease [28]. This then becomes a major limitation of this study, as a one-off collection of samples was done for 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 this test every 3 hours) and consequently increase the accuracy of the test.

Distinguishing between uncomplicated and complicated appendicitis is very important in determining whether to operate. Some authors even suggest that medical treatment could be suitable in uncomplicated appendicitis, although this is not a standard of care [29]. In the present study, it was observed that CRP was able to distinguish normal appendix from acute appendicitis. This was in keeping with previous studies by Ortega-Deballon et al [29] and Yokoyama and Erkasap et al. [30-31].

5. CONCLUSION

With acute inflammation of the appendix, the level of CRP was elevated. A normal pre-operative CRP measurement in patients with suspected acute appendicitis is most probably associated with a normal appendix. Deferring surgical intervention and planning further investigation(s) in this category of patients would likely reduce the prevalence of negative appendicectomies.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Authors hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

CONSENT

As per international standards or university standards, patient(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standards or university standards written ethical approval has been collected and preserved by the author(s).

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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