

# Serum CA-125 Level in Patients with Chronic Obstructive Pulmonary Disease with and without Pulmonary Hypertension

Mohammad Hossein Rahimi-Rad<sup>1</sup>, Parvaneh Rahimi<sup>1</sup>, Behzad Rahimi<sup>2</sup>, Mahdia Gholamneghad<sup>1</sup>

1. Department of Internal Medicine, Faculty of Medicine, Urmia University of Medical Sciences, Urmia, Iran

2. Department of Cardiology, Faculty of Medicine, Urmia University of Medical Sciences, Urmia, Iran

Correspondence:

Dr. Parvaneh RAHIMI, Bronchoscopsy Unit, Imam Khomeini Hospital, Urmia, West Azerbaijan, IRAN (postal code: 5715781351) e-mail: rahimi.parvaneh@outlook.com

## Abstract

**Background:** Chronic obstructive pulmonary disease (COPD) is a progressive and debilitating disease and is going to be the 3rd most common cause of death worldwide. Pulmonary hypertension (PH) has severely bad influence on prognosis in COPD patients. Hence, early diagnosis of it is important for appropriate therapy. Echocardiography is used for this purpose, which requires cardiologist and expensive equipment which may not be available anywhere. CA-125, a biomarker of ovarian cancer, has shown to be associated with left ventricular failure. We aimed to show the relationship between CA-125 levels and PH in patients with COPD.

**Methods:** Ninety patients with stable COPD were enrolled into the study. Levels of CA-125 were measured from venous blood, and in the same day systolic pulmonary artery pressure (sPAP) was measured by transthoracic echocardiography.

**Results:** Of 90 Patients 51 had PH and 39 had not. Patients with PH had significantly higher CA-125 levels compared with controls (mean 39.15 U/ml vs. 24.22 U/ml,  $P < 0.04$ ). Levels of CA-125 were correlated with sPAP ( $r=0.17$ ,  $P=0.01$ ).

**Conclusions:** The CA-125 biomarker can be used to identify COPD patients with pulmonary hypertension. Since it is cheap and easily available it can help in centers with less access to echocardiography.

**Keywords:** CA-125, chronic obstructive pulmonary disease, pulmonary hypertension

## Rezumat

**Nivelul seric de CA-125 la pacienții cu bronhopneumopatie obstructivă cronică cu și fără hipertensiune pulmonară**

**Introducere:** Boala pulmonară obstructivă cronică (BPOC) este o boală progresivă și debilitantă și va fi a 3-a cauză de deces la nivel mondial. Hipertensiunea pulmonară (HP) are o influență negativă severă asupra prognosticului la pacienții cu BPOC. Prin urmare, diagnosticul precoce este important pentru un tratament adecvat. Ecocardiografia este folosită în acest scop, dar necesită cardiolog și echipamente costisitoare care nu sunt disponibile oriunde. CA-125, un biomarker de cancer ovarian, a fost asociat cu insuficiența ventriculară stângă. În acest studiu ne-am propus să arătăm relația dintre nivelul CA-125 și HP la pacienții cu BPOC.

**Metodă:** Nouăzeci de pacienți cu BPOC stabil au fost înrolați în studiu. Nivelurile de CA-125 au fost măsurate din sânge venos, și în aceeași zi a fost măsurată presiunea sistolică arterială pulmonară (sPAP) prin ecocardiografie transtoracică.

**Rezultate:** Din 90 de pacienți, 51 au avut HP și 39 nu au avut. Pacienții cu HP au avut nivel de CA-125 semnificativ mai mare comparativ cu lotul martor (media 39.15 U/ml față de 24.22 U/ml,  $p < 0.04$ ). Nivelurile de CA-125 au fost corelate cu sPAP ( $r = 0.17$ ,  $p = 0.01$ ).

**Concluzii:** biomarkerul CA-125 poate fi utilizat pentru identificarea pacienților cu BPOC cu hipertensiune pulmonară. Având în vedere că este ieftin și ușor accesibil poate ajuta în centre cu acces mai redus la ecocardiografie.

**Cuvinte-cheie:** CA-125, bronhopneumopatie obstructivă cronică, hipertensiune pulmonară

## Introduction

Chronic obstructive pulmonary disease (COPD) is a common disease and is estimated to be the 3<sup>rd</sup> or 4<sup>th</sup> most common cause of death worldwide<sup>1,2</sup>. It is a progressive disease and some patients may develop pulmonary artery hypertension and cor pulmonale, which worsens the prognosis. Echocardiographic examination of the heart is used for diagnosis and confirmation of presence of pulmonary hypertension and/or cor pulmonale. However, there are some limitations for echocardiographic examination, such as requirement for cardiologist and relatively expensive equipment that may not be available in anywhere and/ or anytime, and transfer of severely ill patients during acute exacerbation from wards or ICUs to echocardiography unites may have some risks. In addition, maximum tricuspid regurgitation velocity cannot be evaluated in one-third of COPD patients due to the low echogenicity of emphysematous lungs<sup>3</sup>.

Cancer antigen-125 (CA-125) is a tumor marker of ovarian cancer, however it is nonspecific and its level increases in various malignant and nonmalignant disease. In pulmonary disease, increased CA-125 level is reported in tuberculosis<sup>4-6</sup> and non-tuberculosis mycobacterial disease<sup>6</sup>, idiopathic pulmonary fibrosis<sup>7</sup>, bronchiectasis<sup>6</sup>, pneumonia<sup>6</sup> and malignant disease in lung and pleura<sup>8</sup>. Also, there are reports of increase of CA-125 level in patients with congestive heart failure<sup>9,10</sup>. In a study CA-125 level was correlated with pulmonary artery pressure (PASP) in patients with right ventricular dysfunction<sup>11</sup>. The aim of this study was to evaluate association of CA-125 level with severity of COPD and pulmonary hypertension in patients with COPD.

## Methods

Our study consisted of 90 patients with stable COPD who were referred for echocardiography. There were selected patients whose spirometry were compatible with ATS guide-

**Table 1** Comparison of COPD patients with and without systolic pulmonary artery hypertension

		PH n=51 (56,7)	No PH n=39 (43,3)	Total n=90	P value
Sex	Male n (%)	31 (60,8)	26 (66,7)	57 (63,3)	0,56
	Female n (%)	20 (39,2)	13 (33,3)	33 (33,3)	
Age mean $\pm$ SD		63,39 $\pm$ 8,90	65,31 $\pm$ 11,2	65,22 $\pm$ 9,92	0,61
Smoking	Yes n (%)	37 (72,5)	31 (79,5)	68 (75,6)	0,44
	No n (%)	14 (27,5)	8 (20,5)	22 (24,4)	
FEV1 (percent of predicted) mean $\pm$ SD		32,42 $\pm$ -13,05	43,56 $\pm$ 18,23	37,30 $\pm$ 16,41	0,001
SPAP value (mm Hg) mean $\pm$ SD		53,52 $\pm$ 14,18	32,30 $\pm$ 5,60	44,33 $\pm$ 15,43	0,000
CA-125 level (U/ml) mean $\pm$ SD		41,28 $\pm$ 41,46	19,52 $\pm$ 15,92	31,85 $\pm$ 34,51	0,003
Elevated Ca-125	Yes n (%)	24 (47,1)	5 (12,8)	29 (32,2)	0,001
	No n (%)	27 (52,9)	34 (87,2)	61 (67,8)	

PH: Pulmonary hypertension

lines and were measured with only one spirometer (Spirolab II, Mir Italy). Patients were assigned to mild, moderate, and severe COPD according to GOLD classification of COPD<sup>1</sup>.

Each patient underwent a 2-dimensional Doppler transthoracic echocardiographic examination (kontron) with use of a 2.5-MHz transducer. Right ventricular enlargement was classified to mild, moderate, and severe enlargement after measuring right ventricular end-diastolic and end-systolic dimension. Patients with COPD were divided into 2 groups: with or without pulmonary hypertension. Pulmonary hypertension was defined as pulmonary artery systolic pressure greater than 35 mm Hg. After echocardiography, venous blood sample were taken from peripheral vein and frozen. The echo cardiologist was blind to results of CA-125. All CA-125 samples were measure by ELISA method using of commercially available kit (Accu-Bind ELISA Microwells Monobind Inc Lake Forest, CA 92630, USA).

### Statistical analysis

SPSS version 19 (IBM corporation) is used for statistical analysis. Nominal variables were compared with x2 test and the continuous ones with Student's t-test. All results were expressed as the percentage for Nominal variables, continuous variables as mean  $\pm$  standard deviation, and correlations were examined by Pearson's test. P value of less than 0.05 was considered statistically significant.

### Results

Of 90 patients, 51 patients (56.7%) had PH and 39 (43.3%) didn't have PH. The comparison of two groups is presented in Table 1. The two groups did not differ significantly for age, sex, and current smoking, so they cannot act as confounders. Patients with pulmonary hypertension had significantly higher CA-125 levels than those without hypertension (p value=0.003). Of all patients 57 (63%) had right ventricular dilatation which were mild in 29 (32.2%), moderate in 20 (22.2%), and severe in 8 (5.9%). The mean serum level of CA-125 in 57 patients with and 33 patients without RV failure

were 39.15 $\pm$ 6.10 U/ml and 24.22 $\pm$ 3.55 U/ml respectively (p value=0.04). There was a positive correlation of systolic pulmonary artery pressure and CA-125 with Pearson coefficient r=0.17 and p value=0.01 (Figure 1).

### Discussion

In the current study there was correlation between serum CA-125 level and PASP, which is in agreement with Uz et al<sup>11</sup>; they measured CA-125 levels of 52 patients with COPD and found that patients with PASH had significantly higher CA-125 levels than those without PASH. In another study, among 40 patients with COPD, CA-125 level was correlated with right heart dilatation and positively correlated with PASP (r = 0.550, p < 0.001)<sup>12</sup>. Ordu et al<sup>13</sup>, measured proBNP and CA-125 in 102 patients with congestive heart failure and concluded that: "baseline NT-proBNP and CA-125 levels are comparably reliable as heart-failure markers", and suggested that CA-125 can be used for prognosis prediction in heart failure. In a study by Bulut et al<sup>14</sup> among 52 patients with COPD, those with cor pulmonale had significantly higher mean serum levels of CA-125, CEA, and CA 19.9 with p < 0.05. Brain natriuretic peptide (BNP) and CA-125 were significantly higher in patients with congestive heart failure than in those without congestive heart failure. Elevated CA-125 and BNP may be more valuable than separately detection of CA-125 or BNP for diagnosis and evaluation of treatment in congestive heart failure<sup>15</sup>.

However, little is known about the patho- physiologic mechanism of elevation of CA-125 level in non-neoplastic conditions. Neoplastic cells do not secrete CA-125 by themselves<sup>16</sup>; it is produced by peritoneal mesothelial cells which are activated directly or indirectly by mediators such as interleukin-6. In non-malignant conditions, it is hypothesised that serosal irritation due to inflammation, mechanical stress or fluid congestion stimulates mesothelial cells to release CA-125<sup>17</sup>. Huang et al<sup>18</sup>, in a study of 109 patients with congestive heart failure showed that patients with serous cavity effusion demonstrated higher serum CA-125

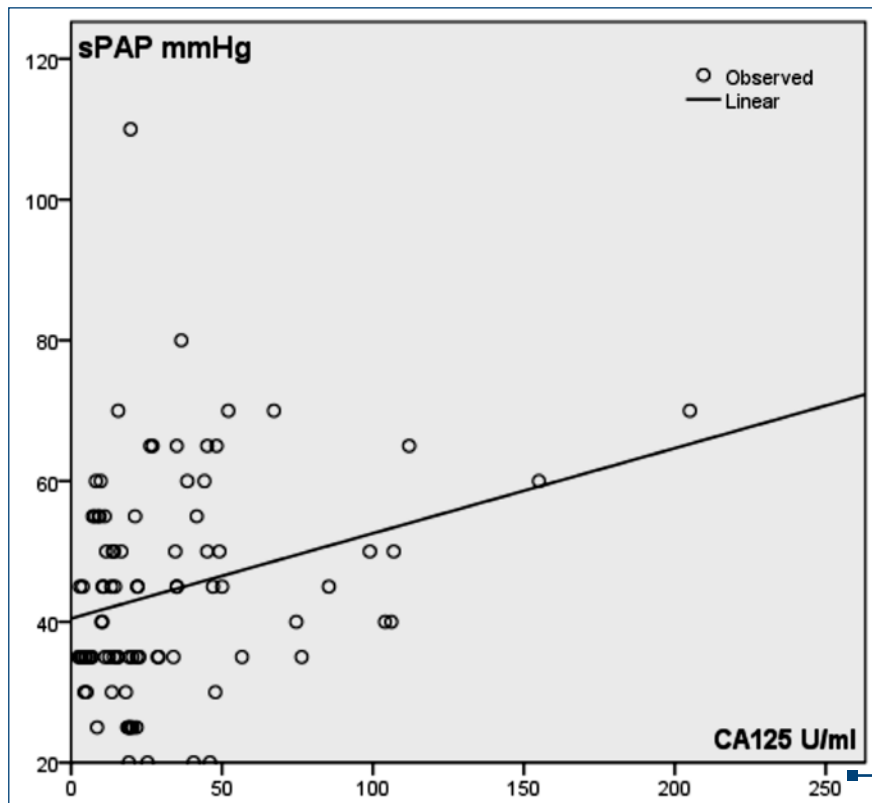
than patients without effusion (82.91 vs. 44.98 U/ml). They conclude that mechanical excitation of mesothelial cells from serous fluid effusion plays an important role in increased CA-125 secretion.

The limitation of this study is that, sPAP estimated by Doppler echocardiography may overestimate or underestimate the values comparing to those obtained by right heart catheterization<sup>3</sup>. However, as in both group of patients (with and with-

out sPAP/PH) sPAP was measured by the same method this limitation cannot have significant effect on results

## Conclusion

In conclusion, serum levels of CA-125 appear to be useful to identify patients with PH. Since it is both cheap and easy, it could be used as a valuable blood test for the screening of PH in patients with COPD. ■



**Figure 1.** Correlation between serum CA-125 level and systolic Pulmonary artery pressure (sPAP)

## References

- Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2014. Available from: <http://www.goldcopd.org/>.
- Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS medicine*. 2006 Nov;3(11):e442.
- Fisher MR, Forfia PR, Chamera E, Houston-Harris T, Champion HC, Girgis RE, et al. Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. *American journal of respiratory and critical care medicine*. 2009 Apr 1;179(7):615-21.
- Kim ES, Park KU, Song J, Lim HJ, Cho YJ, Yoon H, et al. The clinical significance of CA-125 in pulmonary tuberculosis. *Tuberculosis*. 2013 Mar;93(2):222-6.
- Ozsahin SL, Turgut B, Nur N, Dogan OT, Erselcan T, Berk S. Validity of the CA125 level in the differential diagnosis of pulmonary tuberculosis. *Japanese journal of infectious diseases*. 2008 Jan;61(1):68-9.
- Kim SY, Hong Y, Choi CM, Oh YM, Lee SD, Kim WS, et al. Elevated serum CA-125 levels in patients with non-tuberculous mycobacterial lung disease. *Respirology*. 2010 Feb;15(2):357-60.
- Rusanov V, Kramer MR, Raviv Y, Medalion B, Guber A, Shitrit D. The significance of elevated tumor markers among patients with idiopathic pulmonary fibrosis before and after lung transplantation. *Chest*. 2012 Apr;141(4):1047-54.
- Salgia R, Harpole D, Herndon JE, 2nd, Pisick E, Elias A, Skarin AT. Role of serum tumor markers CA 125 and CEA in non-small cell lung cancer. *Anticancer research*. 2001 Mar-Apr;21(2B):1241-6.
- Kouris NT, Kontogianni DD, Papoulia EP, Goranitou GS, Zaharos ID, Grassos HA, et al. Clinical and prognostic value of elevated CA125 levels in patients with congestive heart failure. *Hellenic journal of cardiology: HJC = Hellenike kardiologike epitheoresis*. 2006 Sep-Oct;47(5):269-74.
- Vizzardelli 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. *Journal of cardiac failure*. 2012 Jan;18(1):68-73.
- Uz O, Kardesoglu E, Tas D, Acar G, Isilak Z, Yiginer O, et al. CA-125 level is associated with right ventricular echocardiographic parameters in patients with COPD. *Southern medical journal*. 2011 Sep;104(9):624-8.
- Yilmaz MB, Zorlu A, Tandogan I. Plasma CA-125 level is related to both sides of the heart: a retrospective analysis. *International journal of cardiology*. 2011 May 19;149(1):80-2.
- Ordu S, Ozhan H, Alemdar R, Aydin M, Caglar O, Yuksel H, et al. Carbohydrate antigen-125 and N-terminal pro-brain natriuretic peptide levels: compared in heart-failure prognostication. *Texas Heart Institute journal / from the Texas Heart Institute of St Luke's Episcopal Hospital, Texas Children's Hospital*. 2012;39(1)
- Bulut I, Arbak P, Coskun A, Balbay O, Annakkaya AN, Yavuz O, et al. Comparison of serum CA 19.9, CA 125 and CEA levels with severity of chronic obstructive pulmonary disease. Medical principles and practice. *International journal of the Kuwait University, Health Science Centre*. 2009;18(4):289-93.
- Chen YX, Wang XQ, Fang CF, Wang JF, Tang LJ. Value of BNP and tumour marker CA125 in patients with heart failure. *Acta cardiologica*. 2008 Aug;63(4):501-6.
- Turgut O, Tandogan I, Yilmaz MB, Gul I, Gurlek A. CA125 levels among patients with advanced heart failure: an emerging independent predictor for survival. *International journal of cardiology*. 2010 Nov 5;145(1):71.
- Epiney M, Bertossa C, Weil A, Campana A, Bischof P. CA125 production by the peritoneum: in-vitro and in-vivo studies. *Human reproduction*. 2000 Jun;15(6):1261-5.
- Huang F, Zhang K, Chen J, Cai Q, Liu X, Wang T, et al. Elevation of carbohydrate antigen 125 in chronic heart failure may be caused by mechanical extension of mesothelial cells from serous cavity effusion. *Clinical biochemistry*. 2013 Nov;46(16-17):1694-700.