

AN EVALUATION OF DIAGNOSTIC ACCURACY OF C-REACTIVE PROTEIN, TOTAL LEUKOCYTE COUNT, NEUTROPHIL COUNT AND ULTRASONOGRAPHY IN DIAGNOSIS OF ACUTE APPENDICITIS

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ABSTRACT

BACKGROUND

Acute appendicitis remains the most frequent cause of lower abdominal pain requiring surgery. The diagnosis of acute appendicitis relies largely on clinical assessment, but in the era of evidence based medicine many studies have looked at various simple blood tests and clinical criteria in an attempt to improve diagnostic accuracy. The total leukocyte count (TLC), neutrophil count, ultrasonography (USG) and C-reactive Protein (CRP) are now often used to aid in the clinical assessment in patients with right iliac fossa pain.

To conclude, an exact diagnosis of acute appendicitis is important for proper management. This study aims at comparing the few known and proven investigations for appendicitis like CRP, neutrophil count, total leukocyte count and ultrasonography; comparing how specific and sensitive each one is, which is best and has maximum positive predictive value. This would be done by comparing it with histopathology report.

MATERIALS AND METHODS

The study is observational study. The total sample was 50. Sample size was taken conveniently. Patients who have been clinically diagnosed of having acute appendicitis and posted for emergency appendectomy in General Surgery Department, Basaveshwar Teaching and General Hospital attached to Mahadevappa Rampure Medical College, Kalaburagi, during the period from December 2015 to June 2017 were included in the study. All the appendectomy specimens were subjected to histological examination postoperatively, which was taken as the gold standard. The four investigation results were correlated with histopathological examination reports to evaluate their role in diagnosis of acute appendicitis.

RESULTS

In the present study, USG had the highest sensitivity of 95.56% followed by CRP 66.67%, TLC 57.78% and neutrophil count 51.11%. In terms of specificity TLC had 100%, CRP and neutrophil count had about 80% each and USG had 20%. The most common per operative finding was acutely inflamed appendix (66%) followed by gangrenous appendix (22%), normal appendix (10%) and perforated appendix (2%). However, histopathological diagnosis was acute appendicitis in 90% and normal histology was seen in 10% cases.

CONCLUSION

When all the three tests are combined (either/ all) the sensitivity, specificity, positive predictive value and negative predictive value, chances of negative appendectomies decrease significantly. It was observed that when all the three tests were negative, appendicitis could be safely ruled out and the surgery could be deferred in these patients. We continue to stress that history and clinical examination by a skilled surgeon still remain indispensable in diagnosing acute appendicitis and its importance cannot be undermined.

KEYWORDS

Appendicitis, C-Reactive Protein, Neutrophil Count, Ultrasonography.

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BACKGROUND

Acute appendicitis is the most common cause of an 'acute abdomen' in young adults.¹ Notwithstanding advances in modern radiographic imaging and diagnostic laboratory investigations, the diagnosis of appendicitis remains

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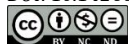
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essentially clinical requiring a mixture of observation, clinical acumen and surgical science. In an age accustomed to early and accurate preoperative diagnosis, acute appendicitis remains an enigmatic challenge and a reminder of the art of surgical diagnosis.¹ Acute appendicitis is one of the most common causes of an abdominal emergency. Acute appendicitis with protean manifestations may simulate almost any other acute abdominal conditions and in turn may be mimicked by a variety of conditions.²

It is estimated that the accuracy of clinical diagnosis of acute appendicitis is lying between 76% and 92%.³

Appendectomy for suspected acute appendicitis is a common procedure. The rate of normal appendices unnecessarily being removed remains high (15% - 30%),⁴ despite several techniques. On one hand a normal appendix at appendectomy represents a misdiagnosis; on the other hand,

a delayed diagnosis of appendicitis may lead to perforation and peritonitis.

Equally distressing is the fact that perforation may occur in up to 35% of cases,⁵ so traditionally surgeons have accepted a higher incidence of unnecessary appendectomies in order to decrease the incidence of perforation. This approach is being increasingly questioned in today's era of evidence based medicine. The high rate of negative explorations for appendicitis is a burden faced not only by the general surgeon, but also by the patient and the society as a whole; since appendectomy like any other operation results in socio-economic impacts in the form of hospital expenses, lost working days and declined productivity.⁶

The goal of surgical treatment is removal of an inflamed appendix before perforation with a minimal number of negative appendectomies.

Objectives of the Study

1. To find out the specificity, sensitivity, predictive value of positive test and predictive value of negative test of CRP, total leukocyte count, neutrophil count and USG in diagnosing acute appendicitis.
2. To correlate HPE report with the blood investigation reports (CRP, total leukocyte count, neutrophil count) and USG in clinically diagnosed cases of acute appendicitis.
3. To interpret the efficacy to improve the diagnosis and decision making of acute appendicitis and hence reduce negative appendectomies with the help of these investigations.

MATERIALS AND METHODS

The study is observational study. The total sample was 50. Sample size was taken conveniently. Patients who have been clinically diagnosed of having acute appendicitis and posted for emergency appendectomy in General Surgery Department, at Basaveshwar Teaching and General Hospital attached to MR Medical College, Kalaburagi, during the period from December 2015 to June 2017 were included in the study.

Inclusion Criteria

All patients who were diagnosed clinically to have acute appendicitis and subjected for appendectomy at Basaveshwar Teaching and General Hospital attached to MR Medical College, Kalaburagi.

Exclusion Criteria

1. Patients who are managed conservatively are also excluded from the study.
2. Patients admitted for interval appendectomy following recurrent appendicitis or appendicular mass previously treated conservatively are also excluded.
3. Concomitant conditions where CRP/ leukocyte count/ neutrophil count is elevated in acute appendicitis patients with associated diseases like:
 - a. Rheumatoid arthritis.
 - b. Systemic lupus erythematosus.
 - c. Glomerulonephritis.
 - d. Gout.
 - e. Inflammatory bowel disease.
 - f. Any other conditions where CRP was raised.

Patients who are clinically diagnosed of having acute appendicitis were subjected to routine investigations and the tests mentioned in the study. TLC count of more than 11,000 cells/mm³ was considered positive and neutrophil count of more than 75% was considered positive.

Ultrasonography results were considered positive if a non-compressible, blind-ending, non-peristaltic bowel loop originating from the caecum (appendix) with maximal compression, the diameter of the appendix was measured in the antero-posterior dimension, if ≥ 6 mm (Bull's eye or target lesion) was suggestive of acute appendicitis. CRP more than 1 mg/dL was considered to be positive.

After obtaining consent, patient was operated and the appendectomy specimen as sent for histopathological examination. The histopathology report was considered as the final diagnosis. The patients were meticulously monitored in the post-operative period for any complications. All patients were followed up in the outpatient department for a period of two months. All the patients recovered uneventfully.

Statistical Method

Descriptive and inferential statistical analysis has been carried out in the present study. The results were analysed by using SPSS version 18 (IBM Corporation, SPSS Inc., Chicago, IL, USA). Microsoft Word and Excel was used to generate graphs, tables etc. Results on categorical measurements were presented in Number (%). Fisher Exact test is used to find the significance of study parameters between the groups. Sensitivity, specificity, PPV and NPV was calculated for diagnostic accuracy. A p-value of < 0.05 was considered to be significant.

RESULTS

In the study, the age of the patient ranged from 7 years to maximum of 50 years with a mean age of 21.76 years. The maximum number of patients presented in the age group of 11 - 20 (52%) followed by age group 21 - 30 years (26%) cases. The least number of patients were seen in age group of 41 - 50 years (2%).

	N	Minimum	Maximum	Mean	Std. Deviation
Age in Years	50	7	50	21.76	9.059

Table 1. Mean Age of Study Participants

Gender Distribution in Acute Appendicitis

In the present study, out of 50 cases only 12 (24%) cases occurred in females and the remaining 38 (76%) cases occurred in males.

Sex	Frequency	Percent
Female	12	24
Male	38	76
Total	50	100

Table 2. Distribution of Study Participants based on Sex

In males, the most common age group of presentation of acute appendicitis was between 11 - 20 years (44.73%) followed by the age group of 21 - 30 years (26.31%). In females, the most common age group of presentation of acute appendicitis was between 11 - 20 years (75%) followed by 21 - 30 years (25%).

Age in Years	Frequency		Total
	Male	Female	
1-10	02 (5.26%)	0	2 (4.0%)
11-20	17 (44.73%)	9 (75%)	26 (52.0%)
21-30	10 (26.31%)	3 (25%)	13 (26.0%)
31-40	08 (21.05%)	0	8 (16.0%)
41-50	01 (2.63%)	0	1 (2.0%)
Total	38 (100%)	12 (100%)	50 (100%)

Table 3. Age Distribution of Patients based on Sex

Distribution of Symptoms, Signs and other Parameters

Among clinical symptoms abdominal pain was present in all patients (100%), anorexia in 36 (72%) patients, migration of pain in 46 (92%), vomiting in 38 (76%) and fever in 31 (62%) patients.

Among clinical signs right iliac fossa tenderness was seen in 49 patients (98%), rebound tenderness was seen in 32 (70%) cases, guarding was seen in 25 (50%) cases, which reflects severity of inflammation. Other peritoneal signs like Rovsing's sign was elicited in 26 (52%) cases. Tachycardia was observed in 28 (56%) of cases.

Total leukocyte counts raised in 6 (12%) females, 20 (40%) male patients with right iliac fossa pain, neutrophil counts raised in 5 (10%) females and 19 (38%) male patients with right iliac fossa pain. Similarly, CRP levels raised in 10 (20%) females and 21 (42%) male patients with right iliac fossa pain.

	Female n (%) n= 12	Male n (%) n= 38	Total
Abdominal pain	12(24)	38(76)	50(100)
Migrating	10(20)	36(72)	46(92)
Anorexia	7(14)	29(58)	36(72)
Vomiting	9(18)	29(58)	38(76)
Fever	08(16)	23(46)	31(62)

Table 4. Clinical Symptoms according to Gender

	Female n (%)	Male n (%)	Total n (%)
RIF Tenderness	12 (24)	37 (74)	49 (98)
Rebound Tenderness	07 (14)	25 (50)	32 (64)
Guarding	06 (12)	19 (38)	25 (50)
Tachycardia	05 (10)	23 (46)	28 (56)
Rovsing Sign	03 (06)	23 (46)	26 (52)
TLC	06 (12)	20 (40)	26 (52)
Neutrophil	05 (10)	19 (38)	24 (48)
CRP	10 (20)	21 (42)	31 (62)

Table 5. Clinical Signs and Blood Investigations according to Gender

Intraoperative Findings of Appendix

Intraoperative findings according to gender showed that in 50 patients, 11 (22%) had gangrenous appendix, 33 (66%) had inflamed and thickened appendix, 5 (10%) had normal appendix and 1 (2%) had perforated appendix.

	Frequency	Percent
Normal appendix (NA)	05	10.0
Inflamed and thickened (IA)	33	66.0
Perforated appendix	01	2.0
Gangrenous appendix	11	22.0
Total	50	100.0

Table 6. Intraoperative Findings of Appendix

Histopathological Examination Report

Histopathological examination findings according to gender showed that in 50 patients, 45 (22%) patients had acute appendicitis, out of which 37 (70%) were male and 10 (20%) were female; 5 (10%) had normal appendix, among which 2 (4%) were female and 3 (6%) were male patients.

	Frequency		Percent
	Female n (%)	Male n (%)	
Acute appendicitis (AA)	10(20%)	35(70%)	90.0
Normal appendix (NA)	02(4%)	03(6%)	10.0
Total	12 (24%)	38 (76%)	100

Table 7. Histopathological Examination Report

USG	Histopathological Examination Report		Total n (%)
	Acute Appendicitis n (%)	Normal Appendix n (%)	
Acute appendicitis	43(86)	04(08)	47(94)
Normal appendix	02(04)	01(02)	3(06)
Total	45(90)	05(10)	50(100)

Table 8. Correlation of Ultrasound Abdomen and Pelvis and Histopathological Examination Report

Fisher exact test, P= 0.276, Sensitivity= 95.56%, Specificity= 20.00%, PPV= 91.49%, NPV= 33.33%, Accuracy= 88.00%.

	Histopathological Examination Report		Total n (%)
	Acute Appendicitis n (%)	Normal n (%)	
Positive	26(52)	0(0)	26(52)
Negative	19(38)	05(10)	24(48)
Total	45(90)	05(10)	50(100)

Table 9. Correlation of Total Leukocyte Count and Histopathological Examination Report

Fisher exact test, P= 0.20, Sensitivity= 57.78%, Specificity= 100%, PPV= 100%, NPV= 20.83%, Accuracy= 62.00%.

Neutrophil Count	Histopathological Examination Report		Total n (%)
	Acute Appendicitis n (%)	Normal n (%)	
Positive	23(46)	01(02)	24(48)
Negative	22(44)	04(08)	26(52)
Total	45(90)	05(10)	50(100)

Table 10. Correlation of Neutrophil Count and Histopathological Examination Report

Fisher exact test, P= 0.20, Sensitivity= 51.11%, Specificity= 80.00%, PPV= 95.83%, NPV= 15.38%, Accuracy= 54.00%

CRP	Histopathological Examination Report		Total n (%)
	Acute Appendicitis n (%)	Normal n (%)	
Positive	30(60)	01(02)	31(62)
Negative	15(30)	04(08)	19(38)
Total	45(90)	05(10)	50(100)

Table 11. Correlation of CRP and Histopathological Examination Report

Fisher exact test, P= 0.062, Sensitivity= 66.67%, Specificity= 80.00%, PPV= 96.77%, NPV= 21.05%, Accuracy= 68.00%

DISCUSSION

In the study, out of 50 patients 38 (76%) were male and 12 (24%) were female patients. So, male predominance was seen in the study undertaken. Appendicitis was common in the age group 11 - 20 years, both in male and female patients in the study. Clinical diagnosis was found to be correct in 45 (90%) of cases and hence the rate of negative appendectomies for acute appendicitis in our study was 5 (10%). Out of 50 patients who underwent operative procedure, abdominal pain was present in all patients (100%), anorexia in 36 (72%) patients, migration of pain in 46 (92%), vomiting in 38 (76%) and fever in 31 (62%) patients.

Among clinical signs, right iliac fossa tenderness was seen in 49 patients (98%), rebound tenderness was seen in 32 (64%) cases, guarding was seen in 25 (50%) of cases, which reflects severity of inflammation. Other peritoneal signs like Rovsing's sign was elicited in 26 (52%) cases. Tachycardia was observed in 28 (56%) of cases. The mean age of presentation was 21.76 years. Increased leukocyte count was seen in 26 (52%) cases, neutrophil count in 24 (48%) cases and CRP in 31 (62%) cases. The most common intraoperative finding was acutely inflamed appendix 33 (66%), gangrenous appendix was seen in 11 (22%), normal appendix in 5 (10%) and followed by perforated appendix 1 (2%) of operated cases.

In our study, clinical diagnosis was found to be correct in 45 (90%) of cases and hence the rate of negative appendectomies for acute appendicitis in our study was 5 (10%).

Our Study is Compared with other Studies as follows-

	Study Group	HPE Positive	HPE Negative	Negative Appendectomy
Subedi N et al ⁷	415	317	5	12(3.5%)
Subhajit et al ⁸	155	80	9	3(13%)
Ikramullah Khan et al ⁹	100	54	-	1(5.6%)
Nasir Ali et al ¹⁰	50	39	11	-
Shefkixharra et al ¹¹	173	148	25	-
Haider Kamran et al ¹²	100	58	19	19%
Present Study	50	45	5	5(10%)

Table 12. Comparison of Accuracy of Clinical Diagnosis in Acute Appendicitis with Other Studies

Subedi N et al⁷ concluded that the diagnosis of acute appendicitis is primarily established by the surgeon's evaluation based on clinical features and physical examination. But the cause of acute appendicitis varies. Hence, all appendectomy specimens should be sent for routine histopathological examination in order to determine the surgeon's rate of negative appendectomy with clinical correlation and to determine the aetiological factors.

Histopathological examination showed 1.4% cases of normal appendix. The accuracy of the clinical diagnosis has been estimated between 76% and 92%, because of which accurate diagnosis of acute appendicitis is still difficult. However, delay in diagnosis leads to increased rates of morbidity and mortality. On the other hand, the negative rate of appendectomy varies from 15% - 30%. The problem in making a clinical diagnosis of appendicitis is because of other possible surgical and nonsurgical causes of lower abdominal pain.

Total Leukocyte Count and Acute Appendicitis

	Sensitivity	Specificity	Predictive value Positive Test	Predictive value in Negative Test
Shefkixharra et al ¹¹	79.1%	68%	93.6%	-
Haider Kamran et al ¹²	76.5%	73.7%	92.5%	-
Agarwal C S et al ¹³	78.6%	54.8%	81.05%	51.1%
Nasir Ali et al ¹⁰	74.4%	72.7%	90.6%	44.4%
Pablo Ortega Debellon et al ¹⁴	86.4%	42.9%	73.6%	62.5%
Shehzab Ahmed Abbasi ¹⁵	87.5%	78.6%	91.35%	71%
Present Study	57.78%	100%	100%	20.83%

Table 13. Correlation of Leukocyte Count with Acute Appendicitis

On comparing the results of our study with the above-mentioned studies, it is inferred that the accurate diagnosis of acute right iliac fossa pain remains a difficult clinical problem, as the differential diagnosis of such pain is not straight forward. In spite of development of various diagnostic scores and diagnostic aids like C-reactive protein, the diagnosis has been confusing for the clinician as no laboratory or radiological test is 100% accurate. Total leukocyte count (TLC) is one of the helpful investigations in diagnosis of acute appendicitis. The evaluation of role of leukocytosis in the diagnosis of acute appendicitis has a consideration. The diagnostic accuracy of TLC is increased further if combined with CRP, neutrophil count, shift to the left, sequential leukocyte counts and neutrophil: lymphocyte ratio.

USG Abdomen and Acute Appendicitis

The sensitivity, specificity, positive predictive value of test and negative predictive value of test in our study is 95.56%, 20%, 91.49%, 33.33% and accuracy of 88%. Comparison of USG as an investigation of acute appendicitis is compared to the data reported in literature in the following table.

	Sensitivity	Specificity	Predictive Value of the Positive Test	Predictive Value of Negative Test	Accuracy
Tauro L F et al ¹⁶	91.37%	88.07%	91.37%	88.09%	90%
Lohani B et al ¹⁷	78.72%	60%	94.87%	23.07%	76%
Mohammed B Hassan et al ¹⁸	57.14%	94.87%	95.65%	54.17%	-
Parigajavidi Parsijani et al	71%	72.7%	88.4%	47%	72%
HS Fung et al ¹⁹	75.5%	89.7%	73.2%	91%	-
Shirzad Nasir et al ²⁰	71.2%	83.3%	97.4%	25%	72.4%
Present Study	95.56%	20%	91.49%	33.33%	88%

Table 14. Comparison of Role of USG Abdomen in diagnosis of Acute Appendicitis with other Studies

Tauro LF et al,¹⁶ in the above observation shows that all the cases presented with pain in the right iliac fossa (RIF) and clinical suspicion of acute appendicitis, which were the selection criteria for the present study. Tenderness in RIF was the most common sign elicited in all the cases (100%). Irrespective of the pathology, vomiting was found to be present in 91% of the cases. Murphy’s triad of symptoms, i.e. pain in the abdomen, vomiting and fever held good in the diagnosis of acute appendicitis in their study.

A total of 58 cases were diagnosed to have appendicular pathology by USG and all these patients were operated upon. Out of the 58 operated cases, 53 were HPE positive and 5 were found to be negative on HPE. The overall specificity (88.09%) and sensitivity (91.37%) of USG in diagnosing appendicular pathology were high, indicating accurate diagnosis by USG in almost all patients with pain in RIF.

C-Reactive Protein and Acute Appendicitis

C-reactive protein (CRP) was first found in the serum of patients suffering from pneumonia caused by Streptococcus pneumoniae. Together with other acute phase proteins, the serum level of CRP rises in response to any tissue injury. It also increases in response to infections (bacterial and viral) and in non-infectious conditions like myocardial infarction, malignancies and rheumatic disorders. CRP concentration increases within 8 hours of the onset of tissue injury, peaks in 24 - 48 hours and remains high as long as there is continuing infection or tissue destruction. Due to its short half-life (4-7 hours), serum CRP concentration rapidly declines as the acute inflammatory process subsided. Many reports have investigated the value of CRP in improving the diagnostic accuracy of acute appendicitis with conflicting result.

In our study serum CRP estimation in diagnosis of acute appendicitis yielded a sensitivity of 66.67%, specificity of 80%, positive predictive value of 96.77%, negative predictive value of 21.05% and accuracy of 68%. The sensitivity in our study are compared with other studies as shown in the table below. It is shown that the sensitivity values are comparable with that of the other studies done in the past.

	Sensitivity	Specificity	Predictive Value of Positive Test	Predictive Value of Negative Test
Shefkixharra et al	81.1%	72%	94.7%	
Agarwal CS et al	74.8%	66.7%	84.9%	51.9%
Nasir Ali et al	84.6%	90.9%	97.1%	62.5%
Pablo Ortega Debellon et al	90.9%	74.3%	79.8%	74.3%
Asfar S et al	93.6%	86.6%	96.7%	76.6%
Present Study	66.67%	80%	96.67%	21.05%

Table 15. Comparison of Role of CRP in diagnosis of Acute Appendicitis with other Studies

Neutrophil Count and Acute Appendicitis

Out of 50 cases in the study, 24 (48%) patients had elevated neutrophil count and rest 26 (52%) patients had normal neutrophil count. Out of those 24 (48%) patients who had elevated neutrophil count, 23 (46%) had acute appendicitis and 1 (02%) normal appendix histopathologically. Out of the 26 (52%) patients where neutrophil count was within normal limits, 22 (44%) had acute appendicitis and 4 (08%) had normal appendix as histopathological report. In our study, serum neutrophil count estimation in diagnosis of acute appendicitis yielded a sensitivity of 51.11%, specificity of 80%, positive predictive value of 95.83% and negative predictive value of 15.38% and accuracy of 54%.

In a study done by Zuhoor K Al-Gaithy,²¹ four hundred and fifty-six patients (273 males and 183 females) who underwent appendectomy with a clinical diagnosis of Acute Appendicitis in Surgery Department at King Abdulaziz Medical Centre, Jeddah, Saudi Arabia, were recruited in this retrospective

study between January 2003 and January 2007. The diagnosis of acute appendicitis was established by history, clinical examination and laboratory tests including WBCs and neutrophil counts.

From the study done by Zuhoor K Al-Gaithy, it was concluded that clinicians should not rely on either elevated TLC or neutrophil count as appendicitis indicator, as clinical data are superior in decision making for appendectomy.

CONCLUSION

Acute appendicitis was the most common abdominal surgical emergency with male predominance. Appendicitis was commonly observed in the age group of 11 - 20 years followed by 21 to 30 years in this study. The rate of negative laparotomies for acute appendicitis in our study is 10%.

In the present study, USG had the highest sensitivity (95.56%) followed by CRP (66.67%), TLC (57.78%) and neutrophil count (51.11%). In terms of specificity TLC had 100%, CRP and neutrophil count had about 80% each and USG had 20%. When all the three tests are combined (either/ all) the sensitivity, specificity, positive predictive value and negative predictive value chances of negative appendectomies decrease significantly. It was observed that when all the three tests were negative, appendicitis could be safely ruled out and the surgery could be deferred in these patients.

We continue to stress that history and clinical examination by a skilled surgeon still remain indispensable in diagnosing acute appendicitis and its importance cannot be undermined.

We concluded that if patients with right iliac fossa pain are explored on the basis of USG, preoperative serum CRP levels and TLC and due respect given to the percentage of neutrophil count, negative explorations could be prevented thus preventing the morbidity and burden on hospital resources associated with the negative explorations. Therefore, we recommend performing all three of these laboratory tests in combination along with USG in patients with an equivocal diagnosis of acute appendicitis based on clinical signs alone before surgical exploration.

Limitation of the Study

Due to short duration of study convenience sampling technique was followed, thus sampling size was taken conveniently. The results of the study cannot be generalised due to the potential bias resulting from the sampling technique and sample size estimation.

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