

Diagnostic Feasibility of Total Leukocyte Count, Neutrophil Percentage, and C-Reactive Protein in Suspicious Cases of Acute Appendicitis

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Abstract

Background: Acute appendicitis is quite common in general surgical practice. The classical history of central abdominal pain with anorexia migrating to the right lower abdomen is present in <50% of cases. The diagnosis of equivocal cases still represents clinical dilemma and diagnostic challenge. **Objectives:** The main purpose of this study was to evaluate the feasibility of triple blood tests for total leukocyte counts, percentage of neutrophils, and C-reactive protein (CRP) as inflammatory markers to diagnose cases with a suspicion of acute appendicitis. **Methods:** A total of 132 patients (78 males and 54 females) were diagnosed clinically by blood investigations as cases of acute appendicitis for whom appendectomy had been performed. **Results:** The results showed that the overall diagnostic accuracy rate was 91.7% after the final histopathological confirmation of acute appendicitis. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy rate of CRP were high than those of total leukocyte count and neutrophil percentage; the difference, however, was not significant. The sensitivity, specificity, PPV, NPV, and accuracy rate of combined results of the three tests were significantly high than those of any test alone, which could be good adjuncts that help in the diagnosis of equivocal cases of acute appendicitis. More importantly, we found that when the results of the three tests were within the normal reference ranges, acute appendicitis is quite remote and very unlikely. **Conclusion:** It can be concluded from this study that the combined positive results of the three blood tests could be good predictors of acute appendicitis with high sensitivity, specificity, and accuracy rate. Moreover, when the results of these tests are normal, the likelihood of acute appendicitis reaches to zero.

Keywords: Acute appendicitis, C-reactive protein, leukocyte counts, neutrophilia

INTRODUCTION

Acute appendicitis is still the most frequent emergency abdominal condition encountered in general surgical practice, and it is one of the most common causes of lower quadrant abdominal pain. The condition has a diverse clinical presentation which overlaps with other intra-abdominal conditions. Appendicitis could carry a significant morbidity and even mortality in certain circumstances, mainly due to late presentation and diagnostic delay.^[1] Although the diagnosis of acute appendicitis is largely a clinical one, still no single symptom, sign, or investigation can accurately predict the diagnosis of appendicitis because the clinical presentations are quite variable and the classical history of central or peri-umbilical pain with loss of appetite migrating to right iliac fossa with nausea, infrequent vomiting, and low-grade fever is present only in 50% or even less number of cases. The diverse

and inconsistent presentation of appendicitis is mainly due to variation in the position of appendix, severity of inflammation, and patient age.^[2]

The principal aim in the assessment of the atypical cases of acute appendicitis is to decrease the rate of negative appendectomies without increasing the rate of complications such as rupture and peritonitis which increase the morbidity and mortality. It has been reported that the prevalence of normal appendix is found in 15%–40% of patients who had emergency appendectomy,

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and one of the five cases of appendicitis is misdiagnosed. The diagnostic error rate ranges from 25% to 40% for female and 12% to 20% for male patients.^[3] The diagnosis of query cases of acute appendicitis with atypical presentation can be perplexing and challenging for expert physicians or surgeons. Therefore, accurate diagnosis is paramount and crucial to avoid unnecessary surgery to prevent unwanted complications.

Although ultrasonography and computed tomography (CT) scan have been increasingly used recently in the evaluation of equivocal and query cases of acute appendicitis with noticeable improvement in the diagnostic accuracy, the use of these diagnostic modalities has their own disadvantages and limitations. First, the normal appendix usually cannot be viewed with ultrasonography, and it is user and interpreter dependant. Second, CT scan is expensive, is not always available, and exposes patient to radiation which is contraindicated in pregnant patients presenting with right lower abdominal pain as the prevalence of acute appendicitis in pregnant patients is similar to that of nonpregnant patients. Besides, with the frequent use of CT scan for the diagnosis of atypical cases of acute appendicitis, the overall negative appendectomy rate remains at a range of 15%–20% which is no longer accepted as it is cost noneffective.^[4] Therefore, there was an urgent and continuous need for other easier, cost-effective, and highly accurate alternatives for the diagnosis of acute appendicitis.

The use of inflammatory markers such as leukocytosis, left shift (neutrophilia), and C-reactive protein (CRP) which is an acute-phase protein for the diagnosis of acute appendicitis has been tried by many researchers. However, none of these individual marker alone has a high diagnostic yield and accuracy.^[5]

It has been documented that when combined results of the positive C-reactive protein, leucocytosis with neutrophil more than 75%, the diagnosis of acute appendicitis can be made with high degree of accuracy. All these three blood tests are cost-effective, are available, and are feasible, and their results can be obtained rapidly within 1 h or less. These tests are beneficial and advantageous especially for clinicians or surgeons on duty or in emergency department who receive and examine large number of patients presented with lower abdominal pain of different etiology including acute appendicitis with aim of high diagnostic accuracy and specificity approaching 100% in time. Cost and efficient manner and thus unnecessary laparotomy can be avoided without missing or delaying any real cases of appendicitis.^[6]

The main purposes of this study was to evaluate the combined results of three blood inflammatory markers including leucocytes counts, leucocytes differential (mainly neutrophil percentage) and C-reactive protein in diagnosis the suspicious cases of acute appendicitis. The assessment includes determining the accuracy of preoperative diagnosis, specificity, sensitivity, and predictive values of these combined results in patients supposed to have acute appendicitis who presented for appendectomy.

MATERIALS AND METHODS

Study design and patients

This is a prospective controlled study conducted in one major hospital in Basrah between August 2014 and July 2018, in which 132 consecutive patients (78 males and 54 females) with age ranges between 12 and 56 years (mean 34.2 years) who presented with acute lower abdominal pain with a presumptive diagnosis of acute appendicitis and who were offered appendectomy were enrolled.

After a detailed history and careful clinical examination, all patients upon admission to hospital had a routine blood test including complete blood count and high-sensitive CRP. Besides, urinalysis and ultrasound examination were done to rule out the other causes of lower abdominal pain. Pregnancy test by serum beta human chorionic gonadotropin was done for all female patients of childbearing age. Exclusion criteria were patients presenting with generalized peritonitis and patients with right iliac fossa mass highly suspicious of appendicular mass.

The duration of symptoms ranged between 6 h and 36 h from the onset of abdominal pain. All the patients (132 patients) presented for appendectomy were principally diagnosed depending on history and physical examination and relevant investigations. The appendices were assessed intraoperatively and categorized as inflamed, perforated, and normal-looking appendix. The excised specimens after surgery were sent for histopathological examination to confirm or to exclude appendicitis, and thus patients accordingly were classified as having negative appendectomy: normal appendix (Group 1), inflamed appendix (Group 2), and perforated and gangrenous appendix (Group 3).

The results of preoperative blood tests, mainly leukocyte counts, white blood cell (WBC) differential, particularly the neutrophil count and CRP, were reviewed and compared with the final results of histopathological examinations to evaluate the sensitivity, specificity, accuracy rate, and predictive values of the preoperative blood tests represented by triple inflammatory markers (leukocytosis, neutrophilia >75%, and positive CRP) as a diagnostic tool of acute appendicitis using SPSS test version 22 (SPSS, IBM Company, Chicago, IL, USA) and *t*-test. Leukocyte count >11,000/L, neutrophil percentage >75%, and CRP value >10 mg/dl were considered elevated.

Ethical consideration

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with patients' verbal and analytical approval before sample was taken. The study protocol, the patient information, and the consent form were reviewed and approved by a local ethics committee.

RESULTS

A total of 132 consecutive patients who complained of central and lower abdominal pain mainly on the right side

diagnosed provisionally as cases of acute appendicitis and subsequently offered appendicectomy were included in this study. There were 78 (59%) males and 54 (41%) females, with a male-to-female ratio of about 1.4:1. The age ranged between 12 and 56 years, with a mean of 34.2 ± 14 years.

Acute appendicitis proved by histopathological examination was present in 121 patients (91.7%), giving an overall negative appendectomy rate of 8.3%. Thus, 11 patients (seven females and four males) had normal appendix (Group 1), in whom eight cases (six females and two males) discovered intraoperatively to have other established diagnosis and the other three cases (two males and one female) remained with a final diagnosis of nonspecific abdominal pain. Simple acute appendicitis (Group 2) was observed in 106 (80.3%) patients (55 males and 51 females) and complicated appendicitis (Group 3) was found in 15 (11.4%) patients (9 males and 6 females), mainly perforated severely inflamed appendix (11 cases) and gangrenous appendix (4 cases). Hence, the majority of patients with acute appendicitis were of simple noncomplicated type (Group 2).

The male gender was predominant in both groups of acute appendicitis (simple and complicated), whereas negative appendicectomy was highly prevalent among female patients [Table 1].

The total WBC count increased in 115 patients (87%) and positive CRP was observed in 109 (90.1%) patients with positive appendicectomy (Groups 2 and 3). On the other hand, among 11 patients with negative appendicectomy (Group 1), eight patients had WBC count within the normal reference range and nine patients showed negative CRP results.

The results of complete blood count showed that WBC count was significantly higher ($>10,500$ cells/dl) in both groups of acute appendicitis (Groups 2 and 3) than in those patients in Group 1 of normal appendix (87% vs. 23%). Further analysis showed that the WBC count was higher in complicated appendicitis than in simple acute appendicitis, however the difference was not significant [Table 2].

Regarding the neutrophil percentage, of 121 patients with proved appendicitis (Groups 2 and 3), neutrophilia (neutrophil % $>75\%$) was detected in 109 patients (90.1%) and in four patients with normal appendix (Group 1).

The results of CRP in the present study were higher among patients with complicated appendicitis (14/15, 93.3%) compared with those of simple acute appendicitis 95/106, 86.6%). The differences were not statistically significant ($P < 0.05$).

When all the three tests were combined, the results of these triple tests (WBC count, neutrophil % $>75\%$, and positive CRP) showed that, of 121 patients with acute appendicitis, 108 (89.3%) had all the three tests elevated and the rest of the 13 (10.7%) patients had one or two tests raised. On the other hand, patients with negative appendicectomy (Group 1), only two patients had all the three tests elevated and the rest of the nine patients were found to have either all the three test within normal reference (four patients) or only one or two tests elevated (five patients).

The WBC count ranged from 4.4×10^9 to 12.8×10^9 (mean 6.8×10^9) in Group 1 of a normal appendix, in Group 2 of simple appendicitis from 6.7×10^9 to 14.2×10^9 (mean 13.8×10^9), and in Group 3 of complicated appendicitis from 9.2×10^9 to 22.4×10^9 (mean 16.8×10^9). The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy rate of WBCs were 87.2%, 64.4%, 79.1%, 86.8%, and 68.6%, respectively.

The neutrophil percentage ranged from 38.8 to 90.2 (mean 45.8%) in Group 1, from 67.2% to 88.4% (mean 81.6%) in Group 2, and from 66.2% to 92.7% (mean 81.3%) in Group 3, with estimated sensitivity, specificity, PPV, NPV, and accuracy rate of 81.2%, 73.2%, 80.8%, 92.2%, and 80.3%, respectively [Table 3].

The values of CRP ranged from 0 to 88 mg/dl, with a mean of 11.2 mg/dl in Group 1; from 6 to 210 mg/dl, with a mean of 32 mg/dl in Group 2; and from 6 to 198 mg/dl, with a mean of 80.2 mg/dl in Group 3. CRP results were normal only in 13 patients with appendicitis (Groups 2 and 3). The estimated sensitivity, specificity, PPV, NPV, and accuracy rate of CRP were 90.2%, 82.3%, 88.6%, 96.2%, and 85.1%, respectively [Table 3].

When the three tests were combined (total leukocyte count, CRP, and neutrophil percentage), the sensitivity, specificity, PPV, NPV, and accuracy rate were 96.8%, 94.8%, 98.1%, 97.2%, and 98.1%, respectively [Table 3]. Among 121 patients with proved acute appendicitis (Groups 2 and 3), 109 were

Table 1: Patient characteristics and mean results of white blood cells, neutrophil percentage, and C-reactive protein among appendicitis groups

Appendicitis	Variables					
	n (%)	Male:female	Mean age (year)	Total WBC count (mean)	Neutrophil percentage (mean)	CRP mg/dl (mean)
Negative appendicectomy (Group 1)	11 (8.3)	4/7 (1:2)	26.6 $\pm$ 3	6.8×10^9	45.8	11.2
Simple acute appendicitis (Group 2)	106 (80.3)	70/36 (1.5:1)	29.5 $\pm$ 12	13.8×10^9	81.6	32
Complicated appendicitis (Group 3)	15 (11.4)	9/6 (1.2)	36.8 $\pm$ 9	16.8×10^9	81.3	80.2
Overall proved appendicitis (Groups 2 and 3)	121 (91.7)	79/42 (1.3:1)	33.4 $\pm$ 3	15.3×10^9	81.45	56.1
Total	132	78/54 (1.4:1)	34.2 $\pm$ 14	-	-	-

CRP: C-reactive protein, WBCs: White blood cells

found to have all the three tests elevated and the rest of the 12 patients had one or two test positive.

DISCUSSION

Acute appendicitis is the most common condition in general surgical practice. Although the diagnosis of acute appendicitis could be easy and straightforward, especially when the disease manifests in its classic way, this classic presentation occurs in <50% of patients or even less. Therefore, there are many atypical and equivocal cases of acute appendicitis which mimic or overlap with various other intra-abdominal conditions presenting with lower abdominal pain, resulting in either delay in diagnosis or unnecessary surgery.^[1,6] The diagnosis of these atypical cases is still one of the most frequent perplexing and clinical dilemma, and the debate about the most accurate and efficient method for the diagnosis of these atypical cases of acute appendicitis continues. Although ultrasound and CT scan are widely used recently for the diagnosis of equivocal cases, the rate of perforated appendicitis or negative appendectomies has not effectively decreased.^[3,7]

There is a growing trend for the use of certain specific inflammatory markers to improve and consolidate the diagnosis of acute appendicitis in particularly those with atypical presentations in accurate and timely manner. The main inflammatory markers that could help in the diagnosis of such cases are mainly total leukocyte count, neutrophil percentage, acute-phase protein, CRP.^[5,7,8]

Several studies^[7,9,10] found that about 80%–90% of patients with acute inflamed appendix have total WBC counts more

than 11,000 cells/dl (ranging from 10,000 to 18,000 cells), with neutrophil percentage more than 75% (left shift) observed in 80%–90% of patients. Other studies^[5,8,11] have shown that <4% of patients with appendicitis have total leukocyte counts <10,500 cells/ml. Complicated appendicitis including perforated and gangrenous changes is associated with WBC count >18,000 cells/dl. It has been reported that the combination of a raised WBCs, neutrophilia >75%, and elevated CRP improves the sensitivity to 97%–100%.^[10]

CRP is an active-phase reactant produced by the liver in response to inflammation, which progressively raises within the initial 12–24 h. Despite the fact that CRP is nonspecific and increases in various infectious and inflammatory and malignant disorders, several studies^[7,10–12] had shown it to be a useful test in the investigation of equivocal cases of acute appendicitis. CRP value >10 mg/dl is commonly recorded in patients with acute appendicitis and higher levels usually correspond with complications such as gangrenous evolution and perforation.

These three or triple blood tests are simple, cost-effective, rapid, and feasible. They could be a good adjunct for the diagnosis of both typical and atypical cases of acute appendicitis that could decrease the rate of negative appendectomy, which is estimated between 15% and 25% of the cases, with some studies recorded higher negative appendectomy rates of up to 50% in females of childbearing age.^[4,6,13] Negative appendectomy might result in increased rate of complications such as bowel obstruction, abdominal and pelvic abscesses, and enterocutaneous fistula in addition to wound infection and complications of general anesthesia. Several researches^[7,10,12] reported that the risk of adhesion and bowel obstruction is increased by up to 5% following negative appendectomy.

In a trial to overcome this diagnostic dilemma, this research was conducted to evaluate the validity and feasibility of the three blood tests in the diagnosis of acute appendicitis, and the results of these triple tests were recorded, analyzed, and compared with definite histopathological diagnosis of appendicitis.

Our results showed that the positive results of CRP were more accurate than the results of WBCs and neutrophil percentage, and they were a good adjunct for the prediction of the severity of acute appendicitis. However, the accuracy rate of CRP was not significantly greater than that of total WBC count and neutrophil percentage. None of these tests alone were specific or sensitive for appendicitis. These

Table 2: Diagnosis of suspicious cases of acute inflamed appendix at laparotomy

Diagnosis	n (%)
Acute simple appendicitis	106 (80.3)
Complicated appendicitis	15 (11.4)
Perforated	11
Gangrenous	4
Normal appendix (negative appendectomy)	11 (8.3)
Complicated ovarian cyst	3
Mesenteric adenitis	2
Ectopic pregnancy	2
PID	1
Meckels diverticulitis	1
Nonspecific abdominal pain (no cause identified)	2

PID: Pelvic inflammatory disease

Table 3: Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy rate of white blood cells, neutrophil percentage, C-reactive protein, and the combined results of these tests

Blood tests	Sensitivity	Specificity	PPV	NPV	Accuracy rate
Total WBC count	87.2	64.4	79.1	86.8	68.6
Neutrophil (%)	81.2	73.2	80.8	92.2	80.3
CRP	90.2	82.3	88.6	96.2	85.1
Triple tests (WBC, neutrophil percentage, and CRP)	94.6	91.8	92.1	99.2	91.7

PPV: Positive predictive value, NPV: Negative predictive value, WBCs: White blood cells, CRP: C-reactive protein

findings were consistent with similar studies by Exadaktylos *et al.*^[13] and Yokoyama *et al.*^[14] Siddique *et al.*^[15] found in their similar study that total WBC count had a higher diagnostic accuracy and higher sensitivity than CRP in diagnosing simple acute appendicitis. The sensitivity of combined results of WBCs and CRP increased to 95% and 100% for diagnosing simple acute appendicitis and complicated appendicitis, respectively.

We found that the results of the three tests together greatly improved the diagnostic probability of acute appendicitis, especially in cases with atypical presentation represented by increased sensitivity, specificity, PPV, NPV, and accuracy rate of 94.6%, 91.8%, 92.1%, 99.2%, and 91.7%, respectively. Similar observations were recorded by Shafi *et al.*^[11] and Xharra *et al.*^[16] Wu *et al.*^[17] reported that the combined results of the three tests (WBC count, neutrophil percentage, and CRP) increased the PPV.

On the other hand, Anshuman *et al.*^[12] reported in their similar study, which included total WBC count and CRP as inflammatory markers for acute appendicitis diagnosis, that raised levels of these inflammatory markers are unlikely to expect a certain diagnosis such as acute appendicitis because many inflammatory processes can result in an acute-phase response. Their findings also failed to show that the raised level of WBCs and CRP can predict the occurrence of complications such as gangrene and rupture. An important finding of their research was that if both WBCs and CRP are normal, the NPV of acute appendicitis is 100%. This fact is clearly observed in our results with a NPV of 99.2%. Grönroos *et al.*^[18] and Sengupta *et al.*^[19] found that when both the WBC count and CRP are normal, the diagnosis of acute appendicitis is unlikely and can be excluded.

Yang *et al.*^[20] recorded in their study of 740 patients with inflamed appendix that, six patients (0.8%) only had a total WBC count <10,500 cells/mL, neutrophil percentage <75%, and a normal CRP, giving an overall sensitivity of 99.2% for these triple tests. In another prospective controlled study of 216 young patients with suspected appendicitis, Mohammed *et al.*^[21] recorded that the sensitivity and NPVs of the triple screen tests were 86% and 81%, respectively.

Xharra *et al.*^[16] found in their similar study that out of 106 patients with triple positive tests, 101 (95.2%) had appendicitis. The sensitivity, specificity, and PPVs of the triple screen tests were 95.3%, 72.2%, and 95.35%, respectively.

CONCLUSION

Atypical presentation and equivocal cases of acute appendicitis which occur in about one-third to one-half of the patients still represent a major diagnostic dilemma. The role of inflammatory markers, mainly WBC count, neutrophil percentage, and CRP, was thoroughly studied and discussed. Although none of these tests alone was specific or sensitive for diagnosing acute appendicitis, the combined results of

these triple tests serve as a good diagnostic adjunct with high sensitivity, specificity, and accuracy rate. Furthermore, when the results of the triple test were in the normal reference ranges, acute appendicitis can be confidently excluded, with NPV reaching up to 99%–100%.

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Conflicts of interest

There are no conflicts of interest.

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