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CA-125, A BIOMARKER IN ACUTE-DECOMPENSATED HEART FAILURE. PRELIMINARY STUDY.

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Abstract

Background. *CA-125 is a tumor antigen expressed on the surface of ovarian cells, used to monitor the treatment of ovarian cancer (normal upper limit is 35U/mL), but it seems also to have a role as biomarker in heart failure (HF).*

Aim. *To determine CA-125 changes in acute-decompensated HF (ADHF) patients.*

Method. *The study group included 110 patients (mean age 72±10 years, 63% men) with ADHF caused by ischemic cardiomyopathy. The subjects were clinically, ecocardiographically and biologically (NT-proBNP, PCR, serum uric acid (sUA), CA-125) evaluated.*

Results. *CA-125 at admission was 53±33 U/mL and decreased at discharge to 34±17 U/mL, without any difference between males and females. The mean level of CA-125 was significantly higher in patients with pleural effusion.*

There was a significant difference between NT-proBNP at admission in obese versus normoponderal patients, which was maintained at discharge. In the same time, the CA-125 did not show significant differences between obese and normoponderal subjects at admission and discharge.The mean level of CA-125 was significantly higher for subjects with reduced ejection fraction and with elevated left ventricular filling pressures versus subjects with preserved ejection fraction and normal left ventricular filling pressures.

The CA-125 correlated with LVEF (R=-0.221, p=0.02), with NT-proBNP (R=0.371, p<0.001), with the inflammation marker - PCR (R=0.284, p=0.003) and oxidative stress marker - sUA (R=0.234, p=0.015).

Conclusions. *The wide availability of CA-125, its relatively low cost, its correlation with known prognostic markers in HF and the additional information provided make it a valuable biomarker that can be used in monitoring ADHF patients.*

Keywords: *CA-125, acute-decompensated heart failure, NT-proBNP, obesity.*

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Rezumat

Introducere. *CA-125 este un antigen tumoral exprimat pe suprafaţa celulelor ovariene, utilizat pentru monitorizarea tratamentului cancerului ovarian (limita superioară a normalului este 35 U/mL), dar care pare a avea potenţial rol de biomarker în insuficiența cardiacă (IC).*

Obiectivul *studiului îl reprezintă evaluarea modificărilor CA-125 la pacienții cu IC acut-decompensată (ADHF).*

Material și metodă. *110 bolnavi (vârstă medie 72±10 ani, 63% bărbați) cu ADHF de etiologie ischemică au fost evaluați clinic, ecocardiografic și biologic (NT-proBNP, CRP, acid uric seric (AUs), CA-125).*

Rezultate. *Media CA-125 la internare a fost 53±33U/mL și a scăzut la externare la 34±17 U/mL, fără diferențe semnificative între bărbați și femei. Nivelul CA-125 a fost semnificativ mai mare la pacienții cu revărsat pleural.*

A existat o diferenţă semnificativă statistic între nivelul NT-proBNP la internare la pacienţii obezi faţă de cei normoponderali care s-a menţinut şi la externare. CA-125 nu a prezentat diferențe semnificative statistic între subiecții obezi și cei normoponderali atât la internare, cât și la externare.

Nivelul CA-125 a fost semnificativ mai mare la pacienții cu FEVS redusă și la cei cu presiuni de umplere crescute la nivelul ventriculului stâng. CA-125 s-a corelat cu FEVS (R=-0.221, p=0.02), cu NT-proBNP (R=0.371, p<0.001), cu markerii de inflamaţie - CRP (R=0.284, p=0.003) şi de stress oxidativ - AUs (R=0.234, p=0.015).

Concluzii. *Larga disponibilitate a acestui nou biomarker, costul relativ redus, corelația cu factori de prognostic cunoscuți, furnizarea de informații suplimentare în afara biomarkerilor clasici fac din CA-125 un biomarker cu potenţial în monitorizarea pacienţilor cu ADHF.*

Cuvinte-cheie: *CA-125, insuficiență cardiacă acut-decompensată, NT-proBNP, obezitate.*

Background

Acute decompensated heart failure has an increasing incidence and poor prognosis, being a major cause of death and hospital readmission and requiring urgent optimized therapy[1]. Even though significant progress has been made in chronic HF management, mortality and morbidity rates remain unacceptably high during or immediately after hospitalization for ADHF. It is necessary to find other biomarkers that can provide better prognostic information and new directions in guiding the treatment to decrease morbi-mortality during and after an ADHF episode.

CA-125 is a tumor antigen expressed on the surface of ovarian cells that facilitates the adhesion of metastatic cells, being used to monitor the treatment of ovarian cancer[2]. It seems that it is also expressed on other types of tissue as well: pericardium, pleura, peritoneum or Mullerian epithelium and it is secreted after various stimuli, such as mechanical stress, oxidative stress or inflammatory stimuli[3].

Systemic inflammatory activity and congestion are closely related in HF; therefore, CA-125 may be a surrogate for both pathophysiological processes[4].

The aim of the study was to assess the CA-125 changes in ADHF patients.

Method

The study group included 110 patients with ADHF caused by ischemic cardiomyopathy, treated according to ESC guidelines. The decompensation of HF was proved clinically (NYHA functional class III and IV and at least 2 signs of congestion) and biologically (increasing of NT-proBNP level) and it required hospitalization.

ECG, laboratory tests (NT-proBNP, PCR, sUA, CA-125) and echocardiography were performed in all patients, after a comprehensive clinical examination.

Exclusion criteria were: stroke in the last 3 months, cor pulmonale, significant valvular disease and severe pulmonary, renal or liver disease. The female patients were evaluated with a gynecological exam and an ultrasound to exclude ovarian malignancy.

The results were presented as mean ± standard deviation for numeric variables and as absolute numbers and percentages for categorical variables. For the analysis of numeric variables, parametric (Student's t-test, ANOVA) or non-parametric (Mann-Whitney, Kruskal-Wallis) tests were used. Linear regression and Pearson correlation coefficient r were used for correlations between numerical variables. The statistical significance was considered for a p-value <0.05. The statistical analysis was performed by using 20.0.SPSS.

Results

The baseline characteristics of the study group are presented in table 1. The mean age of the patients was 72±10 years, with male sex predominance - 63% of the patients.

There were 35 (33%) subjects with obesity and the mean BMI was 27.6±5.8 kg/m². The mean LVEF was 37% and the mean NT-proBNP was 4049±2095 pg/mL.

CA-125 at admission was 53±33 U/mL, much higher than the known upper limit of 35 U/mL. There were no differences between CA-125 levels in males and females: 51±32 U/mL versus 55±34 U/mL (p=0.69).

There was a significant difference between NT-proBNP at admission in obese versus normoponderal patients (3207±1432 pg/mL versus 4457±2737 pg/mL (p=0.02)), which

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Demographics and CV risk factors	
Male (n)	67 (63%)
Age (years)	72±10
Obesity (n)	35 (33%)
BMI (kg/m²)	27.6±5.8
Dyslipidemia (n)	59 (55%)
Diabetes (n)	37 (35%)
Hypertension (n)	85 (79%)
Atrial fibrillation (n)	78 (73%)
Echocardiography	
LVEF (%)	**37±11**
LV filling pressures (n)	59 (55%)
Laboratory tests	
Hemoglobin- g/dL	12.7±2.1
BUN - mg/dL	56±27
Creatinine - mg/dL	1.18±0.48
Cl. crea. - ml/min/1.73 m²	63±21
sUA - mg/dL	**7.03±2.39**
Natrium - mmoli/L	136±5
Potassium - mmoli/L	4.41±0.56
Cholesterol - mg/dL	161±51
PCR - mg/L	**6.4±4.4**
NT-proBNP - pg/mL	**4049±2095**
CA-125 - U/mL	**53±33**

Table 1. *Baseline characteristics of the study group*

was maintained at discharge (1711±816 pg/mL versus 2674±1475 pg/mL (p=0.03)).

In the same time, the CA-125 did not show significant differences between obese and normoponderal subjects at admission (56±29 U/mL versus 51±20 U/mL (p=0.63)) and discharge (36±20 U/mL versus 33±16 U/mL (p=0.56)).

The mean level of CA-125 was significantly higher in patients with pleural effusion as in those without radiographic pleural effusion: 63±25 U/mL versus 43±19 U/mL (p=0.02) (figure 1).

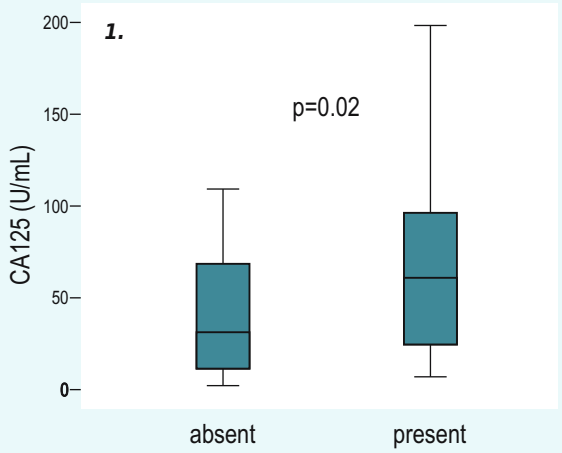
The CA-125 was correlated with LVEF (R=0.371, p<0.001), but it was significantly higher in patients with reduced LVEF compared to those with preserved LVEF: 57±21 U/mL versus 35±20 U/mL (p = 0.013) (figure 2). Moreover, the CA-125 level was significantly higher in patients with elevated LV filling pressures compared to those with normal filling pressures: 61±24 U/mL versus 37±18 U/mL (p=0.005) (figure 3).

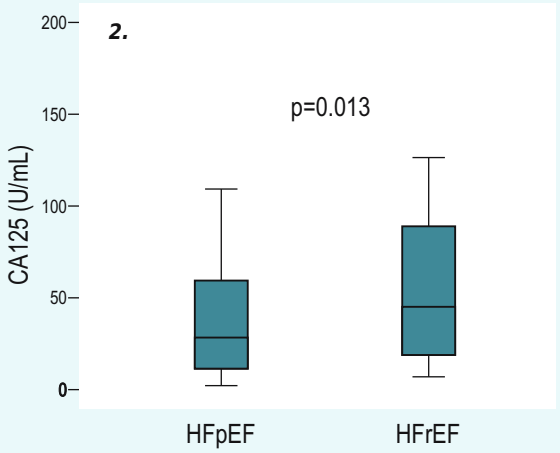
The CA-125 was correlated with NT-proBNP (R=0.371, p<0.001), with the inflammation marker - PCR (R=0.284, p=0.003) and the oxidative stress marker - sUA (R=0.234, p=0.015).

The CA-125 level decreased significantly at discharge: from 53±33 to 34±17 U/mL (p<0.001), and the correlation with the NT-proBNP became stronger: R=0.487, p<0.001 (figure 5).

	Obesity		p
	Yes	No	
NT-proBNP admission - pg/mL	3207±1432	4457±2737	**0.02**
CA125 admission - U/mL	56±29	51±30	0.63
NT-proBNP discharge - pg/mL	1711±816	2674±1475	**0.03**
CA125 discharge - U/mL	36±16	33±14	0.56

Table 2. *The levels of NT-proBNP and CA-125 in obese and normoponderal subjects*





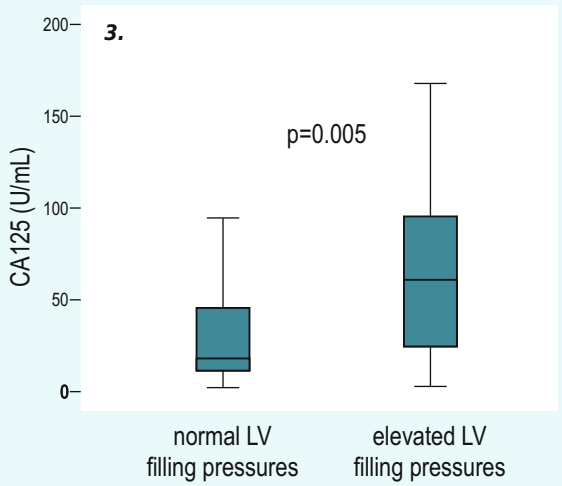
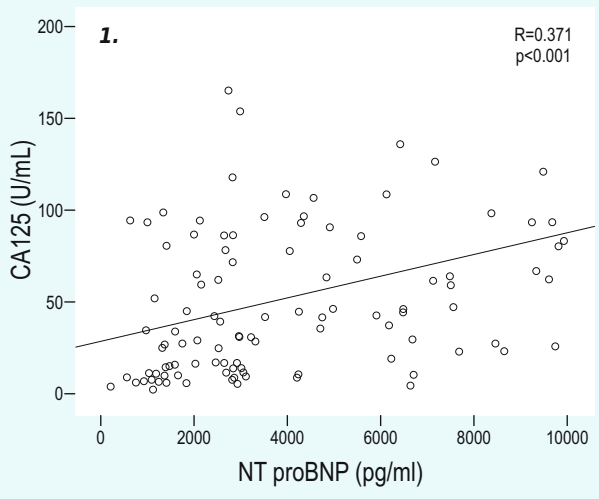
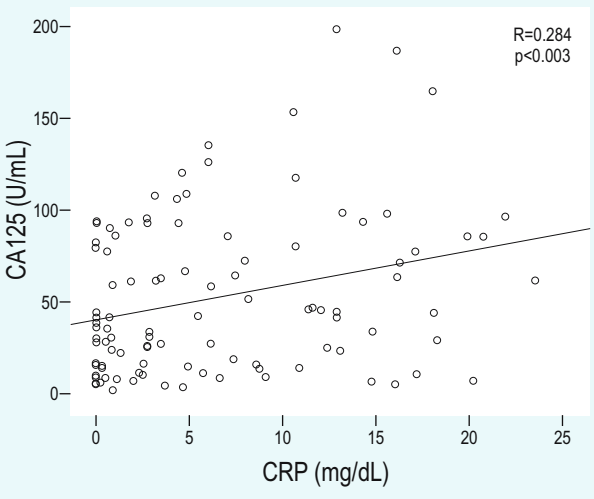


Figure 1. *CA-125 level (U/mL) depending on the presence of the pleural effusion*

Figure 2. *The CA-125 level (U/mL) in HFpEF versus HFrEF*

Figure 3. *The CA-125 level (U/mL) in subjects with normal versus elevated LV filling pressures*





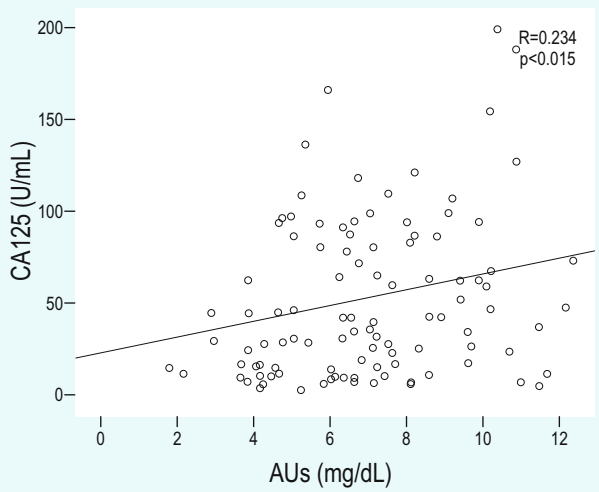


Figure 4. *Corelation between the CA-125 level (U/mL) and the NT-proBNP level (pg/mL), the PCR level (mg/L) and the sUA level (mg/dL) at admission*

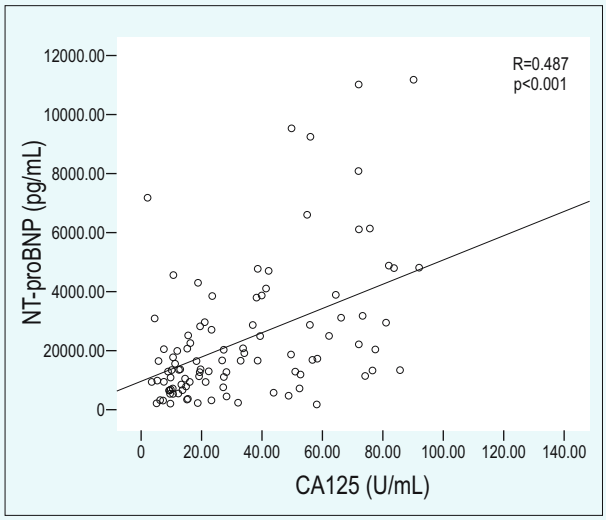


Figure 5. *Corelation between the CA-125 level (U/mL) and the NT-proBNP level (pg/mL) at discharge*

Discussions

CA-125 is a soluble glycoprotein that seems to have a role as biomarker in HF, being secreted by various stimuli such as mechanical stress, oxidative stress or inflammatory stimuli, pathophysiological mechanisms known to be involved in HF[5].

Increased CA-125 levels have been documented in HF in combination with classical biomarkers, beeing a prognostic marker[6].

The CA-125 prognostic role was demonstrated by a group of researchers who found that at the first outpatient visit, after hospitalization for ADHF (average of 28 days after discharge), those patients to whom the CA-125 normalized have showed the lowest risk of death at 6 months. The patients to whom the level of CA-125 decreased but not to normal had an intermediate risk, and those who showed an increase in CA-125 had the highest risk of mortality and morbidity[7].

Zorlu et al.[8] found an increased level of CA-125 in chronic HF that is correlated with the severity of the disease evaluated by the NYHA functional class. The CA-125 level is increased differently depending on the clinical presentation of the patients. In subjects with ADHF and systemic congestion the CA-125 values were significantly higher than those with acute pulmonary edema[9].

These data are consistent with those obtained in our study group: the mean CA-125 at admission was 53±33 U/mL, much higher than the upper limit of normal used in ovarian cancer monitoring: 35 U/mL. There were no significant differences between CA-125 in males and females: 51±32 U/mL versus 55±34 U/mL (p=0.69). In another study on a group of 1111 consecutive ADHF patients, 65% had CA-125 values above 35 U/mL, with an average at 40.4 U/mL[10].

In our study, the patients with radiographically pleural effusion (n=54) showed significantly higher values of CA-125 than those without pleural effusion: 63 ± 25 U/mL versus 43 ± 19 U/mL (p = 0.02). Nunez[11] first identified significantly higher levels of CA-125 in patients with HF and pleural effusion or major edema, showing an association between the radiographic signs of pleurisy and the CA-125 concentration. Nunez mentions that CA-125 estimated better than NT-proBNP the presence of pleural effusion in ADHF. Combining these two biomarkers a better stratification of the risk of fatal and non-fatal cardiovascular events could be obtained[12].

In addition to that, CA-125, could provide complementary information to natriuretic peptides especially in obese patients where the NT-proBNP level is much lower and sometimes difficult to interpret in clinical practice. A significant difference between NT-proBNP at admission and discharge in obese versus normoponderal patients was observed in our study group. In contrast, this difference was not significant for CA-125 at admission, or discharge. Therefore, CA-125, which does not seem to be influenced by

weight, may be useful in ADHF especially in this clinical situation.

The CA-125 level was correlated with LVEF and the NT-proBNP level. Vizzardi et al.13 also have demonstrated that CA-125 correlates with both systolic and diastolic left ventricular function. Moreover, in another study, along with BNP, the CA-125 level was correlated with the LVEF, with the presence of pericarditis and dilatation of the right ventricle. The CA-125 level appears to correlate with the pulmonary or systemic congestion status and with a positive or negative response to treatment. On the other hand, patients with high CA-125 level have showed a significantly lower LVEF and a larger sizes of the left atrium and the right ventricle[14].

The same data were observed in this study. We identified higher levels of NT-proBNP and CA-125 in the subgroup of patients with reduced LVEF – heart failure compared to those with preserved LVEF – heart failure. Also, the NT-proBNP and CA-125 levels were increased in the subgroup of patients with increased filling pressures in the left ventricle versus those without increased filling pressures.

Significant correlations between the CA-125 level and the PCR level or the sUA level were observed. In a small prospective study the NT-proBNP level, the PCR level and the heart rate were significantly higher in the subgroup of patients with higher than normal CA-125 level[15]. Another study that included 132 consecutive ADHF patients found that the levels of CA-125 above 60 U/ml were associated with higher levels of TNF-α, IL6 and interleukin-1β and a lower number of lymphocytes[16].

The systemic inflammatory activity and congestion are closely related in HF; therefore, CA-125 could be a surrogate for both these physiopathological processes. Congestion, as a hemodynamic parameter, is integrated into the vicious circle of the inflammatory process described in HF and thus contributes to the progression of the disease. Theoretically, congestion is also linked to the neurohormonal activation, necrosis, myocardial apoptosis and cardiorenal syndrome resulting from a low infusion gradient[8].

Recent animal studies have confirmed that venous congestion may change the endocrine synthesis profile of the endothelium and perivascular tissue to an activated state by releasing pro-oxidant, pro-inflammatory and vasoconstrictor substances such as TNF-α, endothelin-1, IL-6 or AgII[17]. Thus, CA-125 may be considered a surrogate marker for both congestion and systemic inflammation, this glycoprotein being useful in identifying the onset of cardiac decompensation and in guiding treatment[18].

The CA-125 level decreased significantly at discharge and the correlation with the NT-proBNP level became stronger. The CA-125 half-life is greater than 1 week and this high serum stability may be an advantage for CA-125 as a biomarker in HF. It can bring complementary information to natriuretic peptides with a short half-life and high variability in serum concentrations15. Some authors went even further, comparing the potential role of CA-125 in HF with HbA1c in diabetes[19].

Moreover, the two biomarkers reflect complementary pathophysiological mechanisms involved in HF progression: congestion and inflammation for CA-125 and volume or pressure overload for NT-proBNP. The combination of these two biomarkers could give a better stratification of prognosis in patients discharged after a HF decompensation. Natriuretic peptides give information about the patient's acute hemodynamic status and CA-125 about fluid load and its redistribution over previous weeks[20].

Another study suggests that patients with elevated CA-125 levels would have a greater clinical benefit if they had an aggressive diuretic therapy[21].

Conclusions

The wide availability of CA-125, its relatively low cost (approximately 2 euros for a determination), its correlation with known prognostic markers in HF and the additional information provided make it a valuable biomarker that can be used in monitoring ADHF patients.

CA-125 and the natriuretic peptides should be used together because they bring complementary information. They have different half-life and reflect different pathophysiological mechanisms: congestion and inflammation for CA-125 and volume or pressure overload for NT-proBNP.

CA-125 could be useful especially in monitoring the obese ADHF patients where the NT-proBNP level is much lower and sometimes difficult to interpret in clinical practice.

Bibliography

1. McMurray JJ V, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart. Rev Port Cardiol. 2013;32(7-8):e1--641--e61.doi:10.1093/ eurheartj/ehs104.

2. Ma J, Zhao Y, Wang Y, Guo Y, Li J. Tumor marker levels in patients aged 85 years and older with chronic heart failure. Eur J Intern Med. 2013;24(5):440-443. doi:10.1016/j.ejim.2013.04.002.

3. Miñana G, Palau P, Núñez J, Sanchis J. The Tumor Marker CA125 and Heart Failure. Eur Heart J. 2010;31(14):1752-1763. doi:10.1093/ eurheartj/ehq 142.

4. Turgut O, Tandogan I, Yilmaz MB, Gul I, Zorlu A. CA125 in heart failure: Implications for immuno-inflammatory activity. Int J Cardiol. 2011;146(1):99-100. doi:10.1016/j. ijcard. 2010.05. 077.

5. Huang F, Zhang K, Chen J, et al. Elevation of carbohydrate antigen 125 in chronic heart failure may be caused by mechanical extension of mesothelial cells from serous cavity effusion. Clin Biochem. 2013;46(16-17):1694-1700. doi:10.1016/j. clinbiochem. 2013.09. 008.

6. Monteiro S, Franco F, Costa S, et al. Prognostic value of CA125 in advanced heart failure patients. Int J Cardiol. 2010;140(1):115-118. doi:10.1016/j. ijcard.2008.11. 023.

7. Turgut O, Tandogan I, Yilmaz MB, Gul I, Gurlek A. CA125 levels among patients with advanced heart failure: An emerging independent predictor for survival. Int J Cardiol. 2010;145(1):71. doi:10. 1016/j.ijcard. 2009.04.030.

8. Zorlu A, Tandogan I, Yilmaz MB. CA-125, an omitted part of the heart. Hear Lung Circ. 2011;20(5):345. doi:10.1016/j.hlc.2011.01.025.

9. D'Aloia A, Faggiano P, Aurigemma G, et al. Serum levels of carbohydrate antigen 125 in patients with chronic heart failure: Relation to clinical severity, hemodynamic and doppler echocardiographic

abnormalities, and short-term prognosis. J Am Coll Cardiol. 2003;41(10):1805-1811. doi:10.1016/S0735-1097(03)00311-5.

10. Núñez J, Miñana G, González M, et al. Antigen carbohydrate 125 in heart failure: Not just a surrogate for serosal effusions? Int J Cardiol. 2011;146(3):473-474. doi:10.1016/j. ijcard. 2010.12.027.

11. Nunez J, Llacer P, Nunez E, et al. Antigen carbohydrate 125 and creatinine on admission for prediction of renal function response following loop diuretic administration in acute heart failure. Int J Cardiol. 2014;174(3):516-523. doi:10.1016/j. ijcard. 2014.04.113.

12. Núñez J, Núñez E, Sanchis J, et al. Antigen carbohydrate 125 and brain natriuretic peptide serial measurements for risk stratification following an episode of acute heart failure. Int J Cardiol. 2012;159(1):21-28. doi:10.1016/j.ijcard.2011.02.001.

13. Vizzardi E, D'Aloia A, Pezzali N, Bugatti S, Curnis A, Dei Cas L. Long-term prognostic value of CA 125 serum levels in mild to moderate heart failure patients. J Card Fail. 2012;18(1):68-73. doi:10.1016/j. cardfail.2011. 09.012.

14. Miñana G, Palau P, Núñez J, Sanchis J. The Tumor Marker CA125 and Heart Failure. Rev Española Cardiol (English Ed. 2010;63(10):1213-1214. doi: 10.1016/S1885-5857(10)70240-1.

15. Yilmaz MB, Nikolaou M, Solal AC. Tumour biomarkers in heart failure: Is there a role for CA-125? Eur J Heart Fail. 2011;13(6):579-583. doi:10.1093/eurjhf/hfr022.

16. Topatan B, Basaran A. CA-125 and heart failure: Deja vu or "still to be seen." Int J Cardiol. 2010;145(3):626-629. doi:10. 1016/j.ijcard. 2010.09.060.

17. Huang F, Chen J, Liu Y, Zhang K, Wang J, Huang H. New mechanism of elevated CA125 in heart failure: The mechanical stress and inflammatory stimuli initiate CA125 synthesis. Med Hypotheses. 2012;79(3):381-383. doi:10.1016/j.mehy.2012.05.042.

18. Napan S, Aussawapokee T, Nargileci E, Qureshi A, Khadra S, Stroger JH. Prognostic Significance of Carbohydrate Antigen 125 in Patients With Heart Failure and Preserved Ejection Fraction. J Am Coll Cardiol. 2010;55(10):A30.E292. doi:10.1016/S0735-1097(10)60293-8.

19. Nunez J, Minana G, Nunez E, Sanchis J. Antigen carbohydrate 125 in heart failure: A promising clinical tool. Int J Cardiol. 2011;150(3):369-370. doi:10.1016/j.ijcard.2011.05.089.

20. Sánchez-Marteles M, Rubio Gracia J, Giménez López I. Pathophysiology of acute heart failure: a world to know. Rev Clin Esp. 2015;216(1):38-46. doi:10.1016/j.rce.2015.09.010.

21. Nunez J, Merlos P, Facila L, et al. Prognostic effect of carbohydrate antigen 125-guided therapy in patients recently discharged for acute heart failure (CHANCE-HF). Study design. [Spanish]. Rev Esp Cardiol. 2015;68(2):121-128. doi:http://dx.doi.org/ 10.1016/j.recesp.2014. 03.018.