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ORIGINAL ARTICLE

Value of Serum Carbohydrate Antigen 19-9 and Carcinoembryonic Antigen in Evaluating Severity and Prognosis of Connective Tissue Disease-Associated Interstitial Lung Disease

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ABSTRACT

Objectives: This study aims to detect serum carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) levels in connective tissue disease-associated interstitial lung disease (CTD-ILD) patients and to demonstrate their values in evaluating the severity and prognosis of CTD-ILD.

Patients and methods: The study included 82 CTD-ILD patients (54 males, 28 females; mean age 67.9 years; range 29 to 91 years) and 82 controls (54 males, 28 females; mean age 68.1 years; range, 30 to 92 years). Patients were followed-up for 12 months. Correlations of serum CEA and CA 19-9 with disease severity parameters (pulmonary function, oxygenation index and involvement score on high resolution computed tomography) were analyzed. Survival analysis was used to evaluate significance of serum CEA and CA 19-9 as prognosis predictors.

Results: Serum CEA and CA 19-9 levels were higher in CTD-ILD patients compared with controls (both $p<0.05$) and correlated with disease severity ($p<0.05$ for all R^2). High levels of serum CEA and CA 19-9 were associated with poor survival (both $p<0.05$). Serum CEA level was indicated as a prognostic factor for cumulative survival (hazard ratio=1.685, 95% confidence interval: 1.405-2.021, p=0.001).

Conclusion: In CTD-ILD patients, serum CEA and CA 19-9 are elevated and can be indicators of disease severity. Moreover, serum CEA is a significant and independent predictor of survival.

Keywords: Carbohydrate antigen 19-9; carcinoembryonic antigen; connective tissue diseases; interstitial lung diseases; prognosis.

Interstitial lung diseases (ILDs) are a diverse group of lung diseases that affect the lung parenchyma. They are characterized by an initial inflammation of pulmonary alveoli that extends to the interstitium and then leading to diffuse pulmonary fibrosis. ILDs are classified by their etiology (known or unknown causes), and radiological-pathological features. Connective tissue disease-associated ILD (CTD-ILD) is ILD occurring due to CTD. In CTD, rheumatoid arthritis (RA), systemic lupus erythematous (SLE), Sjögren's syndrome (SS), polymyositis/dermatomyositis (PM/DM), systemic sclerosis (SSc), and mixed connective tissue disease (MCTD) are susceptible to respiratory involvement.[1]

Interstitial lung diseases are common in CTDs and they are the leading cause of significant morbidity and mortality.[2] Clinically, acute exacerbation of ILD in CTD-ILD patients leads to respiratory failure and shortens survival. Due to the absence of any significant prognostic biomarker, histopathological form of ILD is often used as a prognostic predictor for CTD-ILD. However, histopathological diagnosis is usually unavailable.[3] Thus, it is important to find out other markers available to predict prognosis of ILD. Regarding the disease severity of ILD, involvement score on high resolution computed tomography (HRCT),[4] oxygenation index (OI) and pulmonary function are usually used as evaluation tools. Nevertheless, corresponding examinations

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of these tools are not suitable for severe patients. Therefore, it is necessary to develop other markers to evaluate disease severity, which will be useful information for individually-based treatment and post-treatment follow-up.

In our clinical work, we found that some CTD-ILD patients with advanced stage had obviously increased serum carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) levels while no other reasons for their elevation were detected. CEA and CA 19-9 are both biomarkers of malignant tumors. CEA is a complex glycoprotein. Elevated serum CEA is usually found in cancers of digestive system and respiratory system, as well as in non-malignant conditions such as ulcerative colitis, pancreatitis, cirrhosis and ascites.[5] CA 19-9 is a kind of carbohydrate antigen. It is useful as a marker for cancers of digestive system and other non-malignant diseases such as cholecystitis, cholangiolitis and pancreatitis.[6] Previous studies reported that serum CEA and CA 19-9 levels are also elevated in CTD and idiopathic pulmonary fibrosis (IPF).[7-9] So, we speculated that elevation of serum CEA and CA 19-9 in CTD-ILD was related with the pathogenetic condition of CTD-ILD itself.

Therefore, in this study, we aimed to detect CEA and CA 19-9 levels in CTD-ILD patients and to demonstrate their values in evaluating the severity and prognosis of CTD-ILD.

PATIENTS AND METHODS

The study included 82 CTD-ILD patients (54 males, 28 females; mean age 67.9 years; range 29 to 91 years) and 82 controls (54 males, 28 females; mean age 68.1 years; range, 30 to 92 years). The CTD-ILD patients were collected from the Respiratory Department of Tongde Hospital of Zhejiang Province at the time of their first treatment in this hospital between August 2007 and July 2015. CTD-ILD patients met the following inclusion criteria: *(i)* Definite diagnosis: ILD was diagnosed according to the American Thoracic Society/European Respiratory Society consensus classification.[10] ILD patients who met the American College of Rheumatology criteria for CTD were defined as CTD-ILD patients.[11-16] *(ii)* Without a history of malignancy or benign conditions associated with increased CEA and CA 19-9, such as pancreatitis, cholecystitis, and ulcerative colitis. *(iii)* Without environmental exposures and other known causes of ILD. *(iv)* Without pulmonary edema, pulmonary infection, pulmonary embolism and other conditions that could affect the pulmonary function and OI at the time of data being collected, but the existence of pulmonary hypertension was allowed. CTD-ILD patients contained 35 RA patients, 16 SS patients, seven PM/DM patients, seven SSc patients, four SLE patients, and 11 MCTD patients. The control subjects without ILD or CTD were collected from the medical examination center of the same hospital. They were matched with CTD-ILD patients with respect to race, sex, height (within 4 cm), body weight (within 5 kg), smoking status, age (within five years) and other diseases they were diagnosed with.

For CTD-ILD patients, disease severity was judged by pulmonary function, involvement score on HRCT and OI. Detection of serum CA 19-9 and CEA levels, arterial blood gas analysis, thoracic HRCT and pulmonary function were all finished in the first day of inclusion into this study. All CTD-ILD patients were designed to follow-up for 12 months. Follow-up was performed every month. Death caused by CTD-ILD was defined as the end point. Data of controls were obtained from their health examination records. The study protocol was approved by the Ethics Committee of Tongde Hospital of Zhejiang Province. Written informed consent was obtained from all participants. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Blood specimens were obtained by a standard procedure between 06:00 and 07:00 in the morning. Detection procedures were conducted in two hours after blood specimens were obtained. Serum CEA and CA 19-9 levels were analyzed by microparticle enzyme immunoassays using Abbott reagent sets (AxSYM, Abbott Laboratories, Chicago, IL, USA).

Pulmonary function, including percentage predicted diffusing capacity of the lung for carbon monoxide (DLco %) and percentage predicted forced vital capacity (FVC %), were measured by the Masterscreen PFT (Viasys/Jaeger; Höchberg, Germany).

Fraction of inspired oxygen (FiO_2) was gained from the parameter of ventilation, or calculated from the flow rate of inspired oxygen. Partial pressure of oxygen PaO_2 (mmHg) was obtained from arterial blood gas analysis. OI was calculated as $OI=PaO_2/FiO_2$.

Thoracic HRCT scans were evaluated by three observers who were blinded to all the results above. The entire lung was scored on a scale of 0-5 for both alveolar and interstitial abnormality. Ground-glass score represented the extent of alveolar abnormality: 0: no ground-glass opacity (GGO); 1: GGO involving ≤5% (minimal, but not normal); 2: involving 6%-24%; 3: involving 25%-49%; 4: involving 50%-75%; 5: involving >75%. Fibrosis score represented the extent of interstitial abnormality: 0: no fibrosis; 1: interlobular septal thickening; no discrete honeycombing; 2: honeycombing (with or without septal thickening) involving <25%; 3: involving 25%-49%; 4: involving 50%-75%; 5: involving >75%. Final involvement percentage was acquired from the average of three observers.[4]

Statistical analysis

Statistical analysis was carried out using SPSS version 16.0 software (SPSS, Inc., Chicago, IL, USA). Serum levels of CEA and CA 19-9 in patients and controls were compared using Wilcoxon-Mann-Whitney test. Correlations between serum markers (CEA and CA 19-9) and disease severity parameters (pulmonary function [DLco % and FVC %] and OI) were evaluated by Pearson's correlation. Correlation between serum markers and involvement score on HRCT were analyzed by Spearman's correlation. The median of serum CEA and CA 19-9 values was used as the cut-off value for dichotomizing serum CEA and CA 19-9. Survival time was calculated from the date of data collecting to the date of death or loss to follow-up. Survival curves were generated using the method of Kaplan-Meier. Equality of survival distributions was tested using log-rank testing, univariate and multivariate Cox regression analysis. All reported *p* values were two-sided. A *p* value of <0.05 was considered statistically significant. Based on a pilot experiment containing

Table 1. Demographics and clinical characteristics of study participants

Category	CTD-ILD patients						Controls					
	n	%	Mean±SD	Median	P25th percentile	P75th percentile	n	%	Mean±SD	Median	P25th percentile	P75th percentile
Participants	80						80					
Age (year)			67.0±13.5						65.2±11.2			
Sex												
Male	53	66.3					53	66.3				
Female	27	33.8					27	33.8				
Smoking												
Ex	39	48.8					39	48.8				
Current	7	8.8					7	8.8				
Never	34	42.5					34	42.5				
Pack (year)			25.0±12.6						23.2±10.1			
Pulmonary function												
FVC (%)*			80.3±13.2						92.3±7.1			
DLco (%)*			66.3±16.5						92.2±8.6			
Ground-glass score on HRCT												
0	18	22.5					80	100				
1	19	23.75					0	0				
2	18	22.5					0	0				
3	14	17.5					0	0				
4	9	11.25					0	0				
5	2	2.5					0	0				
Fibrosis score on HRCT												
0	0	0					80	100				
1	42	52.5					0	0				
2	16	20					0	0				
3	11	13.75					0	0				
4	7	8.75					0	0				
5	4	5					0	0				
Oxygenation index			375.5±85.3						NA			
Serum CEA (ng/mL)*			7.2±3.9						3.4±1.4			
Serum CA 19-9 (U/mL)*				72.95	30.57	243.96				25.65	9.00	38.92

CTD-ILD: Connective tissue disease-associated interstitial lung disease; SD: Standard deviation; FVC %: Percentage predicted forced vital capacity; DLco %: Percentage predicted diffusing capacity of the lung for carbon monoxide; HRCT: High resolution computed tomography; CEA: Carcinoembryonic antigen; CA 19-9: Carbohydrate antigen 19-9; NA: Not available; * P<0.05 for comparison between connective tissue disease-associated interstitial lung disease patients and controls.

Table 2. R^2 of correlation analyses between serum markers and severity evaluation tools

Severity parameter	CEA		CA 19-9	
	R^2	*p*	R^2	*p*
Percentage predicted forced vital capacity	0.523	0.000	0.616	0.000
DLco %	0.621	0.000	0.792	0.000
Ground-glass score on HRCT	0.320	0.000	0.386	0.000
Fibrosis score on HRCT	0.578	0.000	0.679	0.000
Oxygenation index	0.720	0.000	0.860	0.000

CEA: Carcinoembryonic antigen; CA 19-9: Carbohydrate antigen 19-9; DLco %: Percentage predicted diffusing capacity of the lung for carbon monoxide; HRCT: High resolution computed tomography.

14 CTD-ILD patients and 14 controls, the required sample size is 57. The accrual time during which patients were recruited was eight years and there was no additional follow-up time after the end of recruitment. Finally, power analysis was carried out using PS software (Power and Sample Size Calculation version 3.1.2, 2014).

RESULTS

Two CTD-ILD patients were excluded because of the occurrence of malignancy. Accordingly, data were analyzed for a total of 80 patients and 80 controls. In addition, two patients suffered from severe respiratory failure, so pulmonary function test was unavailable for them. For pulmonary function related statistical analysis, these two patients and their controls were excluded. Within the follow-up period of 12 months, none of the patients was lost to follow-up. But one patient died of renal failure at 2.5 months and one died of cerebrovascular accident at 7.7 months. Related data were considered as censored data. Sixteen patients (20%) died of CTD-ILD with a median survival time of 5.785 months (range 2.17-11.2 months). Demographics and clinical characteristics of the study population were shown in Table 1.

Serum CEA and CA 19-9 levels were significantly higher in CTD-ILD patients compared with controls (both p=0.001) while pulmonary function of CTD-ILD patients was lower (p=0.001 for both FVC % and DLco %, Table 1).

In correlation analysis (Table 2), serum CEA and CA 19-9 levels were correlated with disease severity in CTD-ILD patients ($p<0.05$ for all R^2). Among disease severity parameters, OI had strong negative correlations with serum CEA and CA 19-9 levels (R^2=0.720 and 0.860, respectively), while ground-glass score on HRCT had very weak correlations (R^2=0.320 and 0.386, respectively). Negative correlation between serum CEA level and OI in CTD-ILD patients is shown as a typical example in Figure 1.

Figure 2 shows the Kaplan-Meier survival curves of patients with serum CEA values >6.145 ng/mL and <6.145 ng/mL. High levels of serum CEA were significantly associated with poor survival (p=0.001, log-rank test). Figure 3 shows the Kaplan-Meier survival curves of patients with serum CA 19-9 values >72.95 U/mL and <72.95 U/mL. High levels of serum CA 19-9 were also significantly associated with poor survival (p=0.001, log-rank test).

Univariate Cox regression analysis identified that serum CEA and serum CA 19-9 levels were significantly associated with survival in

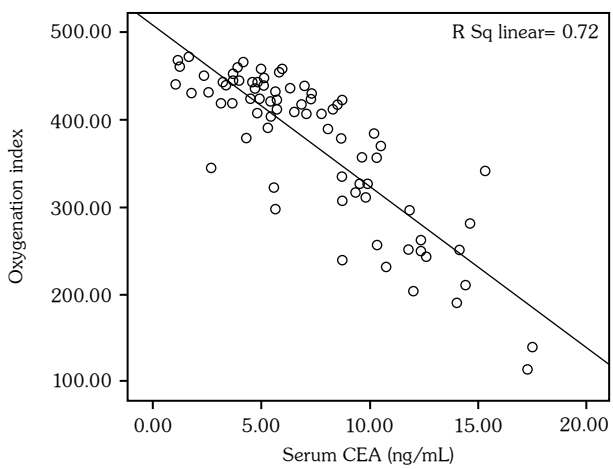

Figure 1. Correlation between serum CEA level and oxygenation index in connective tissue disease-associated interstitial lung disease patients (p=0.001; R^2=0.720). CEA: Carcinoembryonic antigen.

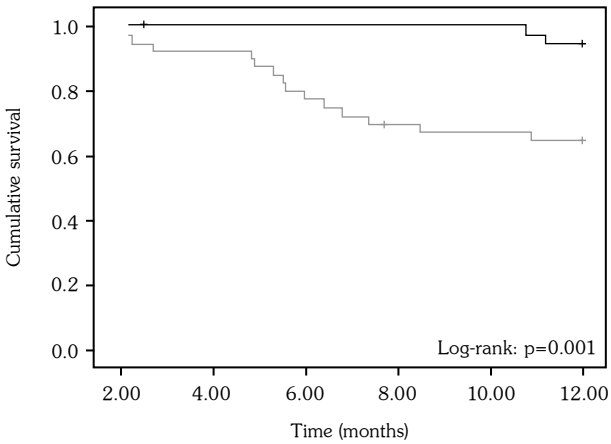

Figure 2. Kaplan-Meier estimates of one-year survival of connective tissue disease-associated interstitial lung disease patients grouped by serum carcinoembryonic antigen level (n=80, median= 6.145 ng/mL). Low serum carcinoembryonic antigen levels (n=40; <median) and high serum carcinoembryonic antigen levels (n=40; >median) are represented by solid and broken line, respectively. Vertical bars indicate cases with censored data.

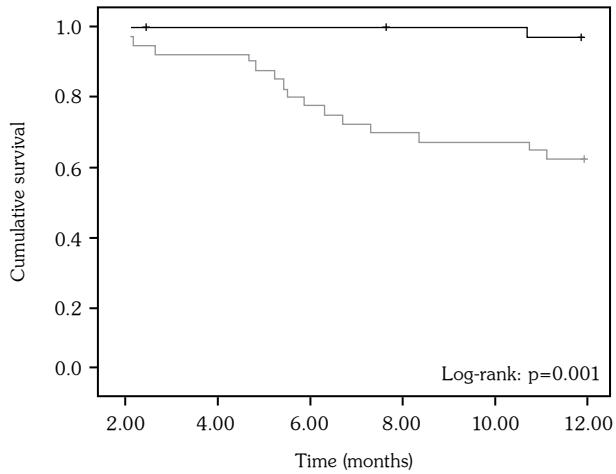

Figure 3. Kaplan-Meier estimates of one-year survival of connective tissue disease-associated interstitial lung disease patients grouped by serum carbohydrate antigen 19-9 level (n=80, median=72.95 U/mL). Low serum carbohydrate antigen 19-9 levels (n=40; <median) and high serum carbohydrate antigen 19-9 levels (n=40; >median) are represented by solid and broken line, respectively. Vertical bars indicate cases with censored data.

CTD-ILD patients (Table 3). Because serum CEA and CA 19-9 levels were strongly correlated (R^2=0.826, p=0.001), multivariate Cox regression analysis was performed respectively to evaluate the potential of serum CEA and CA 19-9 as independent predictors for survival of CTD-ILD. Smoking was also included in multivariate analysis since its *p* value in univariate analysis was less than 0.1 (p=0.071). In multivariate Cox regression analysis of smoking and serum CEA as prognostic factors in CTD-ILD patients, serum CEA was demonstrated as a significant and independent predictor with impact on survival, while smoking was excluded as a prognostic factor (Table 4). In multivariate Cox regression analysis of smoking and serum CA 19-9 as prognostic factors, serum CA 19-9 had little significance as a prognostic factor, while smoking was also excluded as a prognostic factor (Table 5).

Power analyses were performed post hoc as per the method described by Dupont and Plummer[17] In the analysis of serum CEA and CA 19-9 levels compared with controls, the power of CEA was 99.9% and that of CA 19-9 was 88.2%. The power of FVC % and DLco % were both 99.9%. The powers of correlation analysis ranged from 81.6% to 100%. In survival analysis, hazard ratio of the low CEA level group relative to high CEA level group was 0.502, and finally the power was 81.7%. We calculated the hazard ratio of the low CA 19-9 level group relative to high CA 19-9

Table 3. Univariate Cox regression analysis of clinical parameters and carcinoembryonic antigen and carbohydrate antigen 19-9 levels as prognostic factors for cumulative survival in connective tissue disease-associated interstitial lung disease patients

Variable	HR	95% CI	*p*
Age	1.033	0.989-1.078	0.142
Sex	0.616	0.199-1.911	0.402
Smoking	1.027	0.998-1.057	0.071
Serum CEA	1.615	1.381-1.888	0.000
Serum CA 19-9	1.007	1.005-1.010	0.000

HR: Hazard ratio; CI: Confidence interval; CEA: Carcinoembryonic antigen; CA 19-9: Carbohydrate antigen 19-9.

Table 4. Multivariate Cox regression analysis of smoking and serum carcinoembryonic antigen as prognostic factors for cumulative survival in connective tissue disease-associated interstitial lung disease patients

Variable	HR	95% CI	*p*
Smoking	1.034	0.999-1.070	0.059
Serum CEA	1.685	1.405-2.021	0.000

HR: Hazard ratio; CI: Confidence interval; CEA: Carcinoembryonic antigen.

Table 5. Multivariate Cox regression analysis of smoking and serum carbohydrate antigen 19-9 as prognostic factors for cumulative survival in connective tissue disease-associated interstitial lung disease patients

Variable	HR	95% CI	*p*
Smoking	1.019	0.980-1.060	0.336
Serum CA 19-9	1.007	1.005-1.010	0.000

HR: Hazard ratio; CI: Confidence interval; CEA 19-9: Carcinoembryonic antigen 19-9.

level group of 0.487, and the power value was 84.9%. In univariate Cox regression analysis of CEA and CA 19-9 levels as prognostic factors for cumulative survival in CTD-ILD patients, the powers were 89.3% and 75.6%, respectively.

DISCUSSION

In this study, we demonstrated elevated serum CEA and CA 19-9 levels in CTD-ILD patients. In previous studies, elevation of serum CEA and CA 19-9 was also found in CTD.[8,18] In RA patients, CEA can be extracted from rheumatoid synovial membranes.[7] Whether lesions of CTD on other sites of body can express CEA and CA 19-9 is still unknown. Fortunately, recent studies showed that pulmonary tissue could release CEA in IPF. In a study of bronchoalveolar lavage fluid and serum measurement of CEA in 26 patients with histologically confirmed IPF, the CEA/albumin ratio of bronchoalveolar lavage fluid was significantly higher than that of serum, suggesting that CEA in bronchoalveolar lavage fluid is derived from pulmonary tissue.[19] In another study, a lung biopsy specimen from a patient with IPF demonstrated strong staining for CEA in metaplastic epithelium lining the honeycombed cysts and respiratory bronchioles.[9] In our study, fibrosis score on HRCT had obvious correlations with serum CEA and CA 19-9 levels, while ground-glass score on HRCT had very weak correlations. These findings indicate that pulmonary fibrosis tissue but not GGO of lung may be the origin of CEA. In patients with pulmonary fibrosis, there is evidence of an increased incidence of lung cancer;[20-22] however, this does not mean that elevated tumor markers standard for malignant change. Furthermore, there are mechanistic and biological similarities between pulmonary fibrosis and malignant disorders.[23] During the process of pulmonary fibrosis, epithelial cells undergo a series of changes: morphological changes of epithelial cells;[24] cytoskeletal changes; expression changes of adhesion molecules; and formation of abnormal phenotypes of epithelial cell between type II and type I cells. Finally, abnormal epithelial proliferation and metaplastic change are formed.[25] In severe pulmonary fibrosis, cuboidal pneumocytes are the predominant source of epithelial renewal, and these cells are the most likely source of tumor markers release.[9,26] Nonetheless, exact mechanism of these changes and tumor markers release and elevation are still unknown and requiring further studies.

Our results suggest that serum CEA and CA 19-9 levels are related with disease severity of CTD-ILD. This is in accordance with previous research on IPF. In Fahim's study,[9] totally 41 IPF patients were included and final research results suggested a correlation between serum CEA and pulmonary physiological derangement and fibrosis scores. Traditionally, severity of ILD was measured by involvement score on HRCT, OI and pulmonary function.[27] However, pulmonary function and HRCT examinations are unsuitable for severe patients. OI can be influenced by lung infection, heart failure and other factors. In these conditions, serum CEA and CA 19-9 levels can be used as available markers to evaluate disease severity of CTD-ILD.

In recent years, survival in ILD has been improved because of the proper use of medications.[28,29] It is also demonstrated that the presence of CTD modifies survival in patients with pulmonary fibrosis.[30] Nevertheless, it is still difficult to evaluate the prognosis of CTD-ILD. In survival analysis, we found that cases with high serum levels of CA 19-9 and CEA had significantly poorer prognosis. In multivariate Cox regression analysis, serum CEA was finally demonstrated as the only parameter that was obviously associated with one-year survival of CTD-ILD cases. In fact, previous research also demonstrated the prognostic role of serum CEA in RA patients and its correlation with other prognostic factors such as serum rheumatoid factor levels.[17] For serum CA 19-9, a larger cohort is needed to observe its significance as a prognostic factor. In our study, we provided one-year survival analysis due to the high rate of loss to follow-up in the second year

of research, while five-year survival is much more significant for prognosis evaluation. On the whole, serum CEA can be a cost-effective and convenient predictor for short-term survival of CTD-ILD. To our knowledge, this is the first demonstration of serum CEA as a prognostic factor for CTD-ILD patients.

Our study has some limitations. First, we were unable to clarify the cause for the elevation of serum CA 19-9 and CEA in CTD-ILD patients and whether it was caused by CTD, ILD or the interaction between CTD and ILD? Second, in order to evaluate the effect of interaction between CTD and ILD on the elevated levels of serum CEA and CA 19-9, we should carry out a clinical study to compare serum CEA and CA 19-9 levels among CTD-ILD patients, ILD patients without CTD, and CTD patients without ILD. These issues may constitute a base for future researches on related mechanisms.

In conclusion, our results suggest that serum CEA and CA 19-9 levels are elevated in CTD-ILD patients, and they correlate with disease severity. Furthermore, we demonstrated that serum CEA is a significant and independent predictor of one-year survival of CTD-ILD patients. For further research, we need a larger cohort and follow-up for at least five years. If available, successive detections of serum CEA and CA 19-9 are favorable to evaluate their correlations with CTD-ILD progression.

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REFERENCES

1. Antoniou KM, Margaritopoulos G, Economidou F, Siafakas NM. Pivotal clinical dilemmas in collagen vascular diseases associated with interstitial lung involvement. Eur Respir J 2009;33:882-96.
2. Khanna D, Mittoo S, Aggarwal R, Proudman SM, Dalbeth N, Matteson EL, et al. Connective Tissue Disease-associated Interstitial Lung Diseases (CTD-ILD) - Report from OMERACT CTD-ILD Working Group. J Rheumatol 2015;42:2168-71.
3. Margaritopoulos GA, Romagnoli M, Poletti V, Siafakas NM, Wells AU, Antoniou KM. Recent advances in the pathogenesis and clinical evaluation of pulmonary fibrosis. Eur Respir Rev 2012;21:48-56.
4. Kazerooni EA, Martinez FJ, Flint A, Jamadar DA, Gross BH, Spizarny DL, et al. Thin-section CT obtained at 10-mm increments versus limited three-level thin-section CT for idiopathic pulmonary fibrosis: correlation with pathologic scoring. AJR Am J Roentgenol 1997;169:977-83.
5. Lee JY, Lee DC, Lee JW. Serum carcinoembryonic antigen is associated with non-alcoholic fatty liver disease in healthy Korean non-smokers. Clin Chem Lab Med 2013;51:1499-504.
6. Levy C, Lymp J, Angulo P, Gores GJ, Larusso N, Lindor KD. The value of serum CA 19-9 in predicting cholangiocarcinomas in patients with primary sclerosing cholangitis. Dig Dis Sci 2005;50:1734-40.
7. Unger A, Panayi GS, Lessof MH. Carcinoembryonic antigen in rheumatic diseases. Rheumatol Rehabil 1975;14:19-24.
8. Bergamaschi S, Morato E, Bazzo M, Neves F, Fialho S, Castro G, et al. Tumor markers are elevated in patients with rheumatoid arthritis and do not indicate presence of cancer. Int J Rheum Dis 2012;15:179-82.
9. Fahim A, Crooks MG, Wilmot R, Campbell AP, Morice AH, Hart SP. Serum carcinoembryonic antigen correlates with severity of idiopathic pulmonary fibrosis. Respirology 2012;17:1247-52.
10. Demedts M, Costabel U. ATS/ERS international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. Eur Respir J 2002;19:794-6.
11. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
12. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Arthritis Rheum 1980;23:581-90.
13. Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). N Engl J Med 1975;292:344-7.
14. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271-7.
15. Sharp GC, Irvin WS, Tan EM, Gould RG, Holman HR. Mixed connective tissue disease--an apparently

distinct rheumatic disease syndrome associated with a specific antibody to an extractable nuclear antigen (ENA). Am J Med 1972;52:148-59.
16. Vitali C, Bombardieri S, Moutsopoulos HM, Coll J, Gerli R, Hatron PY, et al. Assessment of the European classification criteria for Sjögren's syndrome in a series of clinically defined cases: results of a prospective multicentre study. The European Study Group on Diagnostic Criteria for Sjögren's Syndrome. Ann Rheum Dis 1996;55:116-21.
17. Dupont WD, Plummer WD Jr. Power and sample size calculations. A review and computer program. Control Clin Trials 1990;11:116-28.
18. Szekanecz E, Sándor Z, Antal-Szalmás P, Soós L, Lakos G, Besenyei T, et al. Increased production of the soluble tumor-associated antigens CA19-9, CA125, and CA15-3 in rheumatoid arthritis: potential adhesion molecules in synovial inflammation? Ann N Y Acad Sci 2007;1108:359-71.
19. Takahashi H, Nukiwa T, Matsuoka R, Danbara T, Natori H, Arai T, et al. Carcinoembryonic antigen in bronchoalveolar lavage fluid in patients with idiopathic pulmonary fibrosis. Jpn J Med 1985;24:236-43.
20. Kreuter M, Ehlers-Tenenbaum S, Schaaf M, Oltmanns U, Palmowski K, Hoffmann H, et al. Treatment and outcome of lung cancer in idiopathic interstitial pneumonias. Sarcoidosis Vasc Diffuse Lung Dis 2015;31:266-74.
21. Khan KA, Kennedy MP, Moore E, Crush L, Prendeville S, Maher MM, et al. Radiological characteristics, histological features and clinical outcomes of lung cancer patients with coexistent idiopathic pulmonary fibrosis. Lung 2015;193:71-7.
22. Turner-Warwick M, Lebowitz M, Burrows B, Johnson A. Cryptogenic fibrosing alveolitis and lung cancer. Thorax 1980;35:496-9.
23. Vancheri C, Failla M, Crimi N, Raghu G. Idiopathic pulmonary fibrosis: a disease with similarities and links to cancer biology. Eur Respir J 2010;35:496-504.
24. Chilosi M, Poletti V, Murer B, Lestani M, Cancellieri A, Montagna L, et al. Abnormal re-epithelialization and lung remodeling in idiopathic pulmonary fibrosis: the role of deltaN-p63. Lab Invest 2002;82:1335-45.
25. Haddad R, Massaro D. Idiopathic diffuse interstitial pulmonary fibrosis (fibrosing alveolitis), atypical epithelial proliferation and lung cancer. Am J Med 1968;45:211-9.
26. Kawanami O, Ferrans VJ, Crystal RG. Structure of alveolar epithelial cells in patients with fibrotic lung disorders. Lab Invest 1982;46:39-53.
27. Edis EÇ, Hatipoğlu ON, Pamuk ÖN, Eraslan RM, Aktöz M, Tuncel SA. Effectiveness of thoracic ultrasonography in the evaluation of the severity of pulmonary involvement in patients with systemic sclerosis. Arch Rheumatol 2016;31:364-70.
28. Koo BS, Hong S, Kim YJ, Kim YG, Lee CK, Yoo B. Mortality in patients with rheumatoid arthritis-associated interstitial lung disease treated with an anti-tumor necrosis factor agent. Korean J Intern Med 2015;30:104-9.
29. Migita K, Arai T, Jiuchi Y, Izumi Y, Iwanaga N, Kawahara C, et al. Predictors of mortality in patients with interstitial lung disease treated with corticosteroids: results from a cohort study. Medicine (Baltimore) 2014;93:175.
30. Navaratnam V, Ali N, Smith CJ, McKeever T, Fogarty A, Hubbard RB. Does the presence of connective tissue disease modify survival in patients with pulmonary fibrosis? Respir Med 2011;105:1925-30.