

Evaluation of the Accuracy of Total Leucocyte Count, C-Reactive Protein And Erythrocyte Sedimentation Rate In The Diagnosis Of Acute Appendicitis –A Prospective Study

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Abstract:

Background: Acute appendicitis is the most common cause of the acute surgical abdomen, and appendectomy is the most commonly done emergency surgery. Its diagnosis remains an enigmatic challenge, plagued by a high rate of negative explorations (15-30%). There is no single reliable test with satisfactory sensitivity and specificity. The objective of the study was to evaluate the role of few known and proven investigations for appendicitis like Total leukocyte count, CRP, and ESR in diagnosing acute appendicitis and reducing the rate of negative appendectomies. Also, we wanted to study whether combining the investigations in the same patient would improve the diagnostic accuracy.

Materials and Methods: The present study was conducted in 100 patients who have been clinically diagnosed as having Acute Appendicitis and posted for emergency appendectomy in the General Surgery Department of S.V.R.R.G.G. Hospital, attached to S.V. Medical College, Tirupati, during the period from September 2018 to September 2019. Preoperatively blood tests for Total leukocyte count, CRP, and ESR were done. All patients were exposed to histopathological examination postoperatively, which was reserved as a gold standard. Results of all three investigations were correlated with HPE reports to evaluate their role in the diagnosis of acute appendicitis.

Results: In the present study, CRP has the highest sensitivity and specificity (90%, 90%) followed by total leukocyte count (78%, 80%) and ESR (66%, 60%). When all the three tests are combined together (either/all), the sensitivity, predictive value of negative test increases significantly (100%, 100%, respectively). It would reduce the rate of negative appendectomies.

Conclusion: Combining TLC, CRP, ESR significantly increases the diagnostic accuracy. When all three tests are negative acute appendicitis is very unlikely and, surgery can be safely deferred in these patients, thereby reducing the negative appendectomy rates.

Key Word: CRP, TLC, ESR, Acute appendicitis, Sensitivity, Predictive value

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I. Introduction

Acute appendicitis is one of the most common causes of right iliac fossa pain and one of the most common causes of surgical emergencies. Its diagnosis is established by the surgeon's clinical impression depending on presenting history, clinical evaluation, and laboratory tests. Acute appendicitis with variable manifestations may simulate almost any other acute abdominal conditions and in turn, may be mimicked by a variety of conditions. It is estimated that the accuracy of the clinical diagnosis of acute appendicitis is lying between 76% and 92%.¹ Appendectomy for suspected acute appendicitis is a commonly done procedure. The rate of normal appendix unnecessarily removed remains high (15%-30%)² 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 Cases³. So traditionally, surgeons had accepted a higher incidence of unnecessary appendectomies to decrease the incidence of perforation. This traditional 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 the patient and the society as a whole, since

appendicectomy, like any other operation, results in socio-economic impacts in the form of hospital expenses lost working days and declined productivity. The goal of surgical treatment is the removal of an inflamed appendix before perforation with a minimal number of negative appendicectomies. To conclude, as acute appendicitis may simulate many other acute abdominal conditions/illnesses, and despite intensive clinical research and discussion, the exact diagnosis of acute appendicitis still remains a challenge. And the exact diagnosis is essential for proper management. This study aims at comparing and evaluating the few known and proven investigations for appendicitis like CRP, leukocyte count, and ESR. And 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 the HPE report. The need for the study is to find out which is the most accurate and sensitive investigation to improve the diagnosis of appendicitis and decision making and hence decrease negative and unnecessary appendicectomies

II. Material And Methods

This study was performed on 100 patients who have been clinically diagnosed of having Acute Appendicitis and who were posted for emergency appendicectomy in the General Surgery Department of SVRRGGH Hospital, attached to S.V Medical College Tirupati, during the period from September 2018 to September 2019.

Study Design: Prospective Observational Study

Study Location: This was a tertiary care teaching hospital based study done in General Surgery Department of SVRRGGH Hospital, attached to S.V Medical College Tirupati.

Study Duration: September 2018 to September 2019.

Sample size: 100 patients

Sampling Method: 100 consecutive patients who have been clinically diagnosed of having Acute Appendicitis and posted for emergency appendicectomy.

Inclusion criteria:

All patients above the age of 18 years diagnosed clinically to have Acute Appendicitis and subjected for Appendicectomy in SVRRGGH Hospital, Tirupati.

Exclusion criteria:

1. Patients with co-morbid conditions were not included in the study.
2. Patients who were managed conservatively were also excluded from the study.
3. Patients admitted for interval appendicectomy following recurrent appendicitis or appendicular mass previously treated conservatively, were also excluded.
4. Concomitant conditions where CRP/Leucocyte count/ESR is elevated in acute appendicitis patients with associated diseases like;
 - a) Rheumatoid arthritis
 - b) SLE
 - c) Glomerular nephritis
 - d) Gout
 - e) Inflammatory bowel disease
 - f) Any other conditions where CRP was raised

Procedure methodology

Clinical diagnosis of appendicitis was made based on symptoms of pain, migration, nausea, and vomiting, anorexia, fever, and signs of peritoneal inflammation like right iliac fossa tenderness, rebound tenderness and guarding. Once acute appendicitis was suspected, the patient was subjected to routine investigations as per the hospital protocol. Elderly patients were subjected to further investigations as part of pre-anesthetic workup, including X-ray chest, ECG, etc. Total leucocyte count, CRP, and the ESR were done in all cases. TLC of more than $10,000 \text{ cells/mm}^3$ was considered positive. CRP more than 6 mg/dl were considered to be positive. No special preparation of the patient was required before sample collection by approved techniques. When there was a delay, the sample was stored at 2-8°C. The maximum period of storage was 72 hours. ESR is done in every case, and more than 15mm/hr in males and 20mm/hr in females is considered as positive. Patients with a strong suspicion of acute appendicitis were advised emergency appendicectomy. After obtaining consent, the patient was operated, and the appendicectomy specimen was sent for histopathological examination. The histopathology report was considered as the final diagnosis. The histopathologically positive cases among CRP positive group were considered true positives. The histopathologically negative cases in the same group were considered as false positives. The histopathologically positive cases among CRP negative group were considered false negatives. The histopathologically negative cases in the same group were considered as true negatives. Similarly, TLC, ESR, was also classified as true and false positives and true and false negatives after correlating it with HPE reports.

Table 1. The evaluation of TLC, CRP, and ESR in the diagnosis of acute appendicitis, is done as follows.

Test	HPE		
	Positive		Negative
Positive	A		B
Negative	C		D

Sensitivity: $\frac{A}{A + C} \times 100$

Specificity : $\frac{D}{B + D} \times 100$

Predictive value of positive test: $\frac{A}{A + B} \times 100$

Predictive value of negativetest: $\frac{D}{C + D} \times 100$

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. The case study was done as per a detailed proforma, which is shown in the annexure. The hospital ethical committee clearance was obtained prior to undertaking the study.

Statistical analysis

Statistical methods like (descriptive, crosstabs, chi-square test) was applied using the SPSS for (version 16.0) and Minitab (version 11.0).

III. Result

The present study was performed on 100 patients who have been clinically diagnosed as a case of acute appendicitis and who were posted for emergency appendicectomy in the Department of General Surgery of SVRRGGH. Hospital in the period of September 2018 to September 2019. Apart from the routine investigations, all the 100 cases were explicitly subjected to the following three investigations, i.e., Total Leucocyte Count, CRP, and ESR, to evaluate their role in accurately diagnosing a case of acute appendicitis. All the 100 cases were subjected for histopathological examination, which was considered as the gold standard, and the final diagnosis .

DISTRIBUTION OF CASES AS PER HISTOPATHOLOGICAL REPORT

In the present study (90 %), cases were histopathologically found to be positive, and 10 cases were negative on histopathology for acute appendicitis. Therefore the rate of negative appendicectomy in the present study is 10%.

Table 2: Distribution of cases as per the histopathological report

HPE POSITIVE	HPE NEGATIVE
90	10

Out of the 90 cases histopathologically reported to be positive, the reporting was as follows.

Normal appendix	10	(10.0%)
Inflamed appendix	55	(55.0%)
Perforated appendix	9	(9.0%)
Gangrenous appendix	26	(26.0%)

So there were 35 cases of the complicated appendix.

EVALUATION OF THE ROLE OF TOTAL LEUCOCYCE COUNT IN DIAGNOSIS OF ACUTE APPENDICITIS BY CORRELATION WITH HPE REPORTS

Out of 90 cases of acute appendicitis, 73 (81.11%) had elevated WBC count, rest 27 (18.89%) patients had normal WBC count.

Table 3: Role of Total leucocyte count

TLC	HPE		TOTAL
	POSITIVE	NEGATIVE	
POSITIVE	71(78.88%) (TRUE POSITIVE)	2(20%) (FALSE POSITIVE)	73

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NEGATIVE	19 (21.11%) (FALSE NEGATIVE)	8(80%) (TRUE NEGATIVE)	27
TOTAL	90	10	100

$X^2=15.8352$, $P=<0.001$ significant

Sensitivity	78
Specificity	80
Predictive value of positive test	97
Predictive value of negative test	29

The test of significance, i.e., p-value = <0.001, indicating that the test is significant in the diagnosis of acute appendicitis.

EVALUATION OF THE ROLE OF C-REACTIVE PROTEIN IN DIAGNOSIS OF ACUTE APPENDICITIS BY CORRELATION WITH HPE REPORTS

Out of 90 patients of acute appendicitis (confirmed by HPE), 90%(81) had elevated CRP rest 10% (9) patients had normal CRP.

Table 4: Role of C-reactive protein

CRP	HPE		TOTAL
	POSITIVE	NEGATIVE	
POSITIVE	81 (90.0%) (TRUE POSITIVE)	1 (10.0%) (FALSE POSITIVE)	82
NEGATIVE	9 (10.0%) (FALSE NEGATIVE)	9 (90.0%) (TRUE NEGATIVE)	18
TOTAL	90	10	100

$X^2=39.0244$, p-value = <0.001 significant

The sensitivity, specificity, predictive value of positive test, and predictive value of negative tests are as follows.

Sensitivity	90%
Specificity	90%
Predictive value of positive test	98%
Predictive value of negative test	50%

EVALUATION OF THE ROLE OF ERYTHROCYTE SEDIMENTATION RATE IN DIAGNOSIS OF ACUTE APPENDICITIS BY CORRELATION WITH HPE REPORTS

Out of the 90 patients (conformed by HPE), 66.6% (60) had elevated ESR levels rest 33.3% (30) had normal ESR.

Table 5: Role of Erythrocyte Sedimentation Rate

ESR	HPE		TOTAL
	POSITIVE	NEGATIVE	
POSITIVE	60 (TRUE POSITIVE)	4 (FALSE POSITIVE)	64
NEGATIVE	30 (FALSE NEGATIVE)	6 (TRUE NEGATIVE)	36
TOTAL	90	10	100

$X^2=2.778$ P=0.095 Not significant

The sensitivity, specificity, predictive value of positive test, and predictive value of negative tests are as follows.

Sensitivity	66%
Specificity	60%
Predictive value of positive test	93%
Predictive value of negative test	16%

EVALUATION OF THE ROLE OF COMBINING, TOTAL LEUCOCYTE COUNT, CRP & ESR EXAMINATION IN DIAGNOSIS OF ACUTE APPENDICITIS BY CORRELATION WITH HPE REPORTS

In the present study, 95 patients had EITHER/OR ALL of the four investigations elevated. All the HPE positive cases had either/or ALL investigations raised, i.e., none of them had all three investigations normal (100% true

positive). None of the patients who had all four investigations as normal, had acute appendicitis (0% false negative). 5 patients had false positive, and 5 patients had true negative.

Table 6: Role of combining Total leucocyte count, C-reactive protein, ESR

TLC, CRP, ESR	HPE		Total
	POSITIVE	NEGATIVE	
POSITIVE +	90 (100.0%) (TRUE POSITIVE)	5 (50.0%) (FALSE POSITIVE)	95
NEGATIVE -	0 (0%) (FALSE NEGATIVE)	5 (50.0%) (TRUE NEGATIVE)	5
TOTAL	90	10	100

The sensitivity, specificity, predictive value of positive test and predictive value of negative test of combining all the three tests are as follows

Sensitivity	100%
Specificity	50%
Predictive value of positive test	94.73%
Predictive value of negative test	100%

IV. Discussion

Acute appendicitis with variable manifestations may simulate almost any other acute abdominal conditions and in turn, may be mimicked by a variety of conditions. Its diagnosis is established by the surgeon's clinical impression depending on presenting history, clinical evaluation, and laboratory tests. In spite of available clinical, biochemical and radiological investigations, there are increasing number of negative appendectomies. By combining the available investigations such as TLC, CRP and ESR, could aid the surgeons clinical decision.

TLC was the test of choice in diagnosing uncomplicated acute appendicitis, however its a poor predictor of protracted inflammation. The Total count, when done individually, distinguishes normal appendix from uncomplicated acute appendicitis. But does not distinguish uncomplicated from complicated appendicitis⁴. The sensitivity, specificity, predictive value of the positive test, and predictive value of negative test of TLC in our study is 78%, 80%, 97%, and 29%, respectively. Marchand et al⁵ concluded in their study that TLC > 10.5 x 10⁹/L was one of the single best tests for diagnosis of acute appendicitis with the highest sensitivities amongst all the tests examined (81-84%).

Vermenum et al⁶ after evaluating 221 patients, concluded that WBC could do not significantly influence the surgical decision making. In our study, the association of Total Leucocyte count and acute appendicitis has shown to be significant with P value (<0.001). When the count is combined with other tests like CRP, ESR, the sensitivity, and predictive value of negative test increases significantly. Dueholm et al⁷ in his study, demonstrated that TLC had the best sensitivity (83%) and predictive value of the negative tests (88%), and combining these tests with CRP increases the sensitivity to 100%. This is supported by a study done by Khan MN et al.,⁸ which reported that when TLC and CRP are measured together, it increases the positive predictive value.

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 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 a continuing infection or tissue destruction. Due to its short half-life (4-7 hours), serum CRP concentration rapidly declines as the acute inflammatory process subsides. Many reports have investigated the value of CRP in improving the diagnostic accuracy of acute appendicitis with conflicting results. A multivariate analysis by Oosterhuis et al⁷⁶ showed that serial CRP measurement could improve the accuracy of diagnosing acute appendicitis. In our study, serum CRP estimation in the diagnosis of acute appendicitis yielded a sensitivity of 90%, the specificity of 90%, the positive predictive value of 98%, the predictive value of negative test 50%. In this study, CRP and acute appendicitis were highly associated (p value < 0.001). This study proves the adjunct value of serum CRP estimation in suspected cases of acute appendicitis and none of the cases with appendicular perforation or abscess formation had normal CRP. This observation is supported by the study was done by Gronroo's and Gronroo's.⁴ In this study, 9(10%) of cases had normal CRP levels even though HPE was positive. CRP becomes positive if symptoms are present for more than 12 hours. CRP values were found to increase with an advancing stage of the appendiceal inflammation found at operation and the length of the preoperative phase of the illness. Gurleyik et al.⁹ compared serum CRP study of 108 patients suspected of having appendicitis on clinical grounds. The false-negative rate of CRP was 3%, and the false-positive rate was 11%. CRP levels were true (positive or negative) in the remaining 103 patients. On the other hand, the diagnosis depending on the surgeon's clinical impression,

was true in 90 patients and false in 18 patients. This difference was statistically significant ($p = 0.0035$). The sensitivity, specificity, and accuracy of serum CRP measurements were calculated as 93.5, 80, and 91 percent, respectively. Gronroos JM, Gronroos P⁴ in a retrospective study studied the preoperative leucocyte counts and C-reactive protein (CRP) values in three groups of patients operated on for clinical suspicion of acute appendicitis. They concluded that acute appendicitis is very unlikely when both the leucocyte count and CRP value are normal.

ESR is a nonspecific test indicative of inflammation. It is used as an initial screening tool and also as a follow-up test to monitor therapy and progression or remission of disease as its easy to perform and inexpensive making it a widely used screening test. It basically measures how many red cells will settle in a given time. The Unit of measurement in mm/hrs. There is a lot of clinical significance when ESR is increased. Conditions in which there is an increase in ESR are as follows: Pregnancy, Anemia, Macrocytosis, Inflammatory disease, Acute, and chronic infection, Multiple myeloma, Rheumatic fever, Rheumatoid arthritis, Anemia, Tuberculosis, Systemic lupus erythematosus Decreased ESR, Hyperviscosity, Decreased fibrinogen levels, Polycythemia, Sick cell anemia, Spherocytosis, Microcytosis. The sensitivity, specificity, predictive value of the positive test, and predictive value of the negative test of ESR in our study is 66%, 60%, 93%, and 16%, respectively. Our results are in accordance with other studies. In a study done by Yoolhokimet al. on perforated appendicitis in 564 paediatric patients (<16 years) Emergency Department. TLC, CRP, ESR, and Alvarado scores were evaluated and found that TLC and ESR might be better indicators in a perforated appendix in paediatric patients than CRP and Alvarado score. ESR more than 15 mm is taken as positive. The sensitivity, specificity, predictive value of positive test, and predictive value of negative tests of ESR are 59.3%, 70.9%, 53.7%, 75.3%, respectively. Ceren Sentanrikulu¹⁰ et al. studied 278 appendicitis patients indicated that the inflammatory parameter ESR, CRP, PCT (procalcitonin) were not superior to other parameters, but CRP and PCT levels were significantly high in complicated cases. Mostafa Dahmerdehei¹¹ et al. studied 426 patients with appendicitis in 2007 in Zahedan and found a significant correlation was found between ESR and patients' pathologic results ($p=0.02$). The sensitivity, specificity, positive predictive value and negative predictive value of ESR was 71.9%, 39%, 83%, and 25%, respectively. ESR was positive in all individuals under 10 years of age. It was positive in 90.6% of cases aged 11-20 years old. The positive rate of ESR decreased gradually with the increase of age, where findings showed that only 33.3% of patients with 30-40 years old had had positive ESR ($p=0.0001$).

Berenjiet al. found that sensitivity and positive predictive value of ESR, CRP, and TLC can strengthen the clinical diagnosis of acute appendicitis, but the lowered value of negative (NPV) tests showed that negativity of each of the test and all together could not verify acute appendicitis. In another study done by Sakinch Abedi et al.¹², on 125 Appendicitis patients it is found that in addition to essential laboratory findings ESR, CRP, Leucocyte count can also be helpful in correct diagnosis of appendicitis sensitivity, specificity, predictive value of positive test and predictive value of negative test of ESR are 57.1%, 79.4%, 88.1%, 40.9% respectively. Baghi I et al. studied 158 patients of acute appendicitis and concluded that the presence of increased ESR, CRP, and TLC, the probability of appendicitis increased. However, normal values of ESR, CRP, and TLC do not rule out appendicitis. The sensitivity, specificity, predictive value of the positive test, and predictive value of negative test of ESR are 69.2%, 8.3%, 90.2%, 22%, respectively. Omid Amanollahi et al. studied the diagnostic value of inflammatory markers (ESR, CRP, TLC) in children with acute appendicitis and found that the diagnostic value of TLC is higher than that of ESR and CRP. The sensitivity of CRP is higher than that of ESR, but the specificity of ESR is higher than that of CRP. In the present study, it was observed that none of the cases of acute appendicitis had all the three tests within normal limits. The predictive value of negative tests in our study is 100%, i.e., if all three tests are negative acute appendicitis can be excluded. In our study five patients, the tests were false positive, and it was observed that two of them had other intraabdominal causes of elevation of CRP and WBC count. Also, combining the tests increases the sensitivity & predictive value of negative test. The significance of the association of combining the tests and their role in diagnosing acute appendicitis is found to be very high.

V. Conclusion

The sensitivity, specificity, predictive value of the positive test, and predictive value of negative test after combining all three tests (either/all) are 100%, 50%, 94.73%, and 100%, respectively. In the present study, it was observed that none of the cases of acute appendicitis had all the three tests within normal limits. The predictive value of negative tests in our study is 100%, i.e., if all three tests are negative, acute appendicitis can be excluded. Deferring surgery in this group is recommended. Therefore unnecessary appendectomy in the 5 patients in whom the tests were True negatives could be avoided, thereby decreasing the rate of negative laparotomies to 5% and also the associated morbidity. Also, combining the tests increases the sensitivity and predictive value of negative tests. The significance of the association of combining the tests and their role in diagnosing acute appendicitis is found to be very high. But the availability of these tests and cost-effectiveness should be taken into consideration. Acute appendicitis remains a diagnosis based primarily on history and

clinical examination. Clinical examination is indispensable in diagnosing acute appendicitis, and all the above investigations complement clinical skills and not replace it.

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