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Original Article

Serum CA125 level in patients with acute pulmonary thromboembolism

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Abstract: *Background and Aims:* Carbohydrate antigen 125 (CA125) have been found elevated in many diseases other than ovary carcinoma. This study is to investigate the relationship between CA125 level and severity stratification of acute pulmonary thromboembolism. *Methods:* A total of 77 patients suffering from acute pulmonary thromboembolism were enrolled into our study. These patients were divided into 3 groups: Group I (low risk group, n=25), Group II (intermediate-low risk group, n=28) and Group III (intermediate-high risk and high risk groups, n=24) according to the classification standard of 2014 ESC Guidelines. Control group was consisted of 38 age-sex matched healthy persons. CA125 level were measured in all subjects. Data were analyzed with Kruskal-Wallis tests, chi-squared tests or one-way ANOVA. *Results:* The mean level of CA125 in group III (44.6±43.0 U/ml) was significantly higher than that in group II (19.0±11. $P<0.05$), group I (11.0±4.6. $P<0.001$) and control group (11.0±3.8. $P<0.001$). It was also significantly higher in group II than that of group I and control group ($P<0.05$). BNP and PASP were positively correlated with CA125 (respectively, r=0.574, $p<0.001$; r=0.390, $p=0.006$), LVEF were negatively correlated with CA125 (r=-0.102, $P=0.009$). *Conclusions:* CA125 level in patients with acute pulmonary thromboembolism might due to the severity of the disease. The serum level of CA125 was positively correlated with the value of BNP and PASP, but negatively correlated with LVEF.

Keywords: CA125, Acute pulmonary thromboembolism, BNP, Severity stratification, PASP

Introduction

Carbohydrate antigen 125 (CA125) is a high molecular weight glycoprotein derived from the celomic epithelium cells of fallopian tubes, endometrium and mesothelial cells from the pleura, pericardium, and peritoneum [1, 2], which is known as an usual tumor marker for epithelial ovarian carcinoma [3]. In recent years, a considerable amount of research have shown that the level of CA125 will elevate in various benign and malignant conditions, such as acute heart failure and CHF (chronic heart failure) [4, 5], severe symptomatic mitral stenosis patients with normal left ventricular ejection fraction and dimensions [5]. It was also found in patients with serosal involvement diseases including pleural fluid or ascites and in patients on the period of vaginal delivery [6-8]. Some kinds of respiratory diseases such as CDPD (chronic obstructive pulmonary disease) and active pulmonary tuberculosis have also been reported with high levels of CA125 [9, 10].

Acute pulmonary thromboembolism (PTE) is one of the most fatal diseases. It performs from asymptomatic small embolism to urgent shock or hypotension. Patients with acute PTE will present with dyspnea, chest pain, cough, hemoptysis and tachypnea, particular in patients with pulmonary infarction [11, 12]. If not treated immediately, it will cause pulmonary hypertension, decompensation right ventricular dysfunction, and even cor pulmonale [12].

However, there is little attention has been devoted to the relationship between acute PTE and CA125. The aim of this study is to investigate the association of CA125 level with the severity stratification of acute PTE.

Patients and methods

Patients

104 consecutive patients (42 males, 35 females, mean age 62.4±13.1 years) first diagnosed

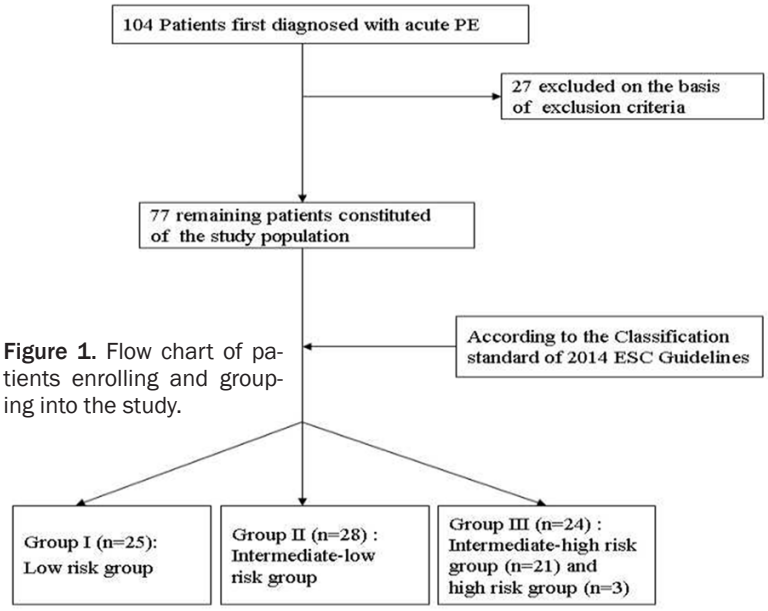

Figure 1. Flow chart of patients enrolling and grouping into the study.

with acute PTE were enrolled into this study in a period from January 2013 to March 2015 at Sir Run Run Shaw Hospital, an university-affiliated tertiary care hospital in China. The diagnosis of acute PTE follows the current guidelines [13]. Mainly according to clinical features of symptoms and signs such as dyspnea, chest pain, hemoptysis, syncope or shock; blood examination such as D-dimer test and arterial blood gas analysis and so on; imaging testing such as computed tomographic pulmonary angiography, V/Q scintigraphy and others. A history disease of DVT (deep venous thrombosis) will also help to diagnosis.

Exclusion criteria included a history diagnosis of malignancy, advanced heart failure with left ventricular ejection fraction (LVEF) less than 50%, coronary heart disease, cor pulmonale, tuberculosis, severe liver disease, endstage renal failure, serous cavity effusion derived from unexplained factor or diseases other than acute PTE, gynecological diseases such as pelvic inflammatory disease, benign ovarian tumors, Interstitial lung disease, severe COPD. In Addition, Children (below 18 years), elderly persons (beyond 80 years), pregnancy, and the collection moment of serum CA125 blood sample beyond 3 days from onset time of acute PTE were also excluded. After screening, 27 patients were excluded due to malignancy (pulmonary carcinoma for 6, malignant fibrohistiocytoma for 1, Intracranial germ cell tumors for 1), pleural effusion caused by unexplained factor (n=1), left ventricular dysfunction (n=1), pregnancy (n=1), beyond collection time of CA125 for 3 days (n=9), elderly beyond 80 years old(n=2), severe liver disease (n=1), endstage renal failure (n=1), coronary heart disease (n=2), cor pulmonale (n=1).

Therefore, the remaining 77 patients constituted the study population. The study polulation were assigned to low (n=25), intermediate-low (n=28), intermediate-high (n=21) and high (n=3) risk groups following the classification standard of 2014 ESC Guidelines (13). The low risk group was defined as Group I. The intermediate-low risk group was defined as Group II. As the amount of high risk group was low, so we combined the high risk group with intermediate-high risk group as Group III (n=24) (**Figure 1**). We recruited 38 age-sex matched persons who have general medical examination in Health Promotion Center of Sir Run Run Shaw Hospital to constitute the Control group.

Measurement of serum CA125 level

Serum CA125 samples were obtained during patient's hospitalization (within 72 h after the onset of acute PTE). 3 ml of venous blood sample taken from peripheral vein was drawn from each study subject, and then collected into EDTA tube. The CA125 level was determined with electrochemiluminescence immunoassay on a Roche Cobas E602 system (Roche Diagnostics GmbH, Mannheim, Germany).

Statistical analysis

SPSS version 19 (IBM corporation) was used for statistical analysis. The Kolmogorov-Smirnov test was used to assess sample distribution. If normally distributed, continuous variables were expressed as mean ± standard deviation. The one-way ANOVA was used to test of homogeneity of variances. If continuous variances were not homogeneous or non-normally distributed, data were compared with Kruskal-Wallis tests. If continuous variances were

Table 1. Baseline characteristics in different groups

	Control group (n=38)	Group I (n=25)	Group II (n=28)	Group III (n=24)	*p* value
Age, mean ± SD, y	60.3±11.5	59.5±14.5	63.6±11.8	64.1±13.1	0.431
Sex (male/female), n	23/15	14/11	15/13	13/11	0.942
CA125 levels, mean ± SD, U/ml	11.0±3.8*	11.0±4.6**	19.0±11.8†	44.6±43.0‡,§	<0.05
D-dimer, mean ± SD, μg/ml		3.6±2.8	4.0±2.6	3.6±2.7	0.856
BNP, mean ± SD, pg/ml		61.5±66.4	640.0±669	2068±2078.5	<0.001
LVEF , mean ± SD		69.9±8.1	67.9±7.7	67.0±9.4	0.47
PASP, mean ± SD, mmHg		31.1±9.5	51.4±13.9	71.6±24.9	<0.001
SBP, mean ± SD, mmHg		138.1±16.2	139.5±21.9	130.8±25.3	0.309
DBP, mean ± SD, mmHg		74.6±9.0	81.5±12.1	76.2±15.6	0.09
HR, mean ± SD, bpm		78.8±14.1	85.4±18.9	91.9±16.0	0.026
DVT, n (%)		28 (72)	14 (50)	11 (46)	0.135
Hypertension, n (%)		11 (44)	17 (60.7)	10 (41.7)	0.317
Diabetes mellitus, n (%)		2 (8)	8 (29)	5 (21)	0.165

BNP, brain natriretic peptide; LVEF, Left Ventricular Ejection Fraction; PASP, systolic pulmonary artery pressure; CRP, C-reaction protein; SBP, systolic blood pressure; DBP, diastolic Blood Pressure; HR, heart rate; DVT, Deep Vein Thrombosis. *P<0.05 between control group and group II; **P<0.05 between group I and group II; †P<0.05 between group II and group III; ‡P<0.001 between control group and group III; §P<0.001 between group I and group III.

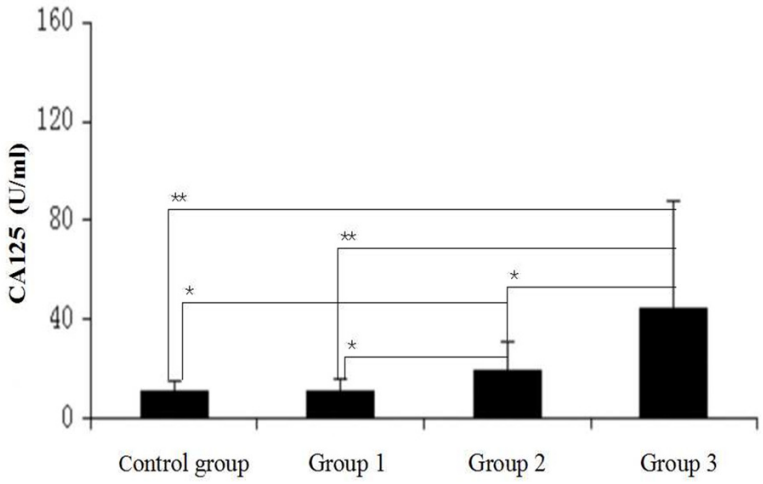

Figure 2. The level of CA125 differs in different group. Group I (low-risk group, n=25). Group II (intermediate-low risk group, n=28). Group III (high-risk and intermediate-high risk group, n=24). *P<0.05; **P<0.001.

homogeneous and normally distributed, the data were compared with one-way ANOVA. Categorical variables were presented as percentages and compared using the chi-squared test. A two-tailed p value of <0.05 was considered to be statistically significant.

Results

Clinical characteristics and serum CA125 levels of the study groups were presented in **Table 1**. The mean level of CA125 in group III (44.6±43.0 U/ml) was significantly higher than that in group II (19.0±11. P<0.05), group I (11.0±4.6. P<0.001) and control group (11.0±3.8. P< 0.001). It was also significantly higher in group II than that of group I (P<0.05) and control group (P<0.05). However, The CA125 levels between group I and control group did not differ significantly (**Figure 2**). Groups did not differ significantly on these clinic characteristics such as age, gender, D-dimer; systolic and diastolic blood pressure, deep venous thrombosis, hypertension and diabetes mellitus. Through univariate analysis and Kruskal-Wallis test, BNP (B-type natriuretic peptide) were positively correlated with CA125 (r=0.574, P<0.001) (**Figure 3**), PASP (systolic pulmonary artery pressure) were also positively correlated with CA125 (r=0.390, P=0.006) (**Figure 4**), LVEF were negatively correlated with CA125 (r=-0.102, P=0.009) (**Figure 5**). After control of LVEF (partial correlation), CA125 kept positive correlation with BNP (P= 0.004) and PASP (P=0.005). In linear regression model, BNP was shown to be positively correlated with PASP (P<0.001). There was no

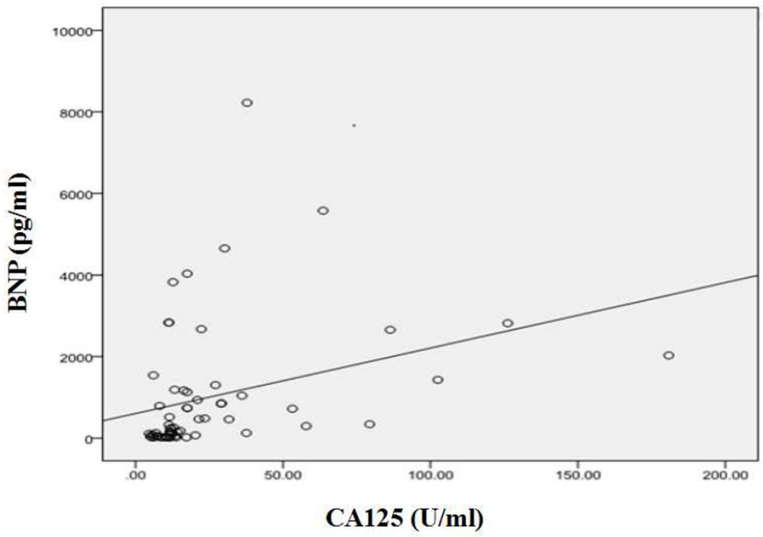

Figure 3. The relationship between BNP and CA125.

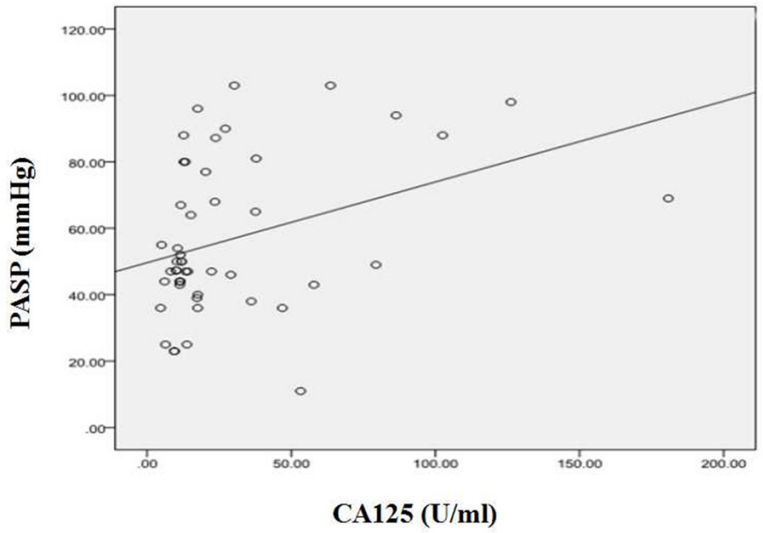

Figure 4. The relationship between PASP and CA125.

significant association between heart rate and CA125 level (r=0.199, *P*=0.162).

Discussion

CA125 is widely used as a tumor marker to diagnose and evaluate the efficacy of therapy and the recurrence of ovarian carcinoma. The rising and falling of CA125 level is parallel to the regression and progression of this disease [14]. The elevation of CA125 has been found in many other malignant diseases and nonmalignant situations [15].

Previous studies have reported various possible factors related to the level of CA125, including some kinds of respiratory diseases, such as COPD and tuberculosis [9, 16]. However, there were few studies concerning about the relationship between CA125 and acute PTE. So we wondered that whether acute PTE was related to the level of serum CA125. In our study, we enrolled 78 patients who were diagnosed with acute PTE for first time; they were subdivided to three groups according to the mortality risk stratification of acute PTE [13]. We found that the mean level of serum CA125 was elevated strikingly from low-risk group to high-risk group, and there was significantly statistical difference between groups. Bulut et al investigated the mean levels of serum CA125 in different stages of COPD. They also found that the levels of serum CA125 in patients might be due to the severity of COPD. We have found a positive relationship between the value of BNP and the level of CA125. Our study also showed that the value of PASP was closely related to the serum concentration of CA125, which was in accordance with the findings of Durak-Nalbantic et al, and Omer Uz et al [17, 18]. LVEF was negatively correlated with the level of CA125 in our study, which agreed well with the findings of Yilmaz et al [1]. These findings suggest us the possibility that the level of CA125 is related to heart disease.

Many studies have reported that the elevation of CA125 was relevant to serous cavity effusion such as pleural effusion, pericardial effusion and ascites [15, 19, 20]. Fluids overload in serosal involvement diseases seems play a crucial role in the synthesis of CA125. Huang et al

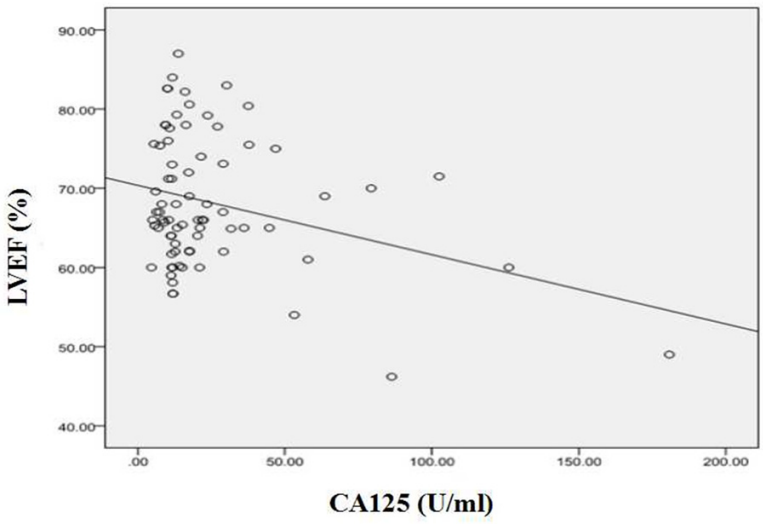

Figure 5. The relationship between LVEF and CA125.

had found that the levels of CA125 with serous cavity effusion were higher than those without serosal involvement in chronic heart failure patients. Their further study in vitro had performed that the expression of MUC16, which was known as the CA125 antigen, would upregulated in stretched cells compared with non-stretched ones [21, 22]. This indicates tissue stretching caused by fluid retention probably give rise to the elevation of CA125 [5]. We assume that the stress from fluids overload may act on mesothelial cells and induce CA125 elevation, which is encoded by MUC16 gene in human [23]. As fluids overload is a common clinic phenomenon in patients with acute PTE. Thus, it might be the main mechanism of elevation of serum CA125. Nagele et al had found that serum CA125 level would elevate even in the absence of fluid accumulation [24], which indicates that many other mechanisms might take great effect on the production of CA125. According to recent studies, systemic inflammation and cytokine activation may also contribute to the synthesis of CA125 [5, 25, 26].

The measurement of CA125 is a noninvasive and convenient assay. A persistent increase or decrease in the value of CA125 may respectively indicate an invalid or valid response to the therapy in patients with CHF [27]. D'Aloia et al had also found that a higher serum level of CA125 was closely associated with a worse prognosis after 6 month's follow up in patients with CHF [5]. Thus, we may assume the possibility of the serum assay of CA125 as a prognostic value in patients suffering of acute PTE. The level of CA125 may probably become a useful index to therapy guiding. BNP is widely applied in the evaluation and severity stratification of cardiac dysfunction, and it was also a predictor of long-term prognosis in patients with acute PTE [28]. On the basis of our and others studies, the level of CA125 was positively correlated with the level of BNP [29]. We assume CA125 may not only act as a promising biomarker for the severity prediction and prognostic evaluation of acute PTE, but contribute to therapeutic schedule adjustment in subsequent follow-up.

Many limitations need to be acknowledged: firstly, the population who were enrolled into this study came from a single centre with a small sample size, which will limit the extrapolation of our research into different populations and a larger cohort. Secondly, as the level of CA125 and many other parameters in our study were measured only during the period of hospitalization, there is no subsequent follow-up examination on these patients; further study is still needed to investigate the predicted value of CA125 in forecasting prognosis of disease in patients with acute PTE. Thirdly, the values of PASP estimated by Doppler echocardiography will differ from those measured by right heart catheterization.

In conclusion, CA125 levels in patients with acute PTE might due to the severity of disease. Our results also suggest that CA125 level was positively correlated to the value of BNP and PASP, however negatively correlated to LVEF. Further studies are still necessary to investigate the severity prediction and prognosis evaluation role of CA125 as a biomarker in patients with acute PTE.

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Disclosure of conflict of interest

None.

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