Original Research

Clinical and Prognostic Value of Elevated CA125 Levels in Patients with Congestive Heart Failure

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Background: Increased serum levels of carbohydrate antigen 125 (CA125), a tumor marker associated with ovarian cancer, have also been reported in other malignant and non-malignant diseases. We assessed the correlation of the CA125 serum levels with the severity of congestive heart failure (CHF) and investigated their potential prognostic value in relation to major cardiovascular events.

Methods: CA125 levels were measured in 95 male patients aged 70 ± 10 years, admitted for decompensated CHF. The patients were divided into three groups, according to their New York Heart Association (NYHA) functional class. Group A contained 23 patients in NYHA IV, group B 34 patients in NYHA III, and group C 38 patients in NYHA I-II. The patients were also divided into two groups according to their CA125 value on admission. Group 1 included 45 patients with normal CA125 levels and group 2 50 patients with elevated CA125. All patients were followed for 15 ± 8.5 months and the major cardiovascular events (death and re-hospitalizations due to CHF) were recorded.

Results: Serum levels of CA125 were higher in groups A and B than in group C (36.4 [19.8-82] U/ml and 34.6 [26-78] U/ml vs. 25.3 [9.1-29] U/ml, respectively, $p<0.05$). No correlation was detected between CA125 levels and left ventricular ejection fraction. However, patients with pulmonary congestion and peripheral edemas had higher levels of CA125 ($p=0.002$ and $p<0.03$, respectively). Nineteen patients died during the follow-up period, but the mortality rate was not significantly different between groups 1 and 2 ($p=0.8$). Nevertheless, the patients of group 1 reported fewer re-hospitalizations than patients of group 2 ($p=0.003$). The relative risk (RR) for re-hospitalization was calculated to be RR: 0.4, 95% CI: 0.215-0.76 ($p<0.005$), in patients with elevated levels of CA125. Cox regression analysis revealed that CA125 had independent prognostic value (OR: 1.007 [95% CI: 1.004-1.010], $p<0.0001$) for re-hospitalizations.

Conclusion: Serum levels of CA125 are associated with the severity of CHF and are also independent predictive markers for re-hospitalizations. We therefore conclude that CA125 can be used as a prognostic marker of disease severity and increased morbidity in patients with decompensated CHF.

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Serum tumor markers, when first introduced into clinical practice, appeared to be promising new tools for the early detection of malignancy. However, results from several studies have reported that these markers, with the exception of prostate-specific antigen, demonstrated low sensitivity and, as a consequence, virtually all tumor markers have failed as screening tests for cancer.[1] The problem of the low specificity of tumor markers is well documented by carbohydrate antigen 125 (CA125), a tumor marker initially related to ovarian cancer and used for the diagnosis of suspected cases (not for screening), for staging and prognostic stratification of overt disease, for monitoring the efficacy of therapy and for detecting recurrences.[2,3] How-

ever, increased serum levels of CA125 have been frequently observed both in patients affected by malignancies other than ovarian cancer and in patients affected by different non malignant diseases, such as acute leukemia,[4] non-Hodgkin lymphoma,[5] melanoma,[6] ascites,[7] pelvic inflammatory diseases[8] and pericarditis.[9] Interestingly, CA125 has recently been shown to increase in patients with chronic congestive heart failure (CHF).[10-13]

The aim of this study was to investigate the clinical and prognostic value of elevated serum CA125 in patients with CHF, in terms of the occurrence of major cardiac events, such as death or re-hospitalization due to decompensated CHF.

Patients and methods

Our population consisted of 95 consecutive male patients, with or without a history of CHF, who were admitted to the cardiology emergency department with symptoms of decompensated CHF or other cardiac symptoms, such as angina, syncope or palpitations. The diagnosis of CHF was based on medical history and initial investigation, which included physical examination, electrocardiogram, chest X-ray, blood and urine laboratory tests and echocardiographic evaluation. Patients were assigned to class I, II, III or IV according to the New York Heart Association (NYHA) classification of heart failure. For estimation of the prognostic significance of elevated CA125, patients were divided in two groups, according to the presence of elevated or normal levels of CA125, independently of their NYHA class. All patients were screened for diseases that could influence levels of CA125, such as malignancies, active infection and liver or renal failure. Symptoms on admission and physical findings, such as rales on chest auscultation and the presence of peripheral edema, were also recorded. Additionally, the presence of pulmonary congestion and pleural fluid on chest X-ray, the renal functional status and medications prescribed during hospitalization were evaluated. All patients underwent a two-dimensional Doppler echocardiographic examination within 4 hours of admission. Echocardiographic examination included measurement of left ventricular end-diastolic (LVEDD) and end-systolic diameters (LVESD), estimation of left ventricular ejection fraction (LVEF) (using the modified Simpson method) and the presence of pericardial fluid. On Doppler examination, E and A velocities, E/A ratio and early filling deceleration time (DTE) were measured on transmitral filling pattern. Right ventricular systolic pressure (RVSP) was estimated from the maximum velocity of tricuspid regurgitation on continuous Doppler using the Bernoulli equation: $RVSP = 4Vmax^2 + RAP$ (RAP: right atrial pressure, approximately 10 mmHg).

The patients' clinical characteristics are shown in Table 1.

Following the patients' discharge major cardiac events (deaths, re-hospitalizations due to decompensation of CHF) were recorded during the follow-up period.

CA125 measurements

Serum levels of CA125 were determined on admission and before hospital discharge. The assessment of CA125 levels was made by an enzyme immunoradiometric assay (Immunotech CA125 Antigen IRMA kit, ref. 2233; Beckman Coulter, USA) with an upper normal limit of 35 U/ml. The intra-assay and inter-assay coefficient of variation were 2.1% and 4.4%, respectively. A two-site "sandwich" assay, with two mouse monoclonal labeled antibodies directed against two different epitopes of the molecule, was performed for each patient in duplicate. The bound radioactivity, measured in a gamma counter, was proportional to the CA125 concentration.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software.[14]

Table 1. Clinical characteristics of the patients

Age (years)	70±10
LVEF (%)	27±11
NYHA functional class, n (%):	
I-II	38 (40%)
III	34 (36%)
IV	23 (24%)
Underlying heart disease, n (%):	
CAD	53 (56%)
DCM	6 (6%)
HTHD	16 (17%)
Unknown	20 (21%)
Medications, n (%):	
Diuretics	73 (77%)
ACE inhibitors	66 (69%)
beta-blockers	35 (37%)
Digitalis	47 (50%)
No medication	20 (21%)

ACE – angiotensin converting enzyme; CAD – coronary artery disease; DCM – dilated cardiomyopathy, HTHD – hypertensive heart disease; LVEF – left ventricular ejection fraction.

The normal distribution of CA125 was checked with the Kolmogorov-Smirnov test. As the measured data were markedly skewed, all values are expressed as median - interquartile range. Analysis of the differences between subgroups was performed using the non-parametric Mann-Whitney test. Correlations between CA125 and clinical, laboratory and echocardiographic parameters were measured using Spearman's rho method. Mortality and morbidity were compared by Cox regression analysis and expressed by Kaplan-Mayer curves. A p-value <0.05 was considered statistically significant.

Table 2. Symptoms and clinical signs in association with CA125 serum levels.

	Patients (n)	CA 125 values Median-interquartile range (U/ml)	p
Lung congestion			
Yes	62	32.2 (18.3-65.6)	0.002
No	33	13.9 (6-23.3)	
Pleural effusion			
Yes	24	61 (18.3-95.2)	0.06
No	71	21 (10.7-32.6)	
Peripheral edema			
Yes	30	32.8 (18.8-96.4)	<0.03
No	65	21.8 (8.4-32.6)	

Results

The patients' mean follow-up time was 15 ± 8.5 months. During follow-up, 19 patients died, while 4 were lost to follow-up and their data were not included in the analysis. Median values of CA125 in each group were: NYHA I-II, 20.9 (10.7-60.7) U/ml; NYHA III, 48.6 (25.6-84.8) U/ml; and NYHA IV, 53.4 (22.5-91) U/ml. Clinical, laboratory and echocardiographic parameters and serum levels of CA125 in all patients, classified according to NYHA functional class, are presented in tables 2 and 3. Patients in NYHA classes III and IV demonstrated higher values of CA125 than patients in NYHA class I-II (p<0.05) (Table 3, Figure 1). Additionally, serum levels of CA125 were higher in patients with pulmonary congestion and peripheral edema (p=0.002 and p<0.03, respectively). A trend towards higher values of CA125 was also found in patients with pleural effusion (p=0.06, Table 2). A weak correlation was found between levels of CA125 and renal function (r=0.3, p=0.04), as well as RVSP (r=0.33, p=0.05). No significant correlation was found between the levels of CA125 on admission and LVEDD, LVEF, DTE, liver function, etiology of CHF, or medications.

No statistically significant difference was found between the two groups of patients with elevated or normal levels of CA125, as far as cardiac deaths were concerned (p=0.8). In contrast, patients with normal serum levels of CA125 demonstrated fewer re-hospitalizations compared to patients with elevated levels of CA125 (p=0.003). The relative risk (RR) for re-hospitalization due to decompensated CHF during the follow-up period in patients with elevated levels of CA125, was calculated to be RR: 0.4, 95% CI: 0.215-

Table 3. Laboratory and echocardiographic parameters and CA125 serum levels in patients with CHF.

	NYHA I-II (n=38)	NYHA III (n=34)	NYHA IV (n=23)
Creatinine (mg/dl)	1.0 (0.89-1.1)	1.1 (0.9-1.5)	1.1 (0.9-1.7)
SGPT (IU/l)	16 (15-39)	17 (12-27)	15 (12-22)
SGOT (IU/l)	19 (16-40)	18 (15-20)	22 (15-27)
CA125 (U/ml)	20.9 (10.7-60.7)	48.6 (25.6-84.8)*	54.3 (22.5-91)†
LVEF (%)	45 (25-55)	25 (18-30)*	19 (15-25)‡
DTE (ms)	170 (145-180)	150 (125-160)*	128 (122-132)‡
LVEDD (mm)	64 (46-69)	71 (62-76)	70 (61-77)
RVSP (mmHg)	48 (34-54)	54 (47-57)*	56 (50-64)†

Analysis of differences by using the Mann-Whitney U-test. Data presented as median-interquantile range.

*p<0.05 between NYHA I-II and III; †p < 0.05 between NYHA I-II and IV; ‡p<0.005 between NYHA I-II and IV.

DTE – early filling deceleration time; LVEDD – left ventricular end-diastolic diameter; LVEF – left ventricular ejection fraction; RVSP – right ventricular systolic pressure.

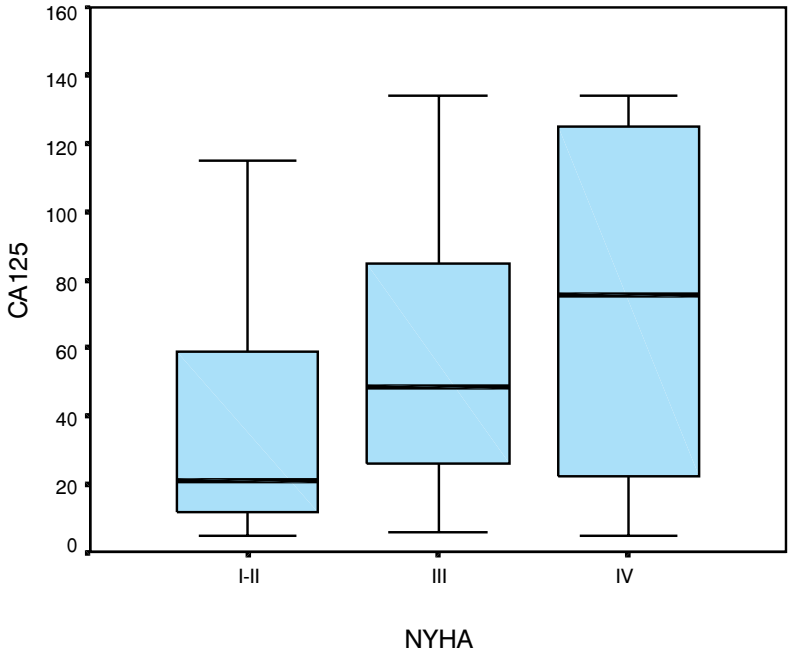

Figure 1. Boxplot showing the difference in CA125 levels (U/ml), according to New Heart Association NYHA functional class. The p-value was <0.05 for the comparison between NYHA IV and NYHA I-II and also for the comparison between NYHA III and NYHA I-II. p=NS between NYHA IV and NYHA III.

0.76, p<0.005 (Figure 2). Univariate Cox regression analysis revealed that CA125 had independent prognostic value (OR: 1.007, 95% CI: 1.004-1.010, p<0.0001) for re-hospitalizations. Also, in multivariate Cox regression analysis (backward stepwise) only CA125 and NYHA class were found to be independent prognostic markers of morbidity (CA125 OR: 1.006, 95% CI: 1.002-1.009, p=0.001; NYHA class OR: 2.302, 95% CI: 1.125-4.712, p<0.03).

Discussion

The underlying mechanism for the production and secretion of CA125 antigen remains unclear, as far as its production from cancer cells is concerned.[15-17] However, most reports agree that CA125 is also produced by normal mesothelial cells of the peritoneum, pleura and pericardium, when they are stimulated by cytokines that are secreted from cancer cells.[15,18] Interestingly, CA125 levels are more frequently abnormal in cancer patients with serosal involvement and/or effusion, as well as in patients with pleural and/or pericardial effusions not related to malignancy. As far as the relationship between CA125 and cardiac dysfunction is concerned, interleukin-6, which has been found to be elevated in CHF,[18] might play an important role, since there are data suggesting that proliferation of CA125-producing cells is stimulated by this cytokine.[19] To our knowledge, at this time there is no evidence of myocardial production of CA125, although it cannot be ruled out.

According to the results of our study, serum CA125 levels correlate significantly with the clinical status of patients with CHF, as demonstrated by the higher values of CA125 in NYHA class III and IV patients, compared to those in NYHA class I and II. Moreover, serum CA125 correlates with the presence of fluid congestion, based on rales on auscultation, peripheral edema and signs of congestion on chest X-ray. This finding is verified by the fact that in patients with dyspnea of cardiac origin as the predominant symptom on admission, levels of serum CA125 were higher compared to those who were admitted due to angina, acute coronary syndrome, syncope or ventricular arrhythmias, regardless of the severity of CHF. Interestingly, there were two patients with a history of severe CHF (NYHA IV) who were hospitalized twice: the reasons for their first hospitalization were sustained ventricular tachycardia and paroxysmal atrial fibrillation, while the second admissions were due to decompensated CHF. CA125 serum levels were within normal range in both patients when they were admitted for arrhythmias, but levels were elevated when fluid congestion was the reason for admission. Only 4 patients had evidence of mild to moderate pericardial effusion on echocardiography. In these patients levels of CA125 were high, a finding consistent with the report of Seo et al,[9] who also reported that levels of CA125 were related to the amount of pericardial effusion.

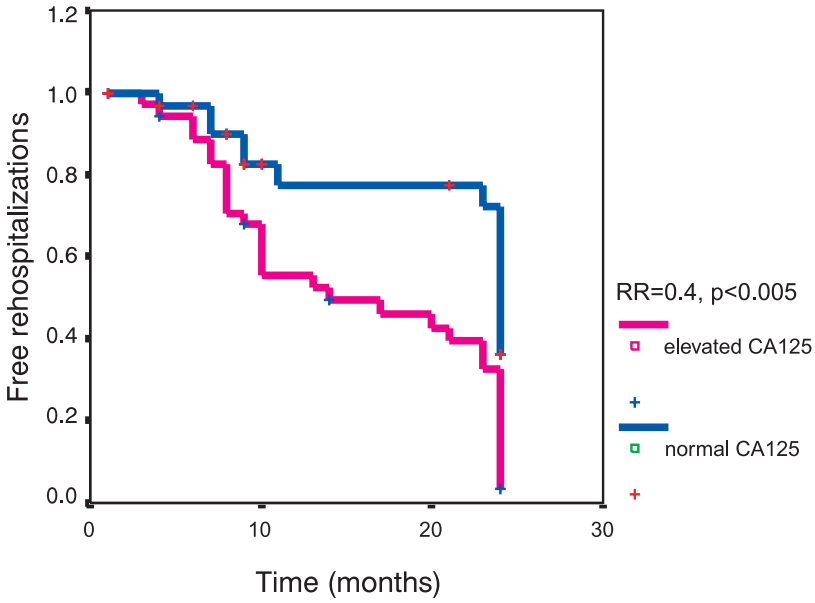

Figure 2. Kaplan–Mayer curves showing re-hospitalizations due to congestive heart failure decompensation in patients with normal and elevated CA125 serum levels.

Our findings are in agreement with other recent published studies,[10-13] which indicate fluid congestion as the main cause for CA125 elevation, although primarily it was suggested that acute congestion was probably not the cause of CA125 secretion.[20] Moreover, the aforementioned studies reported a significant decrease in CA125 values after proper therapeutic intervention and compensation of CHF.[10,20] However, up to now the prognostic value of elevated CA125 levels has not been reported by any study.

According to our results, mortality rate was somewhat similar in patients with normal and elevated levels of CA125, while in contrast patients with elevated serum levels of CA125 demonstrated higher morbidity, as expressed by a statistically significantly greater number of re-hospitalizations due to CHF decompensation. This discordance may be explained by the fact that patients with elevated CA125 levels belong to advanced NYHA functional class, as our study also determined. Moreover, CA125 values after therapeutic intervention and prior to hospital discharge were lower than values on admission, but the difference was not statistically significant ($p=0.09$), as was found in other studies.[10,20] This discrepancy might be due to the fact that the mean time for repeating measurement of CA125 in our study was only 5.8 days, which might be a too brief period of time for normalization of elevated CA125.

Finally, it has been reported that serum levels of CA125 are elevated in proportion to natriuretic peptides and norepinephrine in patients with CHF.[20] This observation was not studied in our report, but the fact is that determination of CA125 is both easier and cheaper and, in combination with its proven prognostic value, it can be regarded as a valuable diagnostic "blood test" for patients admitted with symptoms of congestion.

In conclusion, serum levels of CA125 appear to be useful as a complementary laboratory tool for the functional staging of patients with CHF and they additionally reveal a significant prognostic value, as far as the morbidity of these patients is concerned.

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