



ROLE OF SERUM CA-125 IN DIAGNOSIS OF ACUTE APPENDICITIS

Surgery

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KEYWORDS

INTRODUCTION

Acute appendicitis is one of the commonest causes of "Acute Surgical abdomen" and Appendectomy is the most frequently performed emergency abdominal surgery and is often the first major procedure performed by a surgeon in training.¹

The diagnosis of Appendicitis still remains a dilemma despite of advances in the radiological and laboratory investigations. Experienced clinicians accurately diagnose Appendicitis based on a combination of history, physical examination and laboratory studies about 80% of the time.³

RESEARCH PROBLEM

The percentage of appendectomy performed where appendix was subsequently found to be normal varies 15-50%⁴ and postoperative complications can occur in up to 50%⁵ of these patients. Delay in diagnosis of acute appendicitis leads to perforation and peritonitis and increased mortality.^{6,7}

Laboratory studies along with the clinical presentation viz. periumbilical pain caused by the activation of visceral afferent neurons, localization of pain to the right lower quadrant, anorexia, nausea, vomiting, fever, tenderness in the McBurney's point etc can help in diagnosis a case of acute appendicitis. An elevated total white blood cell count >10,000 cells/mm, while statistically associated with the presence of Appendicitis, had very poor sensitivity and specificity and almost no clinical utility.⁸

Numerous recent studies have reported that serum CA-125 concentration are also increased in non malignant disorders, especially in patients with peritoneal irritation caused by infection or surgery, as well as in pelvic inflammatory disease.⁹

Although there are a few studies showing the relation between CA-125 and AA, the evidence is not strong enough for the routine use of CA-125 in cases suspected of AA.

RESEARCH QUESTION- Is there any relation between serum CA-125 level and acute appendicitis.

HYPOTHESIS- There is relationship between serum CA-125 level and acute appendicitis and serum CA-125 can be used routinely in diagnosis of acute appendicitis.

OBJECTIVE

Primary(Specific) Objective- To find sensitivity and specificity of serum CA-125 in diagnosis of Acute Appendicitis.

Secondary Objective- To estimate and compare the serum CA-125 levels in acute appendicitis and acute appendicitis with complications.

METHODOLOGY

PLACE OF STUDY-Department Of General and Laparoscopic Surgery, VIMSAR Burla.

SETTING OF STUDY- Operation theatre and Indoor wards of Department of General and Laparoscopic Surgery, VIMSAR, Burla.

PERIOD OF STUDY-December 2018 TO November 2020

STUDYDESIGN-Observational (Cross sectional) study.

STUDY POPULATION-All male patients of any age with a clinical diagnosis of acute appendicitis and confirmation by histopathological examination (HPE) after appendectomy at Department of Surgery, VIMSAR, Burla, Sambalpur, Odisha.

SAMPLING METHOD- Convenient sampling

SAMPLE SIZE-100 patients attending OPD and getting admission in Indoor of Department of Surgery of this institute with clinical signs and symptoms of suspected acute appendicitis. As per previous information the sensitivity of CA-125 in acute appendicitis is 80%.

$$TP+FN = Z^2 \times [SN(1-SN)] / W^2 = (2)^2 \times 80(20) / 8 \times 8 = 4 \times 1600 / 64 = 6400 / 64 = 100$$

$$N_{\text{min}} = [TP+FN] / 1-p = 100 / 0.92 = 108$$

Therefore a minimum of 100 will be taken as sample size.

(TP+FN=Sensitivity, SN=Sensitivity of previous study, W= Sample error, Z= Constant, Nsn= Sample size)

SELECTION CRITERIA

a) INCLUSION CRITERIA

- All male patients of any age group presenting with signs and symptoms of suspected acute appendicitis.
- All male patients of acute abdomen with USG suggestive of acute appendicitis.

b) EXCLUSION CRITERIA-

- Female patients are excluded from this study because women of childbearing age show changes in CA-125 concentrations during the menstrual cycle and concentration increases by up to two times during menstruation.
- Any patients with severe heart disease, severe psychiatry illness.
- Patients with hypertension, diabetes mellitus, tuberculosis.
- Patients treated conservatively.

STUDY VARIABLES-

- Clinical signs and symptoms and clinical examination-** Right iliac fossa pain, migratory right iliac fossa pain, rebound tenderness, fever, anorexia, nausea, vomiting.
- Demographic-** Age, sex, socioeconomic status.
- Laboratory investigations-** Total Leucocyte Count, serum CA-125 level of the patient and appendicitis.

STUDY TOOLS-

Detailed history, thorough physical examination, complete haemogram, urine analysis, blood sugar level, serum urea and creatinine, serum electrolytes and X-Ray chest in routine investigations. Ultrasonography was carried out as and when indicated. Serum CA-125 level was collected before surgical procedures. Confirmation of diagnosis was made by histopathological examination of appendectomy specimen.

DATA COLLECTION METHODS-

Data was collected in preformed datasheet. Microsoft EXCEL 2016 and SPSS was used for the data analysis. Student's paired t-test was used to compare the serum CA-125 values in simple and complicated Appendicitis. The p-value <0.05 was considered significant.

ETHICAL APPROVAL

The study commenced with the approval of VIREC (VIMSAR Institute of Research and Ethical Committee).

RESULTS-**Table 1. Distribution of the respondents by operative finding.**

Operative findings	Number	Percentage
Simple (non-gangrenous or non-perforated) appendicitis	65	63.4
Complicated appendicitis	31	30.4
Normal appendix	6	6.2
Total	102	100.0

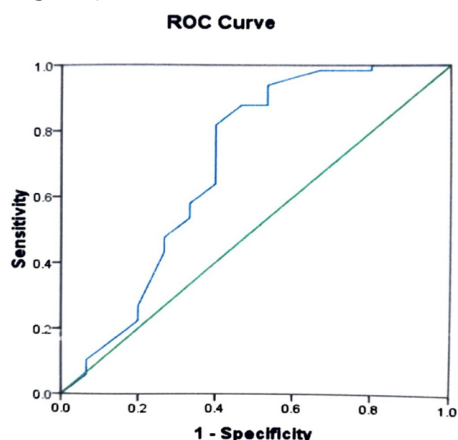
Figure 1: Bar diagram showing distribution of the respondents by operative findings.

Most of the appendix after operation was simple appendicitis (63.4%) followed by complicated appendicitis (30.4%) and 6.2% had normal appendix as shown in table 1 and figure 1.

Table 2. Distribution of respondents by HPE and Mean CA-125 level

HPE report	CA-125 Mean	T test
Appendicitis	24.2 (7.6 – 40.2)	t = 3.418
No appendicitis	9.2 (5.2 – 16.4)	p = 0.018
Total	23.6 (5.2 – 40.2)	

Table 2 shows that mean CA-125 level is higher in appendicitis (24.2) than no appendicitis (9.2) and this finding is found to be statistically significant ($p < 0.05$).



Diagonal segment are produced by ties.

Figure 2: ROC of CA-125 level against HPE report

The area under the curve in Figure 2 is 0.697 i.e. it has an accuracy of around 70% and this is statistically significant ($p = 0.018$). If the cut-off level of CA-125 level is at 10.4 then it gives a sensitivity of 82% and specificity of 60%.

Table 3. CA-125 Levels in complicated and uncomplicated appendicitis

Acute appendicitis patients	CA-125 levels	P=0.178
Uncomplicated appendicitis(n=65)	22.4(7.6 – 40.2)	
Complicated appendicitis(n=31)	28.4(8.4 – 39.4)	

Table 3 shows even though there is CA-125 levels are mildly elevated in complicated appendicitis compared to uncomplicated appendicitis but it is insignificant ($p = 0.178$).

DISCUSSION-

Early diagnosis of acute appendicitis is not always easy. The decision to observe the patient until the diagnosis becomes obvious or to operate early to prevent unwanted complications like perforation and peritonitis represents a serious dilemma for surgeons. An early operation may result in the removal of a normal appendix with a small risk of morbidity.¹⁰⁻¹⁴ Many attempts have been made to determine ways of decreasing the negative laparotomy rate in clinically suspected acute appendicitis. It would be very important to differentiate early appendicitis from non-specific abdominal pain. However, a carefully detailed history, physical examination, and standard laboratory studies do not always clearly detect early acute appendicitis. Furthermore, delay in diagnosis can be harmful and may convert a relatively uncomplicated case to substantial morbidity or even mortality in patients with co-morbid illnesses.

The study investigated the role of serum CA 125 level in the diagnosis of acute appendicitis and to see whether it can play an important role in reducing the negative appendicectomy rate. The study was designed to find out the sensitivity and specificity of serum CA125 level in diagnosis of acute appendicitis and to study the correlation of serum CA125 level with the severity of inflamed appendicitis. The study was conducted in Veer Surendra Sai Institute of Medical Science and Research, Burla, Sambalpur, Odisha from December 2018 to November 2020. The majority of the patients in our study were from Sambalpur district and this may be explained by the location of our hospital and the larger population of Sambalpur.

In the present study the level of serum CA125 level is found raised in all cases of acute appendicitis. CA-125 is a 225 kDa glycoprotein produced by cells in the coelomic epithelium, the epithelium of the female genital tract, the colonic mucosa, stomach mucosa, and mesothelial cells in serous membranes. It is a cell-surface antigen recognized by the OC-125 antibody produced by OVCA433 cells, a carcinogenic ovarian epithelial cell line.¹⁵ This tumour marker is normally used to follow the clinical course of patients with ovarian cancer. In 80% of cases, its concentration increases, which is associated with disease progression or relapse.¹⁶ However, marked increases in plasma CA-125 concentrations also occur during pregnancy and following peritoneal irritation associated with infection or surgery, particularly pelvic inflammatory disease, benign ovarian cysts, ectopic pregnancy and fibroids. Its levels also increase by up to two times during menstruation.¹⁷ Several studies^{18,19} have also suggested that the peritoneum is an important source of CA-125, and that peritoneal inflammation contributes to increases in its serum concentrations in pathological conditions. Inflammatory disorders, including pelvic inflammatory disease, endometriosis (especially with adhesions), malignant pathologies with ascitis, and peritonitis are associated with high circulating CA-125 concentrations. From this context, we evaluated the diagnostic potential of CA-125 in acute appendicitis. Here, we found that patients with acute appendicitis had significantly greater CA-125 concentrations compared with healthy subjects. In the disease process, acute appendicitis starts as a localized inflammatory process and may progress from localized peritonitis to generalized peritoneal inflammation. Accordingly, an increase in CA-125 concentration may be due to peritoneal inflammation, which can involve two mechanisms. First, CA-125 released from damaged peritoneal mesothelial cells is absorbed and transferred to the circulation. Second, Zeilemaker et al²⁰ reported that the secretion of CA-125 from a monolayer of mesothelial cells into culture medium can be enhanced by the inflammatory cytokines interleukin-1 β , tumour necrosis factor, and lipopolysaccharide. Therefore, during the disease process in vivo, increased cytokine levels may augment the secretion of CA-125 from the peritoneal surface. The most commonly used reference value for CA-125 is 35 U/mL, which was originally reported by Bast et al.¹⁵ Barceló et al. suggested that the reference value for healthy subjects should be much lower than that used in clinical practice, and they proposed the reference value of 20 U/mL for men and menopausal women, and 31 U/mL for nonmenopausal women.²¹

In the present study it is observed that 18 patients out of the 102 patients (17.6%) who underwent appendicectomy, the appendix was found to be normal. And in all these patients the serum CA 125 level was found to be normal thus indicating the possibility of preventing negative appendicectomy had serum CA125 value was taken into consideration.

In the present study whether the patient has acute appendicitis or not is

confirmed by histopathology. Out of the total 102 patients that were operated, 84 patients (82.4%) were found to have acute appendicitis while 18 patients (17.6) were found to be normal. The Mean $\pm$ SD of serum CA125 in mg/dl in our study in those patient proved to be having acute appendicitis by histopathology is 24.2 U/ml while those with normal appendix is 9.2 U/ml. In the present study, we found that CA-125 concentrations were significantly greater in patients with acute appendicitis than in the healthy subjects. In ROC curve analysis, the optimal cut-off value for the diagnosis of acute appendicitis was 10.4 U/mL, for which the sensitivity, specificity, PPV, and NPV were 82%, 60%, 88%, and 63%, respectively.

Similar study was done by Ismail B et al¹³, they performed ROC curve analysis and they found out optimal cut-off value of CA125 for the diagnosis of acute appendicitis was 11.78 U/mL, for which the sensitivity, specificity, PPV, and NPV were 83.3%, 80%, 91%, and 67%, respectively. Based on these results, they concluded that The CA-125 cut-off value of 11.78 U/ml had high sensitivity, specificity, PPV, and NPV for the diagnosis of acute appendicitis. These results are similar to the present study.

In the present study we also found that there was difference in CA125 value in uncomplicated appendicitis (22.4 U/ml) and complicated appendicitis (28.2U/ml) but it was statistically insignificant.

Cetinkaya et al¹⁰ evaluated the relation between CA 125 and perforated AA. They concluded that high levels of CA 125 may show perforated cases. They reported the cut-off value for the diagnosis of complicated AA as 35U/mL, with the sensitivity, specificity, and PPVs of 60%, 100%, and 100%, respectively. This result is contradictory to the present study.

Our results suggest that the use of CA125 blood level may be a new diagnostic acute-phase reactant in the diagnosis of acute appendicitis that may be helpful in deciding whether to operate on the patient or to manage with non operative measures thereby reducing negative appendectomy rate but at the same time not delaying the operation till complication arises.

Based on the present study the area under the curve is 0.697 i.e. it has an accuracy of around 70% and this is statistically significant (p=0.018). If the cut off level of serum CA125 level is at 10.4 U/ml then it gives a sensitivity of 82% and specificity of 60%.

CONCLUSION-

Acute appendicitis still remains a very common condition requiring emergent surgery. Early diagnosis plays a key role in preventing complications originating from perforation. However, surgeons must achieve a balance between premature operation with a high negative appendectomy rate and a delayed diagnosis (and surgery) with a higher perforation rate. There is no sign, symptom, or laboratory test that is 100% reliable in the diagnosis of acute appendicitis. However the formulation of more number of diagnostic parameter is recommended as a guide in deciding which patient undergoes emergency surgery or observation. In our study the area under the curve is 0.697 i.e. it has an accuracy of around 70% and this is statistically significant (p=0.018). And if the cut off level of CA125 level is taken at 10.4U/ml then it gives a sensitivity of 82% and specificity of 60%. Thus the addition of CA125 blood level can be a new diagnostic acute-phase reactant in the diagnosis of acute appendicitis. we also conclude that CA125 could not differentiate between complicated and uncomplicated appendicitis as is evident in our study.

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