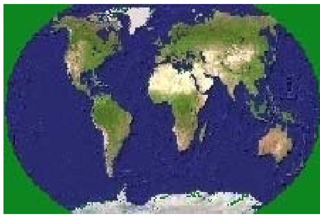

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CA-125 as a marker of peritoneal inflammation in diagnosis of acute appendicitis

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Abstract
Aim: Acute appendicitis is the most common acute condition of the abdomen requiring surgery. To date, several inflammatory markers have been used for the diagnosis of acute appendicitis. The aim of this study was to evaluate the diagnostic utility of CA-125 (cancer antigen 125) in acute appendicitis.
Methods: We prospectively enrolled 52 consecutive male patients and 20 healthy control subjects.
Results: Overall, 48/52 patients had acute appendicitis. Of these, 17 had complicated appendicitis (35%). The CA-125 concentration was significantly greater in patients with acute appendicitis than in healthy subjects (26.3 vs. 9.6 U/mL, $P < .001$). CA-125 concentrations were not significantly different between patients with complicated appendicitis or uncomplicated appendicitis ($P > .017$). Receiver operating characteristic curve analysis suggested that the optimal cutoff CA-125 concentration for acute appendicitis **diagnosis** was 11.78 U/mL. The positive predictive value and the negative predictive value**s** were 91.0% (95% confidence interval 78.14%–97.52%) and 66.6% (95% confidence interval 44.62%–84.33%), respectively.
Conclusions: We conclude that measurement of CA-125 concentration may support the clinical diagnosis of acute appendicitis.

Keywords: CA-125, acute appendicitis, inflammation

1. Introduction

Acute appendicitis is the most frequent cause of right lower quadrant pain, the most common acute condition of the abdomen requiring surgery, and is one of the most serious abdominal illnesses [1]. It is a pathological condition that requires immediate surgical treatment. Although the majority of appendicitis cases are uncomplicated, between 18.3% and 34.0% of cases are complicated by perforation, which significantly increases the rate of postoperative complication [2]. The overall mortality rate of acute appendicitis is 0.3%, but this increases considerably in cases with perforation (6.5%), in older patients (5.5%), and in neonates (80%) [3]. the frequency of appendicitis and the high rates of negative appendectomies, which range from 9%–44%, have prompted continuing efforts to develop new diagnostic methods with high sensitivity and specificity to reduce the rate of negative appendectomies [4]. Many attempts have also been made to decrease the negative laparotomy rate in cases of suspected acute appendicitis. However, despite complete clinical history, physical examination, and routine laboratory tests, we still lack clear tools to aid the early detection of acute appendicitis. Currently, laboratory parameters such as white blood cell count, neutrophil count, and C-reactive protein concentration are widely used in various combinations to improve in sensitivity and specificity as tools to assess risk of appendicitis. Imaging techniques such as ultrasound (US) and computerized tomography (CT) and diagnostic laparoscopy have been used with the hope of yielding a rapid and accurate diagnosis. The main problems with routine use of diagnostic imaging are potentially harmful ionizing radiation (CT), examiner-dependent efficacy (US), and technique-associated morbidity (diagnostic laparoscopy) [5].

Glycoprotein CA-125 (cancer antigen 125), a cell-surface antigen recognized by the OC-125 murine monoclonal antibody, is widely used in the field of gynecologic oncology [6]. Numerous recent studies have reported that serum CA-125 concentrations 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 [7]. Therefore, the purpose of this study was to evaluate whether serum CA-125 concentrations could indicate the presence

Of acute appendicitis and to correlate CA-125 concentrations with the severity of acute appendicitis in patients admitted with a diagnosis of acute appendicitis to an inner-city emergency room.

Materials and methods

This study was conducted prospectively after obtaining approval from the ethics committee at Ankara Numune Teaching and Research Hospital. We prospectively enrolled 52 consecutive male patients who underwent surgery for acute appendicitis and 20 healthy control subjects. Acute appendicitis was diagnosed with clinical, laboratory and radiological findings in 52 patients. All patients were non-smoker. The non-smokers healthy controls were selected from healthy males without known clinical conditions who underwent medical checkups in the Internal Diseases Clinics. We excluded women 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 [8, 9]. Serum CA-125 concentrations were measured using an electrochemiluminescence immunoassay on an auto-analyzer (HITACI COBAS 6000 e601, JAPAN) at the Department of Clinical Biochemistry Laboratory at our hospital. Blood samples were taken at the time of diagnosis, before surgery. All patients and healthy subjects provided written informed consent. Patient age, white blood cell count, CA-125 concentrations, surgical findings, and pathological findings were prospectively recorded. Clinical data and CA-125 levels were also prospectively recorded for the healthy controls at the time of the medical checkups. Patients with diabetes mellitus, hypertension, obesity, or other relevant comorbidities (such as heart failure and tuberculosis status) and smokers were also excluded.

Statistical Analysis

Data from both groups were statistically analyzed using IBM SPSS Statistics version 20.0 (IBM Inc., New York, NY). Patient characteristics and clinical features are shown as the mean ± standard deviation, median, range, and percentage (%), as appropriate. All of the variables were examined visually using histograms and probability plots, and analytically using the Kolmogorov–Smirnov test to determine whether they were normally distributed. Independent samples to test was used to compare for normally distributed variables. Non-normally distributed variables were compared using the Mann–Whitney U test for two groups or the Kruskal–Wallis test for more than two groups. The significance of pair wise differences was tested using the Mann–Whitney U test with Bonferroni adjustment for multiple comparisons. Statistical significance was set at an overall type I error level of 5%. We measured the clinical performance of CA-125 concentrations using receiver-operating characteristic (ROC) curves, which were used to calculate the likelihood ratios for cutoff values showing high sensitivity or high specificity. For power analysis, 0.05 for alpha (Type I) error and 0.2 for beta (Type II) error have been accepted and the power of study was determined as 80%. In that situation, we calculated minimally 16 patients in each group to meet these requirements. Our study included 48 patients with appendicitis and 20 controls without appendicitis.

Results

Overall, 48/52 patients who underwent appendectomy had intraoperatively and histologically confirmed acute appendicitis. Of these, 17 had complicated appendicitis (35%). Cases of perforated (n=15) or plastron appendicitis (n=2) were classified as complicated appendicitis. Intraoperative and histologic findings did not confirm the presence of acute appendicitis in the other four patients. Appendicitis patients and controls characteristics are presented in table one. There was no significant difference in age between the two groups (*P=.748*). The CA-125 concentration was significantly greater in patients with acute appendicitis than in healthy subjects (26.3 vs. 9.6 U/mL, $p < 0.001$). When we compared patients with complicated appendicitis or uncomplicated appendicitis, and the healthy subjects, we found that the CA-125 concentrations were significantly greater in patients with complicated or uncomplicated appendicitis compared with healthy subjects (with Bonferroni adjustment, $p < 0.001$) (Table-2). However, CA-125 concentrations were not significantly different between patients with complicated appendicitis or uncomplicated appendicitis (with Bonferroni adjustment, $p > .017$).

Table 1: Characteristics of the patients and the healthy controls

	Healthy persons (n=20)	Acute Appendicitis (n=48)	p
Age	31.5 (19-46)	31 (16-48)	0.748
WBC count (per mm3)	7680 (4300-10400)	15500 (7070-21200)	<.001
CA-125 (U/mL)	9.6 (4.3-17.4)	26.3 (6.4-46.6)	<.001

WBC= White blood cell

Table 2: CA-125 levels

	CA-125 (U/mL)
Healthy persons (n=20)	9.6 (4.3-17.4)
Uncomplicated appendicitis (n=31)	23.74 (6.4-46.6)
Complicated appendicitis (n=17)	30.9 (8.7-42.4)

The ROC curve analysis suggested that the optimal cutoff CA-125 concentration for acute appendicitis was 11.78 U/mL (area under the curve 0.897, $P < 0.0001$; Figure 1), for which the sensitivity and specificity were 83.3% and 80%, respectively. The positive predictive value (PPV) and the negative predictive value (NPV) were 91.0% (95% confidence interval 78.14%–97.52%) and 66.6% (95% confidence interval 44.62%–84.33%), respectively (Table-3). Positive and negative Likelihood Ratios (LR) was also shown in table three.

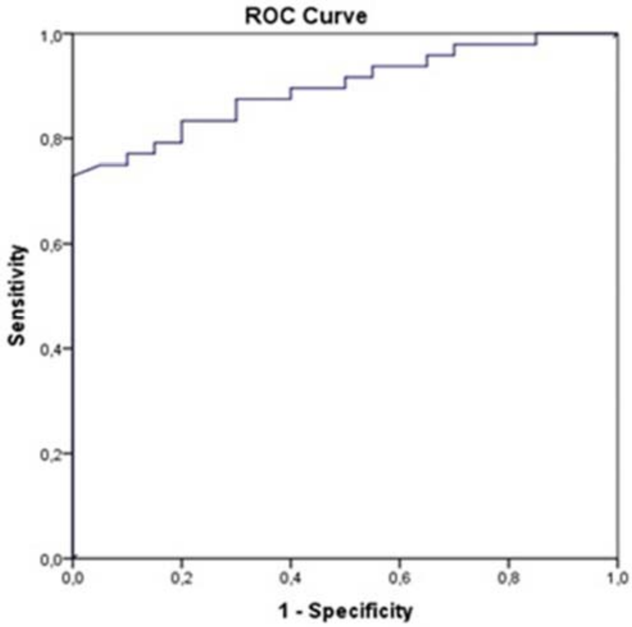

Fig 1: Receiver operating characteristic curves for the CA-125 to identify patients with appendicitis (healthy people's vs acute appendicitis) (Area under the curve 0.897, P<.0001)

Table 3: The optimal cutoff value, sensitivity, specificity, +LR and −LR, PPV, and NPV of CA-125 levels in acute appendicitis

CA-125	Sensitivity (95% CI)	Specificity (95% CI)	+LR (95 % CI)	−LR (95 % CI)	PPV (95% CI)	NPV (95% CI)
≥11.78	83.3 (69,8 - 92,5)	80,00 (56,3 - 94,3)	4,17 (1,7 - 10,1)	0,21 (0,1 - 0,4)	91.0 (78.14 – 97.52)	66.6 (44.62 – 84.33)

Discussion

Although the incidence of acute appendicitis has decreased slightly over the past few decades, it remains a common cause of acute abdominal pain and urgent surgical intervention. If untreated, acute appendicitis will progress from inflammation to perforation with abscess formation or diffuse peritonitis. However, misdiagnosis of acute appendicitis can result in unnecessary laparotomies. Generally, the morbidity and mortality of missing a case of acute appendicitis that subsequently develops peritonitis or abscess formation outweigh the complications associated with a negative appendectomy. Many inflammatory markers have been used to aid the diagnosis of acute surgical conditions, including appendicitis. Leukocyte count and C-reactive protein concentration are the most commonly performed laboratory tests, with procalcitonin and D-dimers more recently proposed as novel biomarkers for acute abdominal disorders [10, 11].

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 [12]. It is a cell-surface antigen recognized by the OC-125 antibody produced by OVCA433 cells, a carcinogenic ovarian epithelial cell line [13]. This tumor 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 [14]. 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 [7]. Its levels also increase by up to two times during menstruation [15].

Several studies [16, 17] 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, 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, Zeillemaker *et al.* reported that the secretion of CA-125 from a monolayer of mesothelial cells into culture medium can be enhanced by the inflammatory cytokines interleukin-1β, tumor necrosis factor, and lipopolysaccharide [18]. 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.* [13]. 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 [19]. However, there is still no consensus for the reference value in healthy men. Therefore, we performed ROC curve analysis to assess the overall diagnostic value of specific parameters in clinical practice.

Because there are no studies describing the sensitivity or the utility of CA-125 concentrations in the diagnosis of acute appendicitis, we could not compare our results with those of prior reports. 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 cutoff value 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, it is possible that CA-125 may be useful for evaluating male patients with little co-morbidity with suspected appendicitis.

Despite the prospective nature of this study, there are several limitations to this study need to be mentioned. First, the sample size was quite small. Second, the assessment of other biomarkers of acute appendicitis may help to determine the diagnostic significance of CA 125 concentrations. Third, we did not include female patients, so we therefore cannot determine the performance of CA 125 in this population when assessing for appendicitis and it will be important to include females in future studies. Our other exclusion criteria such as smoking habits, obesity, and diabetes mellitus may be ignored in large population studies.

In conclusion, despite the limitations of this study, including the small sample size, we conclude that measurement of CA-125 concentrations may help to support the clinical diagnosis of acute appendicitis in adult male patients with typical clinical features. The CA-125 cutoff value of 11.78 had high sensitivity, specificity, PPV, and NPV for the diagnosis of acute appendicitis. Future studies with larger sample sizes and less restrictive population would be would be beneficial to evaluate the role of CA-125 in acute appendicitis.

Competing interests
The author(s) declare that they have no competing interests.

Author Contribution
IB, TD contributed to study design. SG,Sy built a custom database for data acquisition. EK, MMO performed data acquisition, initial analysis, and wrote the initial draft manuscript. CK, IB performed data analysis and wrote the final manuscript. All authors read and approved the final manuscript.

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