Original Article Role of serum CA125 and CA199 concentration in diagnosis and prognosis evaluation of lung cancer patients

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Abstract: Carbohydrate antigens (CA) 125 and 199 have now been widely used in diagnosis in lung cancer. However, the role of metastasis and prognosis of these two markers remains controversial and needs further clarification. Here we retrospectively analyzed CA125 and CA199 in 430 lung cancer patients. All patients were categorized to three groups (negative, moderate and high) according to the increased serum levels of CA125 and CA199. The association between different groups and clinical characteristics, metastasis occurrence and survival status was conducted by SPSS17.0. Then multivariate analyses of Cox regression hazard model were performed to evaluate the prognostic parameters for survival. The results indicated that CA125 related closely to age, tumor types, stages and occurrences of bone and pleural metastasis. While CA199 only related to tumor types and liver metastasis. Kaplan-Meier analyses indicated that increased levels in both CA125 (P<0.001) and CA199 (P<0.05) were related significantly to survival status of lung cancer patients. Cox regression model suggested that CA125 could be used as independent factor in prediction of poor prognosis. In specific tumor type analysis, it was also found that CA125, not CA199, could be independent indicator of poor prognosis in adenocarcinoma patients. Our results indicated that CA125 were more important in lung cancer diagnosis and prognosis than CA199.

Keywords: CA125, CA199, lung cancer, adenocarcinoma, prognosis

Introduction

Serum biomarkers played important roles in cancer diagnosis, therapy monitoring and prognosis due to convenience and non-invasion [1, 2]. Tumor biomarkers were produced by tumor cells during their growth and proliferation, or secreted abnormally by the body due to the reaction to the tumor [3]. They expressed in a low levels in healthy people but increase in cancer patients. Among all tumor biomarkers, carbohydrate antigen (CA) 125 and 129 were reported in many tumors and were commonly applied for post-operative surveillance and evaluating treatment effects, such as pancreatic [4], ovarian [5], gastric [6], colorectal [7] and lung [8], breast cancer [9]. Elevated serum level of CA199 was associated with higher risk of mortality in gastric cancer [10] and was also an independent prognostic factor in gallbladder cancer [11]. However, the role of serum CA125 and CA199 in the prognosis of non-small cell lung cancer (NSCLC) remain controversial. And

different pathological type may have different influence on expression of serum biomarker.

In this research, serum biomarkers CA125 and CA199 were retrospectively analyzed in 430 lung cancer patients. All patients were divided into negative, moderate and high groups according to the circulating levels of CA125 and CA199. Analyses were then introduced to study the association between CA125, CA199 and clinical characteristics, metastases and prognosis. The aim of study was to identify whether CA125 and CA199 could be used as indicator for poor prognosis in lung cancer patients.

Patients and methods

Patients

In this retrospective study, the clinical records of 430 diagnosed lung cancer patients admitted to West China Hospital, Sichuan University, between august 2008 and august 2012 were

CA125 and CA199 in lung cancer

Table 1. The association of serum level of CA125 with basic characteristics and metastasis

			No. (%)			
		<21 (n=123)	21-105 (n=169)	>105 (n=138)	Total (n=430)	P value
Characteristics						
Gender	Male	77 (62.6)	103 (60.9)	80 (58.0)	260	0.737
	Female	46 (37.4)	66 (39.1)	58 (42.0)	170	
Age	<45	5 (4.1)	15 (8.9)	15 (10.9)	35	<0.05*
	45-65	78 (33.1)	78 (46.2)	78 (56.5)	234	
	>65	40 (32.5)	76 (45.0)	45 (32.6)	161	
Smoke history	No	56 (45.5)	94 (55.6)	74 (53.6)	224	0.213
	Yes	67 (54.5)	75 (44.4)	64 (46.4)	206	
Subtypes	SCC	31 (25.2)	50 (29.6)	20 (14.5)	101	<0.001**
	ADC	60 (48.8)	86 (50.9)	102 (73.9)	248	
	SCLC	23 (18.7)	22 (13.0)	11 (8.0)	56	
	Others	9 (7.3)	11 (6.5)	5 (3.6)	25	
Stage	+	26 (21.1)	22 (13.0)	4 (2.9)	52	<0.001**
	III+IV	87 (70.7)	139 (82.2)	128 (92.8)	354	
	Unknown	10 (8.1)	8 (4.7)	6 (4.3)	24	
Metastasis						
Brain	No	112 (91.1)	150 (88.8)	126 (91.3)	388	0.708
	Yes	11 (8.9)	19 (11.2)	12 (8.7)	42	
Bone	No	112 (91.1)	132 (78.1)	98 (71.0)	342	<0.001**
	Yes	11 (8.9)	37 (21.9)	40 (29.0)	88	
Liver	No	115 (93.5)	152 (89.9)	119 (86.2)	386	0.154
	Yes	8 (6.5)	17 (10.1)	19 (13.8)	44	
Adrenal gland	No	116 (94.3)	158 (93.5)	133 (96.4)	407	0.525
	Yes	7 (5.7)	11 (6.5)	5 (3.6)	23	
Lymph node	No	54 (43.9)	57 (33.7)	45 (32.6)	156	0.112
	Yes	69 (56.1)	112 (66.3)	93 (67.4)	274	
Intrapulmonary	No	106 (86.2)	143 (84.6)	123 (89.1)	372	0.511
	Yes	17 (13.8)	26 (15.4)	15 (10.9)	58	
Pleura	No	112 (91.1)	143 (84.6)	98 (71.0)	353	<0.001**
	Yes	11 (8.9)	26 (15.4)	40 (29.0)	77	
Mediastinum	No	120 (97.5)	160 (94.7)	133 (96.4)	413	0.445
	Yes	3 (2.5)	9 (5.3)	5 (3.6)	17	
Peritoneum	No	111 (90.2)	157 (92.9)	127 (92.0)	395	0.712
	Yes	12 (9.8)	12 (7.1)	11 (8.0)	35	

Bold values indicate statistically significant values (*P<0.05, **P<0.001).

enrolled. The diagnosis of lung cancer was confirmed by cytological or histological examination of tumor tissue. Histological subtypes of tumors and pathological stages were classified according to WHO classification criteria. All clinical data were gathered from medical records within 2 weeks of diagnosis and confirmation of metastasis was performed by whole-body CT scan and lymph node biopsy. Follow-up was conducted by telephone inquiry to obtain the date of death. Age was analyzed by dividing into three-groups (<45 years, 45-65 years and >65

years). Tumor types included adenocarcinoma (ADC), squamous carcinoma (SCC), small cell lung cancer (SCLC) and others (large cell lung cancer, adeno-squamous cancer, etc). Stages were categorized as early (I+II), advanced (III+IV) and unknown groups.

Study design

The cut-off level was 21 ng/ml and 22 ng/ml for CA125 and CA199, respectively, according to the previous literature. All patients were

CA125 and CA199 in lung cancer

Table 2. Analysis of serum CA199 level in lung cancer patients

		-	No. %		_	
		<22 (n=296)	22-66 (n=75)	>66 (n=59)	Total (n=430)	P value
Characteristics						
Gender	Male	189 (63.9)	41 (54.7)	30 (50.8)	260	0.093
	Female	107 (36.1)	34 (45.3)	29 (49.2)	170	
Age	<45	29 (9.8)	3 (4.0)	3 (5.1)	35	0.276
	45-65	156 (52.7)	47 (62.7)	31 (52.5)	234	
	>65	111 (37.5)	25 (33.3)	25 (42.4)	161	
Subtypes	SCC	80 (27.0)	12 (16.0)	9 (15.3)	108	0.008
	ADC	152 (51.4)	52 (69.3)	44 (74.6)	248	
	SCLC	44 (14.9)	9 (12.0)	3 (5.1)	56	
	Others	20 (6.8)	2 (2.7)	3 (5.1)	25	
Stage	I+II	43 (14.5)	7 (9.3)	2 (3.4)	52	0.064
	III+IV	240 (81.1)	61 (81.3)	53 (89.8)	354	
	Unknown	13 (4.4)	7 (9.3)	4 (6.8)	24	
Smoke history	No	147 (49.7)	42 (56.0)	35 (59.3)	224	0.302
	Yes	149 (50.3)	33 (44.0)	24 (40.7)	206	
Metastasis						
Brain	No	270 (91.2)	65 (86.7)	53 (89.8)	388	0.492
	Yes	26 (8.8)	10 (13.3)	6 (10.2)	42	
Bone	No	243 (82.1)	57 (76.0)	42(71.2)	342	0.117
	Yes	53 (17.9)	18 (24)	17 (28.8)	88	
Liver	No	273 (92.2)	66 (88)	47 (79.7)	386	0.012
	Yes	23 (7.8)	9 (12)	12 (20.3)	44	
Adrenal gland	No	282 (95.3)	69 (92.0)	56 (94.9)	407	0.529
	Yes	14 (4.7)	6 (8.0)	3 (5.1)	23	
Lymph node	No	105 (35.5)	29 (38.7)	22 (37.3)	156	0.863
	Yes	191 (64.5)	46 (61.3)	37 (62.7)	274	
Intrapulmonary	No	255 (86.1)	64 (85.3)	53 (89.8)	372	0.712
	Yes	41 (13.9)	11 (14.7)	6 (10.2)	58	
Pleura	No	249 (84.1)	60 (80.0)	44 (74.6)	353	0.19
	Yes	47 (15.9)	15 (20.0)	15 (25.4)	77	
Mediastinum	No	284 (95.9)	74 (98.7)	55 (93.2)	413	0.272
	Yes	12 (4.1)	1 (1.3)	4 (6.8)	17	
Peritoneum	No	273 (92.2)	66 (88.0)	56 (94.9)	395	0.319
	Yes	23 (7.8)	9 (12)	3 (5.1)	35	

Bold values indicate statistically significant values (*P<0.05, **P<0.001).

divided into negative, moderate and high groups based on the increased level of biomarkers. In CA125, the moderated group was 1-5 folds of serum concentration and the high group was >5 folds. While in CA199, the moderate and high groups were 1-3 folds and >3 folds, respectively. The factors enrolled in study were basic clinical characteristics (gender, age, smoke, tumor types and stages) and different metastasis (brain, bone, liver, adrenal gland, lymph node, intrapulmonary, pleura, mediastinum and peritoneum).

Statistics methods

SPSS 17.0 was conducted to complete the statistical analyses of this study. The statistical significance of inter-group differences was evaluated by the use of Chi-square test. Survival functions of three groups were analyzed by Kaplan-Meier test and Log-rank test was used to compare the survival significance differences among groups. Multivariate Cox regression model was introduced to identify independent predictors for poor prognosis by combination

Table 3. Association analysis of serum CA125 with lung ADC patients

		No. (%)			_	
		<21	21-105	>105	Total	P value
		(n=60)	(n=86)	(n=102)	n	r value
Characteristics						
Gender	Male	26 (43.3)	44 (51.2)	51 (50.0)	121	0.616
	Female	34 (56.7)	42 (48.8)	51 (50.0)	127	
Age	<45	2 (3.3)	10 (11.6)	12 (11.8)	24	0.095
	45-65	42 (70.0)	42 (48.8)	57 (55.9)	141	
	>65	16 (26.7)	34 (39.5)	33 (32.4)	83	
Stage	+	12 (20.0)	7 (8.1)	2 (2.0)	21	<0.05*
	+ V	44 (73.3)	75 (87.2)	96 (94.1)	215	
	unknown	4 (6.7)	4 (4.7)	4 (3.9)	12	
Smoke history	No	40 (66.7)	60 (69.8)	64 (62.7)	164	0.595
	Yes	20 (33.3)	26 (30.3)	38 (37.3)	84	
Metastasis						
Brain	No	50 (83.3)	72 (83.7)	93 (91.2)	215	0.221
	Yes	10 (16.7)	14 (16.3)	9 (8.8)	33	
Bone	No	52 (86.7)	66 (76.7)	69 (67.6)	187	<0.05*
	Yes	8 (13.3)	20 (23.3)	33 (32.4)	61	
Liver	No	56 (93.3)	78 (90.7)	89 (87.3)	223	0.443
	Yes	4 (6.7)	8 (9.3)	13 (12.7)	25	
Adrenal	No	58 (96.7)	83 (96.5)	98 (96.1)	239	0.978
	Yes	2 (3.3)	3 (3.5)	4 (3.9)	9	
Lymph	No	30 (50.0)	26 (30.2)	36 (35.3)	92	<0.05*
	Yes	30 (50)	60 (69.8)	66 (64.7)	156	
Intrapulmonary	No	49 (81.7)	67 (77.9)	91 (89.2)	207	0.105
	Yes	11 (18.3)	19 (22.1)	11 (10.8)	41	
Pleura	No	54 (90.0)	66 (76.7)	69 (67.6)	189	<0.05*
	Yes	6 (10.0)	20 (23.3)	33 (32.4)	59	
Mediastinum	No	58 (96.7)	83 (96.5)	99 (97.1)	240	0.976
	Yes	2 (3.3)	3 (3.5)	3 (2.9)	8	
Peritoneum	No	55 (91.7)	79 (91.9)	94 (92.2)	228	0.993
	Yes	5 (8.3)	7 (8.1)	8 (7.8)	20	

Bold values indicate statistically significant values (*P<0.05).

analyzing clinical characteristics, metastasis and survival status.

Results

CA125 and CA199 related closely to several metastases in lung cancer patients

All patients were classified to negative, moderate and high groups according to serum levels of CA125 and CA199. In clinical characteristics analysis, CA125 was found to be related closely to age (P<0.05), tumor types (P<0.001) and stages (P<0.001). In metastasis analysis,

CA125 had significantly relationship with bone metastasis, which indicated that in moderate and high level groups, the occurrence of bone metastasis inreased to 21.9% and 29% compared with negative group (8.9%). Pleura metastasis was also related dramatically with increased level of CA125 (negative: 8.9%, moderate: 15.4%, high: 29%) (Table 1). While CA199 was related only to tumor types and liver metastasis (negative: 7.8%, moderated: 12%, high: 20.3%, P<0.05) (Table 2).

As adenocarcinoma (ADC) was the major histological classification of lung cancer, we next analyzed the association between CA-125, CA199 and clinical characteristics and metastasis in ADC patients. The results showed that besides stages (P<0.05), CA-125 also associated closely with metastasis of bone (negative: 13.3%, moderate: 23.3%, high: 32.4%, P<0.05), lymph (negative: 50%, moderate: 69.8%, high: 64.7%, P< 0.05) and pleura (neg: 10%. moderate: 23.3%.

high: 32.4%, P<0.05) (**Table 3**). However, the result of CA199 only related to liver metastasis (neg: 7.2%, moderate: 9.6%, high: 20.5%, P<0.05) (**Table 4**). Our study suggested that CA-125 had more relationships with clinical characteristics and metastasis in lung cancer patients than CA199, especially in ADC patients.

CA125 and CA199 both associated significantly with survival in lung cancer patients but CA125 was more important in ADC patients

Univariate analysis was conducted to analyze the relationship between CA125, CA199 and

Table 4. Analysis clinical characteristics and metastasis in ADC patients according to the level of CA199

		No. (%)				
		<22	22-66	>66	Total	Ρ
		(n=152)	(n=52)	(n=44)	n	value
Characteristics						
Gender	Male	82 (53.9)	20 (38.5)	19 (43.2)	121	0.111
	Female	70 (46.1)	32 (61.5)	25 (56.8)	127	
Age	<45	20 (13.2)	1 (1.9)	3 (6.8)	24	0.059
	45-65	78 (51.3)	37 (71.2)	26 (59.1)	141	
	>65	54 (35.5)	14 (26.9)	15 (34.1)	83	
Stage	+	14 (9.2)	5 (9.6)	2 (4.5)	21	0.543
	III+IV	133 (87.5)	43 (82.7)	39 (88.6)	215	
	unknown	5 (3.3)	4 (7.7)	3 (6.8)	12	
Smoke history	No	95 (62.5)	40 (76.9)	29 (65.9)	164	0.165
	Yes	57 (37.5)	12 (23.1)	15 (34.1)	84	
Metastasis						
Brain	No	133 (87.5)	43 (82.7)	39 (88.6)	215	0.621
	Yes	19 (12.5)	9 (17.3)	5 (11.4)	33	
Bone	No	116 (76.3)	41 (78.8)	30 (68.2)	187	0.441
	Yes	36 (23.7)	11 (21.2)	14 (31.8)	61	
Liver	No	141 (92.8)	47 (90.4)	35 (79.5)	223	<0.05*
	Yes	11 (7.2)	5 (9.6)	9 (20.5)	25	
Adrenal	No	149 (98.0)	49 (94.2)	41 (93.2)	239	0.207
	Yes	3 (2.0)	3 (5.8)	3 (6.8)	9	
Lymph	No	55 (36.2)	23 (44.2)	14 (31.8)	92	0.424
	Yes	97 (63.8)	29 (55.8)	30 (68.2)	156	
Intrapulmonary	No	125 (82.2)	42 (80.8)	40 (90.9)	207	0.332
	Yes	27 (17.8)	10 (19.2)	4 (9.1)	41	
Pleura	No	120 (78.9)	39 (75.0)	30 (68.2)	189	0.327
	Yes	32 (21.1)	13 (25.0)	14 (31.8)	59	
Mediastinum	No	148 (97.4)	51 (98.1)	41 (93.2)	240	0.321
	Yes	4 (2.6)	1 (1.9)	3 (6.8)	8	
Peritoneum	No	141 (92.8)	45 (86.5)	42 (95.5)	228	0.232
	Yes	11 (7.2)	7 (13.5)	2 (4.5)	20	
Rold values indicate	ototiotioolly (oidnificant valu	100 (*D<0 0E	\		

Bold values indicate statistically significant values (*P<0.05).

survival status of lung cancer. In all patients' analysis, we found that CA125 (P<0.001) and CA199 (P<0.05) were both related dramatically with survival status besides age (P<0.001), stages (P<0.05) and metastasis (P<0.001) (Table 5). However, only CA125 had significantly relationship with survival status in ADC patients' analysis (Table 6). The Kaplan-Meier survival functions analysis also indicated that CA125 and CA199 related closely to survival of lung cancer patients (Figure 1) but CA199 did not associate with survival status in ADC patients (Figure 2).

CA125 could be used as an independent factor in predicting poor prognosis in lung cancer patients

Cox regression model was introduced to perform the multiple factor analysis. The results suggested that CA125 was an independent factor in poor prognosis in lung cancer patients (P< 0.001) (Table 7) and ADC patients (P<0.05) (Table 8), while CA199 could not be used as indicator of poor prognosis in either lung cancer patients or ADC patients. The Cox regression results further confirmed the importance of CA125 in diagnosis and prognosis in lung cancer patients.

Discussion

Lung cancer was the leading cause of malignancy-related mortality worldwi-de, which caused almost 1,400,000 new deaths annually [12]. Tumor markers were small molecules circulating in blood or tissue which were produced by tumor or by host immune cells response to cancer. Me-

asurement was important in clinical diagnosis, predicting of poor prognosis and anti-drug surveillance [3]. There were several important biomarkers in lung cancer including carcinoembryonic antigen (CEA), cytokeratin 19 (CYFRA21-1), neuron-specific enolase (NSE), carbohydrate antigen (CA) 125, CA199 and squamous cell carcinoma antigen (SCCag) [3, 13-16]. Although there were many studies have been published about the tumor markers, the role of tumor biomarkers in predicting poor prognosis remained controversial in lung cancer, especially in specific tumor types. Among these biomarkers,

Table 5. Kaplan-Meier univariate survival analysis of the prognostic factors in lung cancer patients

of the prognostic factors in fung carried patients						
Gender Female		260	15	0.439		
	Male	170	20			
Age	<45	35	11	<0.001**		
	45-65	234	25			
	>65	161	11			
Smoke history	No	224	19	0.162		
	Yes	206	15			
Subtypes	Squamous	101	14	0.345		
	Adenocarcinoma	248	19			
	SCLC	56	18			
	Others	25	13			
Stage	I	20	45	<0.05*		
	II	32	29			
	III	92	19			
	IV	262	14			
	Unknown	24	26			
Metastasis	No	87	28	<0.001**		
	Yes	343	15			
Ca125	Negative	123	32	<0.001**		
	Moderate	169	17			
	High	138	11			
Ca199	Negative	296	20	<0.05*		
	Moderate	75	15			
	High	59	10			

Bold values indicate statistically significant value (*P<0.05, **P<0.001).

Table 6. Univiate associated with overall survival among lung adenocarcinoma patients

Co-varibles		Patients (n=248)	MSTH (month)	Р
Gender	Female	121	18	0.372
	Male	127	20	
Age	<45	24	11	<0.001**
	<65	141	25	
	>65	83	11	
Smoke history	No	164	20	0.111
	Yes	84	16	
Stage	+	21	55	<0.05*
	III+IV	215	36	
	Unkown	12	16	
Metastasis	No	40	33	<0.05*
	Yes	208	16	
CA125	Neg	60	36	<0.001**
	Moderate	86	20	
	High	102	12	
CA199	Neg	152	21	0.277
	Moderate	52	17	
	High	44	11	

Bold values indicate statistically significant value (*P<0.05, **P<0.001).

CA125 detection was mainly used for the diagnosis of ovarian cancer and prognosis evaluation [5, 17], and gradually have reported its application in colorectal cancer [7], breast cancer [9], and lung cancer [18]. CA199 was applied in the diagnosis of gallbladder [11], pancreatic cancer [19], colorectal cancer [7] and lung cancer [3].

In this study, 430 lung cancer patients were enrolled to analyzing the association between tumor markers (CA125 and CA199) and clinical characteristic, metastasis and prognosis. Our results indicated that compared with CA199, CA125 was related more closely to age, tumor type and bone, pleura metastasis. CA125 and CA199 both associated significantly with survival status of lung cancer patients and CA125 could also be used as an independent factor in poor prognosis. As adenocarcinoma was the dominant tumor type in non small cell lung cancer, we next analyzed the relationship between CA125, CA199 and ADC type. The results confirmed that CA125 played more important role in ADC prognosis than CA199. Previous study indicated that CA125 acted as poor prognosis factor in patients with brain metastasis of non-small cell lung cancer before and after radiotherapy [20]. Combination detection of circulating serum CEA, CA199 and CA125 was useful in diagnosis of lung cancer [21]. One limitation of previous studies was the fewer patients in analysis (usually <200 cases) and the result could not stand for the generally criteria. Another limitation was that the analyzed factors were prognosis or specific metastases only. To our knowledge, our study was the first report which enrolled large lung cancer populations (430 cases) and we analyzed both clinical characteristics and all possible metastases. Our study indicated the close relationship between CA125 and bone, pleura metastases, which was not consistent with former study which suggested that CA125 was an indicator of brain metastases [22]. The explanation of this difference was that we put all stage lung cancer patients in study, not only advanced stages patients. In specific histological classification study, we found that CA125, not CA199 could be acted as independent indicator of poor prognosis in ADC patients.

In conclusion, increased serum CA125 and CA199 levels associated significantly with survival status of lung cancer patients. CA125

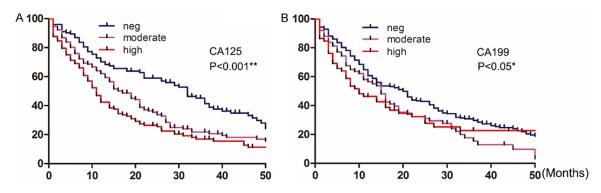


Figure 1. The survival status of lung cancer patients. A: CA125, B: CA199. *P<0.05, **P<0.001.

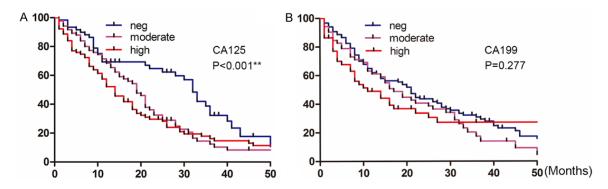


Figure 2. The survival functions analysis in ADC patients correlated with CA125 and CA199. A: CA125, B: CA199. *P<0.05, **P<0.001.

Table 7. Multiple Cox regression models in lung cancer patients

Factor	Hazard ratio	95% confidence interval	P value log-rank
Age	0.868	0.052-14.582	<0.001**
Stage	1.152	0.510-2.603	0.581
CA125	1.297	0.931-1.808	<0.001**
CA199	0.165	0.976-1.888	0.078
Metastasis	1.335	0.917-1.942	0.163

Bold values indicate statistically significant value (**P<0.001).

Table 8. Multiple cox gression model in ADC patients

1			
Factor	Hazard ratio	95% confidence interval	P value
Age	0.553	0.325-0.942	<0.001**
Stage	0.801	0.176-3.641	0.190
CA125	1.374	0.881-2.144	<0.05*
Metastasis	1.197	0.881-2.144	0.340

Bold values indicate statistically significant value (*P<0.05, **P<0.001).

could be used as an independent factor in predicting poor prognosis in lung cancer patients and in ADC patients. Our results indicated that CA125 was more important in lung cancer diagnosis and prognosis in lung cancer patients.

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Disclosure of conflict of interest

None.

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CA125 and CA199 in lung cancer

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