

Diagnostic Utility of Serum CA-125 Levels in Cases of Acute Appendicitis in Male Patients - A Hospital Based Study

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ABSTRACT

BACKGROUND

Appendicitis is one of the common surgical emergencies worldwide affecting all age groups and sexes. Appendicitis is currently diagnosed based on symptoms and using imaging modalities. Biochemical investigations are not specific in diagnosis of acute appendicitis and complete blood cell counts may corroborate the diagnosis. The aim was to study the utility of serum CA-125 level in the diagnosis of acute appendicitis and to assess the value of CA-125 in predicting the severity/complications of acute appendicitis

METHODS

A prospective cross-sectional study was carried out in the Department of General Surgery in association with Department of Biochemistry, Government medical College and General Hospital from January 2018 to December 2019. 102 male subjects with acute appendicitis were included in the study. Age, socio economic status, presenting symptoms, leucocyte and CA 125 levels were recorded. Data obtained was tabulated in a pretested proforma and analysed using appropriate statistical methods. Test performance characteristics were summarized using hierarchical summary receiver operating characteristic (ROC) curves and bivariable random-effect models.

RESULTS

It is observed from the study that acute appendicitis is common in younger age group with mean \pm SD of 37.26 \pm 1.6 belonging to lower socio-economic status. Right iliac fossa pain was present in all cases. About 61.7% cases presented with strong right iliac fossa rebound tenderness. Leucocytosis was present in about 705 study subjects. ROC curve analysis showed that in the current study, 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.

CONCLUSIONS

It can be stated that CA 125 blood level can be a new diagnostic acute-phase reactant that can be used in the diagnosis of acute appendicitis. Serum CA 125 could not differentiate between complicated and uncomplicated forms of acute appendicitis.

KEYWORDS

Acute Appendicitis, CA 125, Complications, Leucocytes, Rebound Tenderness

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BACKGROUND

The term acute appendicitis was coined by Reginald Fitz (1886) who identified the appendix as the primary cause of right lower quadrant inflammation.^[1] Acute appendicitis is one of the primary and commonest cause of "Acute Surgical abdomen".^[2,3]

Though Appendectomy is the most frequently performed abdominal surgery, the diagnosis of appendicitis still remains a dilemma even in this era of radiological and laboratory advancements across the globe. Age old method of diagnosis acute appendicitis involves a combination of history taking, physical examination and laboratory diagnosis in about 80% of the cases.^[4] The diagnosis of acute appendicitis is at times is problematic due to varied presentation of sign and symptoms and absence of condition specific lab methods. The diagnostic dilemma is further complicated when appendix is retrocecal or retro-ileal. Further it is an established fact that delay in diagnosis of acute appendicitis can end in perforation with peritonitis and culminate in increase in morbidity and mortality of the affected patients.^[5,6] The diagnosis of appendicitis is almost always elusive, demands a high index of suspicion so as to prevent complications of this clinical condition.

Many diagnostic criteria like White Blood Cell (WBC) counts, Ultrasonography (USG), evaluation of biochemical markers and C-reactive protein (CRP) values has been put forwarded from time to time to supplement the clinical diagnosis and to reduce the frequency of unnecessary Appendectomy.^[7-11] Various scores that are designed with combination of clinical features and laboratory investigations like Alvarado score,^[12] and the Modified Alvarado score,^[13] are also used to achieve diagnostic accuracy in the cases of acute appendicitis. However, it is not exaggerating to state that no confirmatory laboratory marker for diagnosis of preoperative diagnosis of acute appendicitis or appendicular perforation.

Glycoprotein CA-125, a 225 kDa protein substance produced by cells in coelomic epithelium of epithelial colonic / gastric mucosa etc., is often used as tumour marker in cases of gynecology. It is a cell-surface antigen recognized by the OC-125 antibody produced by OVCA 433 cells, a carcinogenic ovarian epithelial cell line.

CA-125 concentrations in plasma tends to increase in cases of ovarian cancers, pregnancy, menstruation, conditions associated with peritoneal irritation (surgery and infections), ovarian cysts, ectopic pregnancy and uterine fibroids. It is evident from certain recent studies that levels of CA-125 could act as a marker in cases of acute appendicitis though the evidence is not so satisfactory. In this background the current study is aimed to evaluate whether serum CA-125 concentrations could reflect the presence of acute appendicitis and also to correlate CA-125 concentrations with the severity of acute appendicitis.

We wanted to study the role of serum CA-125 levels in the diagnosis and in predicting the severity / complications of acute appendicitis.

METHODS

The current cross-sectional study is taken up at Department of General Surgery, in association with Department of Biochemistry Government Medical College and General Hospital, Anantapuramu, Andhra Pradesh from January 2018 to December 2019 after obtaining Clearance from Institutional Ethics Committee. Study subjects included 100 male patients with a clinically diagnosed acute appendicitis and confirmed by a histopathological examination (HPE) of the specimen post appendectomy. Female patients are excluded from this study because women of childbearing age show changes in serum CA-125 concentrations during the menstrual cycle, and its concentration increases by up to two times during menstruation. The following inclusion and exclusion criteria were used to recruit the patients in the current study. Prior consent was obtained from all the patients of the study and absolute confidentiality is maintained throughout the study. The study was conducted under variables such as age, socioeconomic status, clinical features, total leukocyte count, serum CA-125 level of the patient and appendicitis.

Inclusion Criteria

1. All male Patients presenting with signs and symptoms of suspected acute appendicitis of any age group.
2. All male patients of acute abdomen with USG/CT/MRI suggestive of acute appendicitis.
3. All male patients of diagnosed acute appendicitis being referred to Department of Biochemistry, Government Medical College, Anantapur for estimation of CA-125 levels.

Exclusion Criteria

1. Any patients with severe heart disease, severe psychiatric illness.
2. Patients with hypertension, diabetes mellitus, tuberculosis.
3. Patients unwilling to give their consent.
4. Patients treated conservatively.

The following standard procedural protocol is adopted in all the cases

1. Particulars of patients were taken from record card followed by detailed history and thorough physical examination.
2. Sample of blood around 2 mL in EDTA vial for complete hemogram, 2 mL in sodium fluoride for blood sugar level, 3 mL for KFT with serum electrolytes, urine sample for urine analysis was collected.
3. Chest X-Ray was taken as routine investigation.
4. Ultrasonography or computerised tomography (CT) was advised whenever it is necessary.
5. Blood sample for determining serum CA-125 level was collected before the surgical procedure. Specimens were collected and transported, preserved and serum

was separated as per standard laboratory procedures. The CA-125 concentration was estimated by using the equipment, VITROS ECIQ, chemi-analyser manufactured by Johnson & Johnson Company, USA that works on the principle of Chemiluminescence.

- Under strict aseptic and antiseptic condition, the appendectomy specimen was preserved in formalin and sent to pathology laboratory for histopathological examination. The histopathological finding was used for confirmation of appendicitis.

All the data from the study are tabulated in a pretested proforma. Sensitivity, specificity, and positive predictive value of single test and test combination was calculated at different cut-off levels. SPSS software version 21 is used for statistical analysis. A 'p' value of 0.05 or less was considered significant.

RESULTS

Age and Acute Appendicitis

It is evident from the study that majority of the respondents were in the age group 10-20 years (28.4%) followed by 21-30 years (27.4%). Mean age was 37.26 with a standard deviation of 1.6 years. Similar finding are also reported in other studies conducted by Murata A et al,^[14] Addis DG et al.^[15]

Acute Appendicitis and Socio-Economic Status

Most of the patients with acute appendicitis were from low socioeconomic class (50.9%), followed by middle class (35.4%) and higher socio-economic status (13.7%). This data is supported in some of the studies conducted elsewhere. However, Lee SL et al.^[16] in their study showed that lower socioeconomic background and minority race/ethnicity did not correlate with higher appendicitis rates or a clinically longer length of hospital stay in patients with equal access to care the possible explanation for the higher incidence rate in our study could more number of people from lower economic class seeking health care in a government institute rather than in private hospitals. Based on these findings, we believe that equal health care access leads to equivalent outcomes in all patients with appendicitis.

Acute Appendicitis and Presenting Symptoms

All the subjects recruited in the study were presented with migratory pain in the right iliac fossa and pain in right lower quadrant of abdomen following which the presenting symptoms observed were anorexia, nausea and vomiting in 98.8% cases, 79.3% and 70.3% respectively. These findings are presented in Table no. 1. Similar presentation is observed in study conducted by Patricia A, Pastore et al^[17] and Singh I et al.^[18] However, it is very much important to differentiate these symptoms as they are presented in many abdominal pathologies.

Symptoms	Number	Percentage (%)
Migratory right iliac fossa pain	51	50.0
Pain Right lateral quadrant	102	100.0
Fever	91	89.1
Anorexia	101	98.8
Nausea	82	79.3
Vomiting	72	70.3

Table 1. Distribution of Cases According to Presenting Symptoms

Acute Appendicitis and Rebound Tenderness in the Right Iliac Fossa

It is derived from table no. 2 that majority of cases had strong Right Iliac Fossa rebound tenderness as apparent at clinical examination in 61.7% of cases and another 27.5% of cases revealed medium rebound tenderness in Right Iliac Fossa. Though this is common finding in many of the studies conducted elsewhere, it is imperative to rule out all the other pathologies before coming to conclusion of acute appendicitis as cited in an article by S. W. Ewen, J. Anderson et al and also in.^[19]

Right Iliac Fossa Rebound Tenderness	Number	(%)
Light (tenderness on deep)	11	10.8
Medium (tenderness on medium pressure release)	28	27.5
Strong (tenderness on light pressure)	63	61.7
Total	102	100.0

Table 2. Cases with Right Iliac Fossa Tenderness

Acute Appendicitis and Leukocyte Count

It is to be understood from table No. 3 that variation of leukocyte count is common in cases of acute appendicitis. In the current study majority of the respondents has a Leukocyte count between 10-14 x 10⁹/litre as seen in 59% of cases and the counts more than 15 x 10⁹/L is present in 20.7% of cases. Low to normal counts are observed in 19.7% of cases. Leukocyte count and C-reactive protein concentration are the most performed laboratory tests, with procalcitonin and D-dimers more recently proposed as novel biomarkers for acute abdominal disorders. Similar details were discussed in studies conducted by Thompson MM, Underwood MJ,^[20] and Grönroos JM.^[5]

Leukocyte Count	Number	Percentage (%)
<10 x 10 ⁹ /L	20	19.7
10-14 x 10 ⁹ /L	61	59.6
>15 x 10 ⁹ /L	21	20.7
Total	102	100.0

Table 3. Case Distribution Based on Leukocyte Counts

Acute Appendicitis and Intraoperative Findings

Intraoperative findings revealed simple (non-perforated/non-gangrenous) appendicitis in 63.4% of cases, complicated appendicitis was evident in 30.4% of cases. Incidentally, normal appendix is visualized in six cases.

Acute Appendicitis and Histopathology Examination

Histopathology examination confirmed the diagnosis of appendicitis in 82.4% of cases and another 17.6% of cases appendicitis was absent as seen in Table no. 7 below. It is cited in a study conducted by Frank R Lewis et al^[21] that two thirds of the negative appendectomies were due to

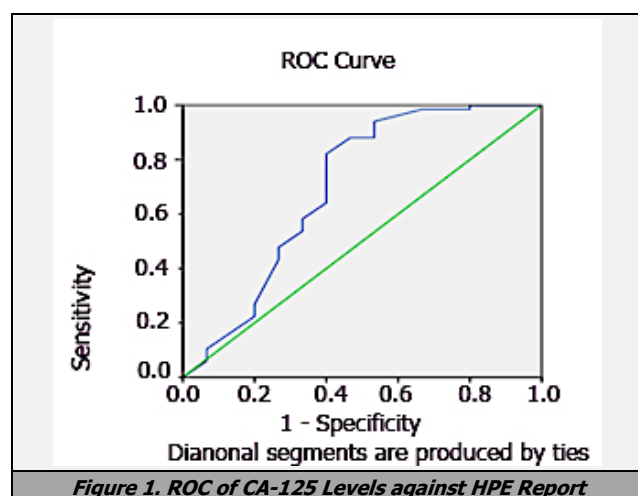
nonsurgical lesions. Mesenteric adenitis, gastroenteritis, and abdominal pain of unknown cause accounted for one third of the errors in females and two thirds in males.

Histopathology Report and Mean of CA-125 Levels

It is seen in Table no. 4 that mean CA-125 level is higher in appendicitis (24.2) cases than in cases where there is no appendicitis (9.2) and this finding of current study is found to be statistically significant ($p < 0.05$). In ROC (Figure. 1.), 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 CA125 level is at 10.4 then it gives a sensitivity of 82% and specificity of 60%.

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

Table 4. Distribution of Cases Based on HPE Reports and Mean CA-125 Values



Complicated and Uncomplicated Appendicitis and CA-125 Levels

Observations from study shows that even though there is CA125 levels are mildly elevated in complicated appendicitis compared to uncomplicated appendicitis, but it is insignificant. ($P = 0.178$).

DISCUSSION

In the present study the level of serum CA 125 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.^[22] It is a cell-surface antigen recognized by the OC-125 antibody produced by OVCA 433 cells, a carcinogenic ovarian epithelial cell line.^[23] 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 strongly associated with disease progression or relapse.^[24] 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.^[25] Several studies^[26] 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 ascites, and peritonitis are associated with high circulating CA-125 concentrations. From this context, it is observed 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, increase in CA-125 concentration may be due to peritoneal inflammation, which can involve two mechanisms. In the first instance CA-125 released from damaged peritoneal mesothelial cells is absorbed and transferred to the circulation. On the other hand, Zeilemaker et al^[27] 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.^[22] 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 non-menopausal women.^[28]

In the current study it is observed that 9.2 patients out of the 102 patients (17.6%) who underwent appendectomy, the appendix was found to be normal and in all these patients the serum CA 125 level was found to be normal. This fact indicate that serum CA 125 values will help in preventing negative appendectomies. It is also observed in the current study that 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 CA 125 in mg/dl in our study in those patients 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 al,^[29] they performed ROC curve analysis, and they found out optimal cut-off value of CA 125 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 like the present study. In the present study it is also found that there was difference in CA 125 value in uncomplicated appendicitis (22.4 U/mL) and complicated appendicitis (28.2 U/mL) but it was statistically insignificant. Our results suggest that the use of CA 125 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 CA 125 level is at 10.4 U/mL then it gives a sensitivity of 82% and specificity of 60%.

CONCLUSIONS

Acute appendicitis remains a common condition that requires emergency surgical management. Early diagnosis and swift action play a pivotal 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 specific sign, symptom, or laboratory test that is 100% reliable in the diagnosis of acute appendicitis. Based on our results it can be stated that Serum CA 125 level can be a new diagnostic marker that can be used in diagnosis of acute appendicitis in males. But serum CA 125 could not differentiate between complicated and uncomplicated forms of acute appendicitis in males.

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