The Role of CA-125 in Differential Diagnosis of Ascites

Asit Ayırıcı Tanısında CA-125'in Rolü

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ABSTRACT Objective: CA-125 has been found to be high in almost all the patients with ascites. In this study, we tried to determine cut-off values of CA-125 in serum and ascitic fluid levels in order to discriminate non-ovarian malignancies, ovarian carcinomas and benign diseases. **Material and Methods:** A total of 119 patients were included in the study. The patients were divided into three groups: non-ovarian malignancies, ovarian carcinoma and benign diseases. Serum and ascitic fluid CA-125 levels were measured by electrochemiluminescence immunoassay, 'ECLIA' method. In determining the discriminitive ability of CA-125 levels between the groups, receiver operating characteristic (ROC) analysis was performed. **Results:** A total of 119 patients were included in the study: 55 males and 64 females. Of patients, 53 had non-ovarian malignancy, 19 had ovarian carcinoma and 47 had benign diseases. Serum and ascitic fluid CA-125 levels were high in all of the three groups. When cut-off value of ascitic CA-125 was taken as 174 U/mL, the sensitivity and specificity were found to be 69.2% and 25.5%, respectively; however, when the value was accepted as 796.5 U/mL, these rates were observed as 30.8% and 80.9% respectively. In the discrimination between ovarian carcinoma and benign diseases, when the cut-off value of ascitic CA-125 was considered as 411 U/mL, the sensitivity and specificity were obtained as 94.7% and 63.8% respectively. When the value was taken as 971.9 U/mL, the sensitivity and specificity rates were 57.9% and 78.7% respectively. **Conclusion:** In discriminating between malign and benign ascites, ascitic CA–125 levels rather than serum values are of significance, and it can be suggested that malignancy should be persistently searched when the value is over 1000 U/mL.

Key Words: CA-125 antigen; ascites

ÖZET Amaç: Asitli hastaların neredeyse tümünde CA-125 yüksekliği görülmektedir. CA-125 serum ve asit düzeylerinin over-dışı malign, over adenokarsinomu ve benign hastalıkları ayırmada cut-off değerlerini belirlemeye çalıştık. **Gereç ve Yöntemler:** Çalışmaya toplam 119 asitli hasta dahil edildi. Hastalar over-dışı malign, over carsinomu ve benign hastalıklar şeklinde gruplandırıldı. Serum ve asit mayi CA-125 düzeyleri ölçüldü. CA-125 electrochemiluminescence immunoassay ''ECLIA'' metodu kullanılarak çalışıldı. CA-125 düzeyinin grupları birbirinden ayırt edebilme becerisini belirlemede "receiver operating characteristic (ROC)" analizi kullanıldı. **Bulgular:** Çalışmaya 64 bayan 55 erkek toplam 119 hasta dahil edildi. Elli üçü over-dışı malign, 19'u over adenokarsinomu ve 47'si benign hastalardı. Serum ve asit mayi CA-125 düzeyleri her üç grupta da yüksekti. Duyarlılık ve özgüllük over-dışı malign ve benign ayırımında asit CA-125 cut-off değeri 174.5 U/mL iken sırasıyla %69.2 ve %25.5; değer 796.5 U/mL iken sırasıyla %30.8 ve %80.9 idi. Over adenokarsinomu ve benign ayırımında cut-off değer 411 U/mL iken duyarlılık ve özgüllük sırasıyla %94.7 ve %63.8; değer %71.9 U/mL iken sırasıyla %57.9 ve %78.7 idi. **Sonuç:** Malign ve benign asit ayırımında serumdan ziyade asit mayi CA-125 düzeylerinin anlamlı olduğu ve 1000 U/mL'in üstündeki değerlerde malignitenin ısrarla aranması önerilebilir.

Anahtar Kelimeler: CA-125 antijeni; asit

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Carbohydrate antigen-125 (CA-125) is a high molecular weight glycoprotein detected by the OC125 monoclonal antibody, which was first described by Bast et al. in 1981.[1] CA-125 is widely used for the diagnosis, monitoring and recurrence in patients with ovarian cancers.[2] While it only increases in approximately 50% of stage 1 patients with epithelial ovarian cancers, it increases in 75–90% of those with advanced disease.[3] CA-125 is not entirely specific for ovarian carcinoma.[4] Furthermore, it has also been reported to increase in benign and physiologic conditions such as menstruation, pregnancy, chronic renal failure, autoimmune disease, pancreatitis, liver cirrhosis and inflammation of peritoneum, pleura and pericardium.[5-15]

Ascites is produced approximately 80% by chronic parenchymal liver disease, and approximately 10% by malignancy.[16] The most benign reason of high level of CA-125 is liver cirrhosis complicated with ascites.[14] Peritoneal mesothelial cells are accepted as the source of CA-125 in conditions associated with ascites.[17] CA-125 has been found to be high in nearly all of the patients with ascites.[10,18] Therefore, CA-125 increases in both malignant and benign diseases causing ascites. So, it is suggested that it has limited diagnostic value as a marker of cancer. In addition, it is still controversial whether it is an appropriate tumor marker.[12,19]

We aimed to investigate the role of CA 125 levels in serum and ascites in differential diagnosis of ovarian and non-ovarian malignancies and benign conditions.

MATERIAL AND METHODS

PATIENTS AND STUDY DESIGN

A total of 119 adult consecutive patients with ascites were enrolled for this study. The cases were collected from Gastroenterology, Medical Oncology and Gynecology departments of Dicle University Hospital between March 2006 and June 2008. The study was carried out in accordance with the principles stated in the Declaration of Helsinki, and signed informed consents were obtained from all patients prior to inclusion in the study. As this study was performed as part of routine clinical practice, ethics committee approval was not required. All data and contact information for these patients have been filed and the patients can be contacted at any time. Routine hematological, biochemical and radiological investigations were performed. Besides, blood and ascites samples were obtained from the patients and processed for CA 125 by using electrochemiluminescence immunoassay ''ECLIA'' method (Roche Modular Analytics E170, Cobas, Roche Diagnostics GmbH Mannheim, Germany).

The inclusion criteria for this study was the presence of clinically detectable ascites, age greater than 15 years and not receiving any treatment for ascites. The patients with malignancy who received any treatment for the disease were excluded in order to avoid a possible negative contribution.

A total of 119 patients were divided into three groups based on the diagnosis.

Group 1 consisted of 53 patients with non-ovarian malignancies. Diagnoses of malignancy were made by positive histopathological evaluation in the specimens obtained by laparoscopy, endoscopy or laparotomy and a positive ascitic fluid cytological examination. Diagnostic distribution of group 1 was as follows: 16 were gastric carcinoma, 10 were colon carcinoma, nine were malign mesothelioma, nine were hepatocellular carcinoma, five were pancreas adenocarcinomas and four were non-Hodgkin's lymphoma.

Group 2 consisted of 19 patients with histologically confirmed ovarian cancer and ascites. All patients with ovarian carcinoma had advanced stage according to FIGO classification.

Group 3 consisted of 47 patients with benign conditions causing ascites. Distribution of Group 3 was as follow: 37 were liver cirrhosis (11 with spontaneous bacterial peritonitis), eight were tuberculous peritonitis, one was pancreatic ascites, and one was granulomatous peritonitis. In the Group 3, malignancy was excluded by history, examination and relevant investigations. Ultrasound examination and/or CT scan revealed liver involvement by malignancy.

STATISTICAL ANALYSIS

The mean values of the variables were calculated. Data were analyzed for the differences among the groups by using one-way ANOVA or student's t test. Receiver operating characteristic analysis (ROC) and area under curves (AUCs) were used to determine the discriminative ability of ascitic fluid and serum CA-125. Perfect discrimination has a ROC plot passing through the upper left corner (100% sensitivity, 100% specificity). The closer the ROC plot to the upper left corner, the higher the overall accuracy of the test (AUC: 0.9-1 indicating excellent; 0.8-0.9 very good; 0.7-0.8 good; 0.6-0.7 average; 0.5-0.6 poor). $P < 0.05$ was considered as statistically significant. The sensitivity and specificity of ascitic fluid and serum CA-125, and cut-off points were calculated. Correlations were calculated using Pearson's correlation coefficient method. Statistical analyses were carried out using the statistical packages for SPSS 15.0 for Windows (SPSS, Inc., Chicago, IL, USA).

RESULTS

Of 119 patients presented with ascites, there were 64 females and 55 males. Patients' characteristics are shown in Table 1. The distribution of cases on the basis of groups and mean values of serum and ascitic fluid CA-125 are shown in Table 2.

A significant positive correlation was found in the correlation analysis between the serum and ascitic fluid CA-125 levels (correlation coefficient 0.518, $p<0.001$).

The mean value of the serum levels of CA 125 (sCA 125) were in a rank order from the highest to the lowest in non-ovarian malignancy, ovarian carcinoma and benign group, respectively. Nevertheless, there was no significant difference among the groups ($p= 0.135$).

TABLE 1: Patients characteristics

Group	Number	Age(years)	Female(%)
Non-ovarian malignancies	53	58,42±18,6	52,8
Gastric carcinoma	16	58,06±16,5	62,5
Colon carcinoma	10	61,60±11,8	60
Malign mesothelioma	9	62,89±8,96	66,7
Hepatocelluler carcinoma	9	54,89±16,2	66,7
Pancreas adenocarcinoma	5	66,2±16,1	20
Non-Hodgkin's lymphoma	4	46±20,7	0
Ovarian carcinoma	19	52,32±18,1	100
Benign condition	47	54,21±18,6	40,4
Liver cirrhosis	37	59,3±16,3	35,1
Tuberculous peritonitis	8	34,75±12,9	50
Pancreatic ascites	1	55	100
Granulomatous peritonitis	1	21	100

Ascitic fluid levels of CA-125 (aCA-125) were highest in ovarian carcinoma. There were significant differences between ovarian carcinoma and the other groups ($p= 0.003$, <0.001 non-ovarian malignant and benign groups respectively). Moreover, ascitic CA-125 (aCA-125) levels of Group 1 were significantly higher than those of Group 3 ($p= 0.048$) Table 2 gives the comparisons of aCA-125 and serum CA-125 (sCA-125) levels between the groups.

Figure 1-A shows the ROC curve for discriminative ability of aCA-125 and sCA-125 in patients with non-ovarian cancers and benign disorders.

TABLE 2: The descriptive statistics and the outcomes of comparation of serum and ascitic fluid CA-125 among the groups

		sCA-125			aCA-125				
Groups	n	Mean	(±)SD		Mean	(±)SD		Tukey HSD (p)	
Group 1	53	765.53	1037.34		1148.41	1130.01		0.003	Group 2
								0.048	Group 3
Group 2	19	694.24	607.26	F: 2.038 P=0.135	2069.23	1671.69	F:12.73	0.003	Group 1
								<0.001	Group 3
Group 3	47	457.20	396.39		651.70	423.08		0.048	Group 1
								<0.001	Group 2

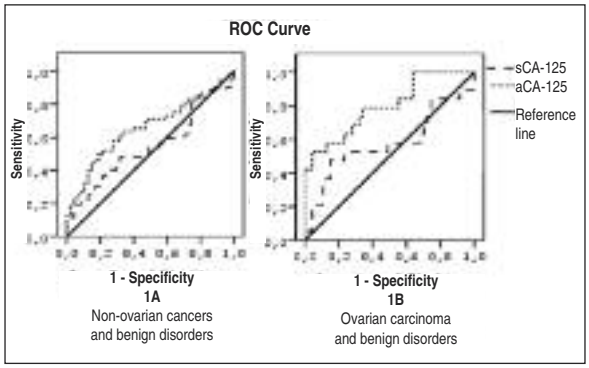

FİGURE 1: Figure 1-A: The ROC curve for discriminative ability of aCA-125 and sCA-125 in patients with non-ovarian cancers and benign disorders (The AUC values were 0.653 and 0.545 respectively) (p values were 0.09, 0.443 respectively). **Figure 1-B:** The ROC curve for discriminative ability of aCA-125 and sCA-125 in patients with ovarian carcinoma and benign disorders (The AUC values were 0.797 and 0.579 respectively) (p values were <0.001, 0.318 respectively).

According to the results of ROC curve and AUC value, discriminative ability of serum CA-125 was not statistically significant (p= 0.596) but ascitic fluid CA-125 was significant (p= 0.09). When cut-off value of aCA-125 was accepted as 174.5 U/ml, the sensitivity and specificity were 69.2% and 25.5%, respectively. When cut-off value of aCA-125 was taken as 353 U/ml, the sensitivity and specificity were 50% and 51.1%, respectively. However, when cut-off value of aCA-125 was accepted as 796.5 U/ml, the sensitivity and specificity were determined as 30.8% and 80.9%, respectively.

Figure 1-B shows the ROC curve for discriminative ability of aCA-125 and sCA-125 in patients with ovarian carcinoma and benign patients. According to the results of ROC curve and AUC value, discriminative ability of sCA-125 was not statistically significant (p=0.318), however, aCA125 was significant (p<0.001). When cut-off value of aCA-125 was accepted as 411.75 U/ml, the sensitivity and specificity were found as 94.7% and 63.8%, respectively. When cut-off value of aCA-125 was accepted as 971.9 U/ml, the sensitivity and specificity were found as 57.9% and 78.7%, respectively.

The possible relationship between serum and ascitic fluid CA-125 levels and level of liver cirrhosis was analyzed according to Child-Pugh stage. There were no statistically significant relationship between the level of CA-125 and the stage of liver cirrhosis (p= 0.781, 0.867, 0.934 for Child-Pugh stage A,B,C respectively).

In benign group, there were 37 patients with liver cirrhosis, and 11 patients with spontaneous bacterial peritonitis. There were no differences between serum and ascetic fluid CA-125 levels (p= 0.853, 0.321 respectively) according to the presence or absence of spontaneous bacterial peritonitis.

DISCUSSION

An ideal marker that can be used to diagnose cancer must be secreted into the patients' sera only in case of the presence of a specific cancer, and have acceptable sensitivity to detect early stage of cancer; it also must be highly specific to avoid confusion with benign diseases.

CA-125, which is the most useful marker, has been most extensively studied for ovarian carcinoma, especially in monitoring patients with this disease. Like many other tumor markers, CA-125 is not a tumor specific antigen, so it has limited specificity when used alone. CA-125 level may also increase in the presence of other cancers such as peritonel carcinamatosis, pancreatic, breast, bladder, liver, lung cancers[4,5] as well as benign diseases such as liver cirrhosis, diverticulitis, leiomyoma, endometriosis, benign ovarian cyst, tubo-ovarian abscess, renal disease[8-11,14,20] and physiologic conditions such as pregnancy and menstruation.[6,7,21]

The origin of CA-125 still remains unclear, and ovarian, peritoneal, pleural, endometrial and amniotic cells have been demonstrated to produce and secrete it.[22] By using tissue culture, Kobayashi showed that the eutopic and the heterotopic endometrium could produce CA-125.[23] Similarly, there is also another study reporting that peritoneum has produced CA-125 in vivo.[22]

High level of CA-125 in benign conditions is mostly encountered in liver cirrhosis complicated with ascites. Collazos et al. suggested that serum CA-125 had excellent sensitivity, specificity, efficiency, predictive values and likelihood ratios to

detect ascites in patients with non-neoplastic liver diseases.[15] There are several data about the increase of CA-125 in liver cirrhosis especially with ascites.[5,11,12,14] Molina *et al.* emphasized that sCA-125 levels increased in infections of the ascitic fluid and decreased after paracentesis, thus suggesting that the ascitic fluid was a reservoir for the antigen, which is synthesized by the peritoneum.[14] In the present study, serum CA-125 levels were below 35 U/ml in only four patients (%3.36), but ascitic fluid levels of CA-125 were higher than 35 U/ml in all of the patients. We found a positive correlation between serum and ascitic fluid levels of CA-125, however ascitic fluid levels were higher than serum levels. Therefore, these findings may support that the antigen is mesothelial rather than tumoral origin.

It was suggested earlier that increase of serum CA-125 levels in liver cirrhosis were closely correlated with ascites rather than a hepatic disorder.[12,24] We could not find any correlation between serum and ascitic fluid CA-125 levels and Child-Pugh score of patients with liver cirrhosis. We also could not detect any correlation between patient with cirrhosis in terms of presence and absence of spontaneous bacterial peritonitis. Peritoneal inflammation with bacterial agent is a significant stimulator of mesothelial cells. Thus, this outcome has confused us. We thought that it could be due to small number of our patients.

CA125 is well established as a tumor marker for epithelial ovarian cancer, and has an important role in diagnosis. In a study in which the role of CA-125 was discussed, it was reported that the sensitivity of CA125 for ovarian cancer in female patients was 88.6%, however the specificity was only 72.0%.[3] The authors suggested that when the CA-125 results over 1000 kU/litre were detected, the specificity of CA-125 increased to 99.1%.[3] Topalak et al. reported that CA-125 level in ovarian carcinoma with ascites was six times higher than those with ovarian carcinoma without ascites.[12] They could not find any correlation between ovarian mass volume and CA-125 levels, thus, they suggested that high serum levels are closely correlated with existence of ascites. Le Thi Huong et al. reported that a CA-125 level higher than 1,000 U/ml was always due to the presence of cancer; lower levels must be interpreted according to the clinical context.[26] In ovarian group, the antigen level increased more than twenty times. In our study, both serum and ascitic fluid CA-125 values in ovarian cancer group were very high. However, particularly ascites fluid CA-125 value was higher than all the other groups with statistical significance.

CA-125 levels may rise in a wide variety of non-malignant diseases, and especially in effusions and infections. Elevated serum CA-125 levels were detected in 100% of patients with nongynecologic peritoneal carcinomatosis.[12] In their study, Kemer et al. determined that serum CA-125 values in cancer group were lower when compared to benign group, however, ascitic fluid CA-125 values were higher than the benign group.[5] In our study, both serum and ascitic fluid levels in non-ovarian malignancy group were higher than benign disorders, and there was a statistical significance in ascitic fluid CA-125 level.

With respect to the mean value of CA-125 levels, our results were high in all groups investigated. In benign group, we found mean serum values 14 and mean ascitic fluid values 19 times higher when compared to CA-125 cut-off levels proposed by manufactured company. In non-ovarian malignancy group and ovarian group, the antigen was increased more than twenty times. According to serum levels of CA-125, there were no significant differences between the two groups. In contrary, ascitic fluid levels of CA-125 in malignant group were significantly higher than benign group. This increase was especially remarkable in ovarian carcinoma. According to the outcomes of the current study, whilst mean values of ascitic fluid CA-125 in non-ovarian and ovarian cancers were found above 1000 U/ml, in benign patients, it was 684 U/ml. In addition, among a total of 119 patients with ascitic fluid CA-125 levels above 1000 U/mL, 51% was diagnosed with non-ovarian malignancies and 25% with ovarian carcinoma.

Inconclusive results from the routine analysis of ascites could lead to a decision to perform a mo-

re invasive diagnostic investigation, such as laparoscopy etc. It would be helpful to have new parameters to speed up the diagnostic process. To our best knowledge, there is no data focused on the cut-off value of ascitic fluid CA-125. In the present study, there were differences, in terms of ascitic fluid CA-125 however the discriminative ability of this marker for non-ovarian malignancy, ovarian cancers and benign group was not efficient. Thus, we could not find an acceptable cut-off value for ascitic fluid CA-125 to distinguish between ovarian, non-ovarian malignant patients and benign disorders. The discriminative ability of ascitic fluid CA-125 was poor, and this finding supports the study of Kemer et al.[5] However, we can speculate that a CA-125 level over 1000 U/ml may indicate the need for an invasive diagnostic application such as laparoscopy.

In conclusion, our findings support the opinion that CA-125 is not a specific tumor marker for ovarian carcinoma, but the levels over 1000 U/ml may be associated with ovarian or non-ovarian malignancies. Therefore, we recommend studying CA-125 in ascitic fluid in a patient presented with ascites due to the fact that CA-125 is produced by mesothelial cells.

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