Relationship between Clinical Characteristics and Serum Tumor Markers in Connective Tissue Disease with Interstitial Lung Disease as the Initial Manifestation

Keywords
Clinical Characteristics, Interstitial Lung Disease, Connective Tissue Disease, Serum Tumor Markers

Abstract

Introduction
Interstitial lung disease (ILD) is a common complication of connective tissue disease (CTD), which seriously affects the prognosis of patients. The abnormal expression of tumor markers in non-neoplastic diseases may be related to the occurrence and development of CTD-ILD. This study aimed to explore the detailed clinical characteristics of CTD-ILD, and to analyze its internal correlation with serum tumor markers.

Material and methods
The clinical data of 128 patients with CTD-ILD were retrospectively analyzed. 79 of ILD patients without CTD were enrolled as the non-combined group. Clinical data included imaging manifestations, laboratory indexes and tumor markers such as carbohydrate antigen (CA) 125, CA153, carcinoembryonic antigen (CEA), neuron-specific enolase (NSE) and squamous cell carcinoma (SCC) antigen were collected. ROC curve was used to analyze the clinical value.

Results
The proportion of clinical manifestations such as arthralgia, rash, Raynaud's phenomenon, dry mouth and dry eyes in the combined group was higher than the non-combined group ($P < 0.05$). The serum albumin and total protein levels in the combined group were lower than the non-combined group ($P < 0.001$). The levels of CA125, CA153, CEA, SCC and NSE in the combined group were higher than the non-combined group ($P < 0.001$). The AUC of combined detection of each index was 0.917, with a sensitivity of 97.47% and a specificity of 76.56%.

Conclusions
The main clinical manifestations for CTD-ILD patients were arthralgia, rash, Raynaud's phenomenon, dry mouth and eyes. The combined detection of tumor markers had a high evaluation value.

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Running title: Serum tumor markers in connective tissue disease.

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Keywords: Interstitial Lung Disease; Connective Tissue Disease; Clinical Characteristics; Serum Tumor Markers.

Abbreviation table

Abbreviation	Full name
AFP	alpha-fetoprotein
AUC	area under the curve
CA125	carbohydrate antigen 125
CA153	carbohydrate antigen 153
CEA	carcinoembryonic antigen
CTD	connective tissue disease
CYFRA21-1	cytokeratin-19 fragment
ILD	interstitial lung disease
NSE	neuron-specific enolase
ROC	receiver operator characteristic curve
SCC	squamous cell carcinoma antigen

Introduction

Connective tissue diseases (CTD) is a disease characterized by autoimmune-mediated damage caused by circulating autoantibodies, which can affect multiple parts such as skeleton, muscle, joints and blood vessels [1]. CTD includes rheumatoid arthritis, dermatomyositis, Sjögren's syndrome, undifferentiated CTD, ANCA-associated vasculitis and systemic sclerosis, and is characterized by chronic inflammation of blood vessels and connective tissue [2-3]. Interstitial lung disease (ILD) is a common complication of CTD and one of the main causes of death [4]. CTD-ILD presents a wide range of clinical manifestations, symptoms can progress from asymptomatic state to severe dyspnea, and the range of involvement can extend from single organ respiratory system to multiple organs.

With the progress of the disease, patients may have lung parenchyma destruction and progressive decline in lung function, which eventually threaten life [5]. Early and accurate diagnosis of CTD-ILD is essential to improve the prognosis of patients. However, due to the complexity and diversity of its clinical manifestations, clinicians face many challenges in early diagnosis, determination of treatment timing, and selection of appropriate therapeutic drugs [6]. Traditional diagnostic methods, such as clinical manifestations, imaging and laboratory tests, often lack specificity or sensitivity [7]. In recent years, with the development of biomarker research, serum tumor markers have gradually attracted attention as a class of important biomarkers. The ideal biomarkers should be non-invasive or minimally invasive, and should have high accuracy for disease prediction [8]. In the past, tumor markers are mainly used as important tools for the screening and diagnosis of common cancers, such as gastric cancer, breast cancer, and liver cancer.

In recent years, serum tumor markers have been revealed to have a certain relationship with the occurrence and development of CTD-ILD. Abnormal expressions of these markers may be related to the inflammatory response, tissue damage and repair process caused by CTD, however, the specific mechanism is not fully understood [9]. Carbohydrate antigen (CA) 125 (CA125) is widely distributed in human mesothelial cells, while CA153 is mainly secreted by human epithelial cells. Both of them are broad-spectrum tumor markers, whose serum levels are significantly increased in patients with various malignant tumors such as ovarian endometrioma [10] and breast cancer [11]. Squamous cell carcinoma antigen (SCC) is a widely used and reliable

marker of squamous cell carcinoma. ILD has been reported to have a higher risk of squamous cell lung cancer and a poor prognosis [12]. As key enzyme in glycolysis, neuron-specific enolase (NSE) catalyzes the conversion of glycerol 2-phosphate to phosphoenyl pyruvate, and has neuroprotective effects. Nervous system injury causes an increase in blood NSE levels, which can help damaged neurons survive., As an autoimmune disease, CTD affects the central nervous system. ILD can cause insufficient cerebral blood oxygen supply, and in severe cases, induce pulmonary encephalopathy, which aggravates the nervous system damage and leads to further increase in blood NSE [13]. Carcinoembryonic antigen (CEA) is extracted from colon cancer and embryonic tissues, and used to be regarded as a specific marker for early diagnosis of colorectal cancer. Later, clinical studies find that it can also be elevated in tuberculosis, CTD and nephrotic syndrome, so the specificity is poor [14].

Based on this, this study innovatively applied serum tumor markers to the diagnosis of CTD-ILD, in order to explore their expression characteristics in the disease and their relationship with clinical characteristics. Through this novel research perspective, we expect to be able to provide new biomarkers and diagnostic methods for early diagnosis of CTD-ILD, thereby improving the quality of life and prognosis of patients.

1 Materials and Methods

1.1 General Data

The clinical data of 207 patients with ILD diagnosed and treated in our hospital from January 2020 to December 2023 were retrospectively analyzed. The inclusion process was shown in Figure 1. According to whether the patients were complicated with CTD, they were divided into combined group (128 cases) and non-combined group (79 cases). In the combined group, there were 56 males and 72 females with the average age was (59.46±8.93) years (28-79 years). The average course of disease was (2.69±1.29) years, and the body mass index (BMI) was (21.41±2.88) kg/m^2. In the non-combined group, there were 32 males and 47 females with the average age was (60.24±11.85) years (31-76 years). The average course of disease was (2.35±1.13) years, and the body mass index (BMI) was (22.02±3.46) kg/m^2. There was no significant difference in general clinical data between the two groups ($P > 0.05$). This study was approved by the ethics committee of our hospital (approval number: YXLL-2024-043).

Among the 128 patients with CTD-ILD, there were 52 rheumatoid arthritis patients with ILD,

5 dermatomyositis patients with ILD, 41 Sjögren's syndrome patients with ILD, 19 undifferentiated CTD patients with ILD, 8 ANCA-associated vasculitis patients with ILD, and 3 systemic sclerosis patients with ILD.

Inclusion criteria: (1) Patients with coexisting ILD met the guidelines for the diagnosis and treatment of interstitial pulmonary fibrosis [15]; (2) The diagnosis was confirmed by imaging examination; (3) Patients with clinical manifestations such as cough, chest tightness, pulmonary rales, and shortness of breath; (4) Patients with complete clinical data. Exclusion criteria: (1) Patients with coronary heart disease, diabetes and autoimmune diseases; (2) Patients with pulmonary hypoplasia or other pulmonary diseases; (3) Patients with malignancies and infectious diseases; (4) Patients with liver and kidney dysfunction.

The contents of the general information section were based on the retrospective analysis of ILD patients diagnosed and treated in our hospital from January 2020 to December 2023, thus, the data were true and reliable. Patients' grouping, inclusion criteria and exclusion criteria were strictly set to ensure the scientific validity of the study.

1.2 Clinical Data Collection

Clinical manifestations: The clinical manifestations included rash, arthralgia, dry mouth and eyes, chest pain, fatigue, fever, cough, shortness of breath after activity, Raynaud's phenomenon, and oral ulcers.

Imaging manifestations: The imaging findings were detected by imaging examinations and analyzed by experts, including ground-glass opacity, reticular opacities, fiber stripe opacities, and other imaging characteristics.

Laboratory indexes: Laboratory indexes included albumin, C-reactive protein, total protein, globulin, and white blood cell count.

Serum tumor markers: Serum tumor markers included alpha-fetoprotein (AFP), CA125, CA153, SCC, CEA, NSE, and cytokeratin 19 fragment (CYFRA21-1).

1.3 Statistics [16]

SPSS v23.0 software was used to analyze the data. Measurement data were expressed as mean ± standard deviation ($\bar{x}\pm s$), and t-tests was used for comparison between groups. Count data were presented as (cases, %), and analyzed by chi-square tests between groups. ROC curve was used to analyze the clinical value of single and combined serum tumor markers for the

diagnosis of CTD-ILD. $P < 0.05$ was considered statistically significant.

2 Results

2.1 Analysis of the clinical characteristics of the two groups

In a detailed comparison of the clinical characteristics of the combined group and the non-combined group , there were significant differences in the manifestations of arthralgia, rash, Raynaud's phenomenon, dry mouth and dry eyes between the two groups . In the combined group, there were 54 patients with arthralgia, 26 patients with rash, 59 patients with Raynaud's phenomenon, and 32 patients with dry mouth and dry eyes, accounting for 42.19%, 20.31%, 46.09% and 25.00%, respectively. In the non-combined group, there were 12 patients with arthralgia, 5 patients with rash, 14 patients with Raynaud's phenomenon, and 10 patients with dry mouth and dry eyes, accounting for 15.19%, 6.33%, 17.72% and 12.66%, respectively. Statistical analysis showed that the differences in these symptoms between the two groups were statistically significant ($P < 0.05$), indicating that ILD-CTD patients with were more likely to have these clinical manifestations. There were no significant difference in age, BMI, course of disease, gender, oral ulcer, fatigue, fever, cough, shortness of breath after activity, chest pain, ground-glass opacities, reticular opacities, and fibrotic stripe opacities between the two groups ($P > 0.05$, Table 1).

2.2 Comparative analysis of laboratory indicator levels between the two groups

There were no significant differences in the levels of C-reactive protein, globulin, and white blood cell count between the combined group and the non-combined group ($P > 0.05$). The levels of serum albumin and total protein in the combined group were significantly lower than those in the uncombined group. The serum albumin in the combined group was (32.79±6.79) g/L, and that in the non-combined group was (37.37±4.02) g/L ($t = 5.433$, $P < 0.001$, Table 2). The total protein in the combined group was (62.53±8.85) g/L, and that in the non-combined group was (68.58±7.79) g/L ($t = 4.997$, $P < 0.001$, Table 2). This may be related to the chronic wasting disease characteristics of CTD patients, leading to decreased nutritional status of the body.

2.3 Analysis of serum tumor marker levels between the two groups

The serum tumor markers in the combined group were CA125 (39.85±4.23 U/mL), CA153 (31.53±8.92 U/mL), CEA (6.96±1.28 ng/mL), SCC (2.18±0.75 ng/mL), and NSE (18.19±2.31 ng/mL), which were significantly higher than those in the non-combined group ($P < 0.001$, Table

3). The abnormal elevation of these tumor markers may be related to the inflammatory response and fibrotic process of CTD-ILD.

2.4 ROC curve analysis

The CTD-ILD diagnosis was used as the state variable and the levels of each serum tumor marker were used as the test variable, to draw the ROC curve. The ROC curve of each tumor marker was produced by the software calculation. The AUC of CA125, CA153, CEA, SCC and NSE were 0.783, 0.778, 0.856, 0.667 and 0.785, respectively. The sensitivity of CA153 and SCC was high, both reaching 97.47%, which meant that these two indicators could detect most patients with CTD-ILD. However, it should be noted that their specificity is relatively low, and there may be many false positive results. The specificity of CA125 was 94.53%, indicating that it could better exclude non-CTD-ILD patients. The P values of each index were less than 0.05, indicating that the diagnostic value of these tumor markers was statistically significant. In addition, the combined detection and analysis of each tumor marker were performed to further improve the diagnostic efficiency. The five indicators of CA125, CA153, CEA, SCC and NSE were combined by software, and the ROC curve of combined detection was calculated. The AUC of combined detection was 0.917, the sensitivity was 97.47%, the specificity was 76.56%, and the Youden index was 0.740 (Table 4 and Figure 2). Compared with single detection, the AUC of combined detection was significantly improved, indicating that the combined detection has higher accuracy and clinical value in the diagnosis of CTD-ILD, and can provide more reliable diagnostic basis for clinicians.

3 Discussion

ILD is one of the most common and clinically important manifestations of CTD, and also one of the main causes of death in patients with CTD. Genetic risk, epigenetic changes, and regulatory immune diseases are all risk factors for the pathogenesis of CTD-ILD [17-18]. CTD-ILD can present with varying degree of inflammation to fibrosis and a wide range of clinical manifestations, making it difficult for clinicians to make early diagnose and make decisionson treatment options, the best time to intervene, and the appropriateness of therapeutic drugs. In this study, the clinical data of 128 patients with CTD-ILD were retrospectively analyzed, and compared with 79 ILD patients without CTD. This study hasexplored the clinical characteristics of CTD-ILD and its relationship with serum tumor markers. The following will analyze the research results from

multiple aspects such as disease mechanism and clinical diagnosis.

The pathogenesis of CTD-ILD is complex, involving multiple aspects such as genetics, epigenetic changes and immune regulation diseases [19]. This study found that patients with CTD-ILD showed more obvious clinical manifestations such as arthralgia, rash, Raynaud's phenomenon, dry mouth and dry eyes than ILD patients without CTD, which might be related to systemic inflammatory response and autoimmune injury caused by CTD. In addition, the significant reduction of serum albumin and total protein levels in the combined group suggested that CTD, as a chronic wasting disease, might lead to a decrease in the nutritional status of the body and further affect the prognosis of patients. However, ILD is sometimes the first manifestation of CTD, and about 70% of patients may not have any respiratory symptoms, only chest HRCT abnormalities. The study has confirmed that respiratory symptoms are the most common symptoms of CTD-ILD [20]. However, it is easy to attribute the symptoms of fatigue and dyspnea on exertion to old age, anemia or other non-rheumatic diseases related cardiac or pulmonary complications, which ultimately delays the diagnosis of CTD-ILD [21]. Therefore, for patients confirmed or suspected CTD, it is necessary to be alert to the manifestations of CTD in the lung, and corresponding diagnosis and treatment should be carried out as soon as possible. In addition, CTD is a chronic wasting disease, which can not only lead to metabolic abnormalities, but also reduce protein intake through the accumulation of lesions in the gastrointestinal tract, and increase protein excretion by involving the kidneys[22]. Intravenous immunoglobulin can be used as an adjunct to the treatment of CTD. Pulse immunoglobulin therapy is an effective option in the salvage treatment of CTD patients with severe or progressive disease after conventional immunosuppressive therapy [23]. Albumin and total protein are indicators reflecting the nutritional status of the body. CTD-ILD should be considered when ILD patients have arthralgia, rash, oral ulcers, and reduced levels of albumin and total protein.

In terms of disease mechanism, serum tumor markers (CA125, CA153, CEA, SCC and NSE) found in this study were significantly increased in patients with CTD-ILD. In patients with CTD-ILD, the elevated level of these markers may indicate active disease. Inflammatory activity plays a key role in the pathogenesis of CTD-ILD, and elevated markers may reflect the degree and extent of inflammation [24]. Although these tumor markers are usually associated with malignancies, the recent study has shown that they may also be abnormally expressed in

non-neoplastic diseases such as ILD [25]. The increase of these markers may be related to the inflammatory response, tissue damage and repair process caused by CTD, but the specific mechanisms need further research to clarify. CA125, CA153, and CEA all belong to glycoproteins. Relevant studies have found that the increase of serum CA125, CA153 and CEA levels may be closely related to the severity of ILD, and can be used as biomarkers related to its pathology, which is helpful for the detection of the disease [26-27]. In addition, the study found that the serum levels of CA125, CA153, NSE and CEA in patients with Sjogren's syndrome complicated with ILD were significantly higher than those in non-ILD patients [28]. The previous study has shown that the CA125 expression in idiopathic nonspecific ILD and idiopathic pulmonary fibrosis is significantly higher than that in CTD-ILD patients [29]. This is different from the results of the present study and may be due to bias due to the small number of patients in this study. In addition, due to the differences in environmental factors, the possibility of large differences in the expression of tumor markers in CTD-ILD patients in different regions cannot be excluded. The reason for the increase of serum tumor markers is still unclear.

Early diagnosis is very important for the treatment and prognosis of CTD-ILD patients. However, due to the diverse clinical manifestations of CTD-ILD and the possible lack of specific symptoms, early diagnosis can be challenging. ROC curve analysis showed that the combined detection of CA125, CA153, CEA, SCC and NSE had a high clinical evaluation value for CTD-ILD. Through the auxiliary diagnosis analysis of combined detection, it was found that the sensitivity and specificity of combined detection of multiple tumor markers were 97.47% and 76.56%, respectively. It indicates that the combined detection had high clinical application value in the diagnosis of CTD-ILD. Through the detection and analysis of serum tumor markers, clinicians can better judge whether a patient has CTD and provide a basis for treatment. In addition, the dynamic changes of serum tumor markers can also be used to evaluate the therapeutic effectand predict disease progression, so as to optimize clinical diagnosis and treatment programs and improve the quality of life of patients . This finding provides a new strategy for the clinical diagnosis of CTD-ILD. Traditional diagnostic methods mainly rely on clinical manifestations, imaging and laboratory tests, but these methods often lack specificity or sensitivity. As a non-invasive and simple method, the detection of serum tumor markers can make up for the shortcomings of traditional diagnostic methods to a certain extent. Combined detection

of multiple tumor markers can improve the diagnostic accuracy of CTD-ILD and provide strong support for the early treatment of patients.

4 Conclusion

In conclusion, CTD patients with ILD as the initial manifestation mainly present with clinical symptoms such as arthralgia, rash, Raynaud's phenomenon, dry mouth and dry eyes. The levels of serum albumin and total protein are significantly lower, while the levels of serum tumor markers (such as CA125, CA153, CEA, SCC and NSE) are significantly higher. The combined detection of tumor markers has a high clinical evaluation value for CTD-ILD, which provides new biomarkers and diagnostic methods for early diagnosis of CTD-ILD. This finding not only enriches our understanding of the pathophysiological mechanism of CTD-ILD, but also provides new ideas and basis for clinical diagnosis and treatment.

Innovation points

1. Analysis of the clinical characteristics of patients with multiple types of CTD-ILD: This study is the first to systematically analyze the clinical manifestations of a variety of CTD-ILD, such as rheumatoid arthritis, dermatomyositis, Sjogren's syndrome, undifferentiated connective tissue disease, ANCA-associated vasculitis and systemic sclerosis, and reveal the specific clinical characteristics of different CTD-ILD.

2. The diagnostic value of serum tumor markers in CTD-ILD: Through retrospective analysis, this study for the first time explores the expression levels of serum tumor markers (CA125, CA153, CEA, SCC and NSE) in CTD-ILD and their relationship with the disease. It is found that these markers are significantly increased in patients with CTD-ILD, which provides new biomarkers for the early diagnosis of CTD-ILD.

3. Clinical application of combined detection of multiple tumor markers: In this study, ROC curve is used to analyze the value of single and multiple serum tumor markers in the diagnosis of CTD-ILD. It is found that the combined detection of multiple tumor markers has higher sensitivity and specificity, which provides a new strategy for the clinical diagnosis of CTD-ILD.

Limitations

Although this study has made some progress in revealing the clinical characteristics of CTD-ILD and the relationship between serum tumor markers, there are still some limitations. Firstly, this study is a retrospective study, and the influence of selection bias and recall bias cannot

be completely excluded. Secondly, the study sample size is relatively small and is from a single center, potentially limiting the generalizability of the findings. Additionally, this study do not have a long-term follow-up of the patients and cannot assess the dynamic changes of serum tumor markers in disease progression and prognosis. In view of these limitations, prospective, multi-center and large-sample design can be considered for future studies to improve the reliability and generalizability of the findings. At the same time, patients can be followed up for a long time to evaluate the dynamic changes of serum tumor markers in disease progression and prognosis, so as to provide a more comprehensive basis for clinical treatment and management of CTD-ILD.

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Not application.

Funding

Not application.

Data availability statement

The data analyzed and used during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of our Hospital.

Competing interests

The authors declare that there is no conflict of interests.

290 **References**

291 [1] Kondeti RD, Venkatesh K, Murthy D, Kameti S, Devi KS, Chandrika KV. A Study of Clinical
292 Manifestations and their Association with Antinuclear Antibodies in Various Autoimmune
293 Connective Tissue Disorders[J]. Indian J Dermatol. 2023 Jul-Aug;68(4):486.
294 [2] Kuryliszyn-Moskal A, Hryniewicz A, Bagiński N, Moskal-Jasińska D, Dzięcioł-Anikiej Z,
295 Dzięcioł J. Foot static disturbances and clinical features in overweight patients with rheumatoid
296 arthritis[J]. Arch Med Sci. 2020 May 28;19(6):1774-1780.
297 [3] Hernández Muñiz S, Olivera Serrano MJ, Jiménez Heffernan JA, Valenzuela C, Caballero
298 Sánchez-Robles P. Interstitial disease associated with connective tissue disease and vasculitis[J].
299 Radiologia (Engl Ed). 2022,64 (Suppl):250-264.
300 [4] Vacchi C, Sebastiani M, Cassone G, Cerri S, Della Casa G, Salvarani C, et al. Therapeutic
301 Options for the Treatment of Interstitial Lung Disease Related to Connective Tissue Diseases. A
302 Narrative Review[J]. J Clin Med. 2020 Feb 3;9(2):407.
303 [5] Cerro C.G, Parimon T. Understanding Interstitial Lung Diseases Associated with Connective
304 Tissue Disease (CTD-ILD): Genetics, Cellular Pathophysiology, and Biologic Drivers[J]. Int J
305 Mol Sci. 2023,24(3):2405.
306 [6] Aparicio IJ, Lee JS. Connective Tissue Disease-Associated Interstitial Lung Diseases:
307 Unresolved Issues[J]. Semin Respir Crit Care Med. 2016 Jun;37(3):468-476.
308 [7] Mlika M, Braham E, Mezni F. Interstitial lung disease: Elementary lesions and diagnosis[J].
309 Semin Diagn Pathol. 2018 Sep;35(5):288-296.
310 [8] Pugashetti JV, Khanna D, Kazerooni EA, Oldham J. Clinically Relevant Biomarkers in
311 Connective Tissue Disease-Associated Interstitial Lung Disease[J]. Immunol Allergy Clin North
312 Am[J]. 2023 ,43(2):411-433.
313 [9] Lim CH, Tseng CW, Lin CT, Huang WN, Chen YH, Chen Y, et al. The clinical application of
314 tumor markers in the screening of malignancies and interstitial lung disease of
315 dermatomyositis/polymyositis patients: A retrospective study[J]. SAGE Open Med. 2018,6(1):1-8.
316 [10] Gao K, Lian W, Zhao R, Xiong J. Characteristics of patients with stage III and IV ovarian
317 endometriomas and trends in postoperative anti-Mullerian hormone changes[J]. Arch Med Sci.
318 2023 May 24;19(3):800-804.
319 [11] Lian M, Zhang C, Zhang D, Chen P, Yang H, Yang Y, et al. The association of five

preoperative serum tumor markers and pathological features in patients with breast cancer[J]. J Clin Lab Anal. 2019 Jun;33(5):e22875.

[12] Hata A, Nakajima T, Matsusaka K, ukuyo M, Nakayama M, Morimoto J, et al. Genetic alterations in squamous cell lung cancer associated with idiopathic pulmonary fibrosis[J]. Int J Cancer. 2021 ,148(12):3008-3018.

[13] Yan P, Han Y, Tong A, Liu J, Wang X, Liu C. Prognostic value of neuron-specific enolase in patients with advanced and metastatic non-neuroendocrine non-small cell lung cancer. Biosci Rep[J]. 2021;41(8):BSR20210866.

[14] Gonzalez-Exposito R, Semiannikova M, Griffiths B, Khan K, Barber LJ, Woolston A, et al. CEA expression heterogeneity and plasticity confer resistance to the CEA-targeting bispecific immunotherapy antibody cibisatamab (CEA-TCB) in patient-derived colorectal cancer organoids[J]. J Immunother Cancer. 2019 Apr 15;7(1):101.

[15] Robalo-Cordeiro C, Morais A. Translating Idiopathic pulmonary fibrosis guidelines into clinical practice[J]. Pulmonology. 2021 Jan-Feb;27(1):7-13.

[16] Mansournia MA, Collins GS, Nielsen RO, Nazemipour M, Jewell NP, Altman DG, et al. A CHecklist for statistical Assessment of Medical Papers (the CHAMP statement): explanation and elaboration[J]. Br J Sports Med. 2021 Sep;55(18):1009-1017.

[17] Oliveira RP, Ribeiro R, Melo L, Pereira CAC. Connective tissue disease-associated interstitial lung disease[J]. Pulmonology. 2022 ,28(2):113-118.

[18] Joy GM, Arbiv OA, Wong CK, Lok SD, Adderley NA, Dobosz KM, et al. Prevalence, imaging patterns and risk factors of interstitial lung disease in connective tissue disease: a systematic review and meta-analysis[J]. Eur Respir Rev. 2023 Mar 8;32(167):220210.

[19] Stanel SC, Callum J, Rivera-Ortega P. Genetic and environmental factors in interstitial lung diseases: current and future perspectives on early diagnosis of high-risk cohorts[J]. Front Med (Lausanne). 2023 Aug 3;10:1232655.

[20] Spagnolo P, Distler O, Ryerson CJ, Tzouvelekis A, Lee JS, Bonella F, et al. Mechanisms of progressive fibrosis in connective tissue disease (CTD)-associated interstitial lung diseases (ILDs) [J]. Ann Rheum Dis. 2021 ,80(2):143-150.

[21] Watanabe K, Horita N, Hara Y, Kobayashi N, Kaneko T. Clinical features of asthma with connective tissue diseases[J]. Clin Respir J. 2023 Apr;17(4):303-310.

[22] Luppi F, Sebastiani M, Silva M, Sverzellati N, Cavazza A, Salvarani C, et al. Interstitial lung disease in Sjögren's syndrome: a clinical review[J]. Clin Exp Rheumatol. 2020 Jul-Aug;38 Suppl 126(4):291-300.

[23] Zhu W, Li Y, Zhao J, Wang Y, Li Y, Wang Y. The mechanism of triptolide in the treatment of connective tissue disease-related interstitial lung disease based on network pharmacology and molecular docking[J]. Ann Med. 2022,54(1):541-552.

[24] Wang Y, Sun D, Song Y, Du X, Wu N, Ye Q. Assessment of tumor biomarkers for prognosis in interstitial lung disease associated with connective tissue disease: a prospective study[J]. J Thorac Dis. 2024 Nov 30;16(11):7383-7396.

[25] Bao Y, Zhang W, Shi D, Bai W, He D, Wang D. Correlation Between Serum Tumor Marker Levels and Connective Tissue Disease-Related Interstitial Lung Disease[J]. Int J Gen Med. 2021 ,14(1):2553-2560.

[26] Wei F, Zhang X, Yang S, Geng J, Xie B, Ren Y, et al. Evaluation of the Clinical Value of KL-6 and Tumor Markers in Primary Sjögren's Syndrome Complicated with Interstitial Lung Disease[J]. J Clin Med. 2023 Jul 27;12(15):4926.

[27] Kwon BS, Kim ES, Lim SY, Song MJ, Kim YW, Kim HJ, et al. The significance of elevated tumor markers among patients with interstitial lung diseases[J]. Sci Rep. 2022 Oct 6;12(1):16702.

[28] Zheng M, Lou A, Zhang H, Zhu S, Yang M, Lai W. Serum KL-6, CA19-9, CA125 and CEA are Diagnostic Biomarkers for Rheumatoid Arthritis-Associated Interstitial Lung Disease in the Chinese Population[J]. Rheumatol Ther. 2021,8(1):517-527.

[29] Shi L, Han XL, Guo HX, Wang J, Tang YP, Gao C, et al. Increases in tumor markers are associated with primary Sjögren's syndrome-associated interstitial lung disease[J]. Ther Adv Chronic Dis. 2020,11(1):1-9.

Tables

Table (1): Analysis of clinical characteristics in two groups of patients (Cases, %)

Groups	Combined group (n=128)	Non-combined group (n=79)	χ^2	P
Age (years)	59.46±8.93	60.24±11.85	0.538	0.591

Gender (%)			0.210	0.647
Female	72 (56.25)	47 (59.49)		
Male	56 (43.75)	32 (40.51)		
BMI (kg/m^2)	21.41±2.88	22.02±3.46	1.369	0.172
Duration of disease (years)	2.69±1.29	2.35±1.13	1.930	0.055
Joint pain (%)	54 (42.19)	12 (15.19)	16.394	<0.001
Rash (%)	26 (20.31)	5 (6.33)	7.502	0.006
Oral ulcers (%)	12 (9.38)	7 (8.86)	0.016	0.901
Fatigue (%)	25 (19.53)	12 (15.19)	0.627	0.428
Raynaud's phenomenon (%)	59 (46.09)	14 (17.72)	17.225	<0.001
Fever (%)	12 (9.38)	4 (5.06)	1.273	0.259
Dry mouth and eyes (%)	32 (25.00)	10 (12.66)	4.601	0.032
Cough (%)	63 (49.22)	42 (53.16)	0.304	0.581
Shortness of breath after qctivity (%)	55 (42.97)	39 (49.37)	0.807	0.369
Chest pain (%)	3 (2.34)	2 (2.53)	0.007	0.932
Ground-glass pacity (%)	38 (29.69)	17 (21.52)	1.671	0.196
Reticular opacity (%)	41 (32.03)	19 (24.05)	1.512	0.219
Fibrotic striations (%)	46 (35.94)	25 (31.65)	0.399	0.527

376

377 Table (2): Comparative analysis of laboratory indicator levels between the two groups ($\bar{x}\pm s$)

Groups	Cases	Serum albumin (g/L)	C-reactive protein (mg/L)	Total protein (g/L)	Globulin (g/L)	White blood cell count (×10^9/L)
Combined group	128	32.79±6.79	8.36±2.37	62.53±8.85	31.37±7.68	7.14±1.07
Non-combined group	79	37.37±4.02	7.74±2.74	68.58±7.79	30.39±5.73	6.88±1.31
t		5.433	1.722	4.997	0.978	1.557

P	<0.001	0.087	<0.001	0.329	0.121	

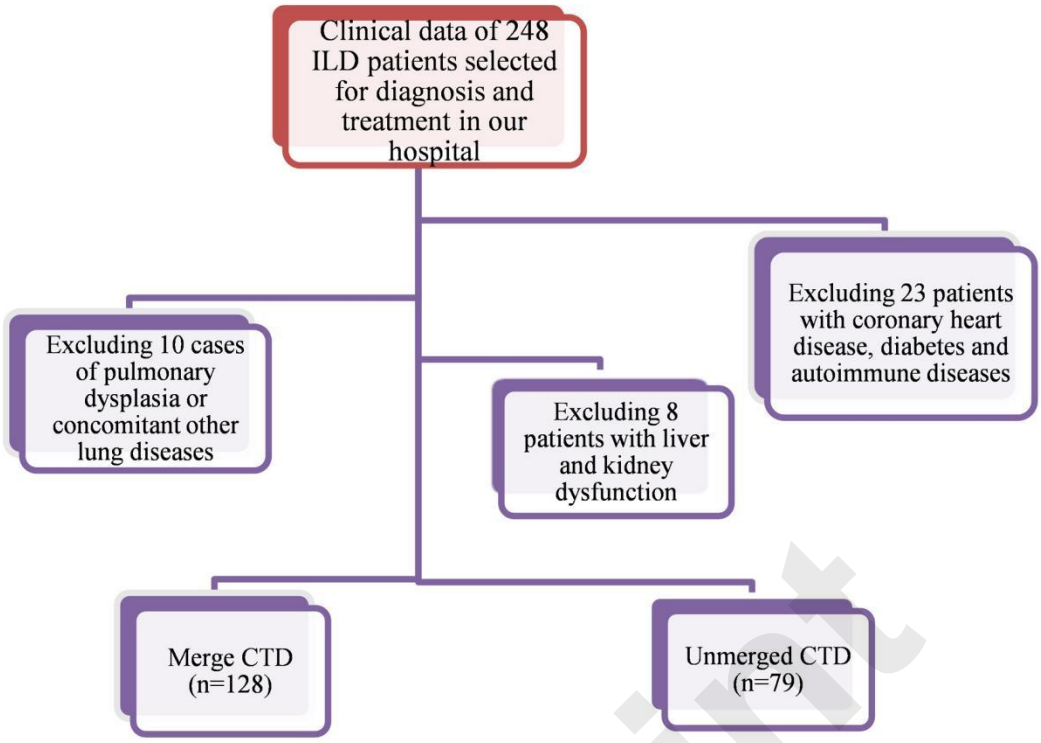
Table (3): Analysis of serum tumor marker levels in two groups of patients ($\bar{x}\pm s$).

Groups	Cases	AFP (ng/mL)	CA125 (U/mL)	CA153 (U/mL)	CEA (ng/mL)	SCC (ng/mL)	NSE (ng/mL)	CYFRA21-1 (μg/mL)
Combined group	128	20.18±4.47	39.85±4.23	31.53±8.92	6.96±1.28	2.18±0.75	18.19±2.31	4.78±1.10
Non-combined group	79	19.27±4.63	25.46±7.19	10.18±2.79	2.79±1.08	0.82±0.25	12.29±2.86	4.56±1.01
t		1.404	18.136	20.643	24.131	15.579	16.277	1.442
P		0.162	<0.001	<0.001	<0.001	<0.001	<0.001	0.151

Table (4): Assisted diagnostic value of serum tumor markers for CTD-IRD

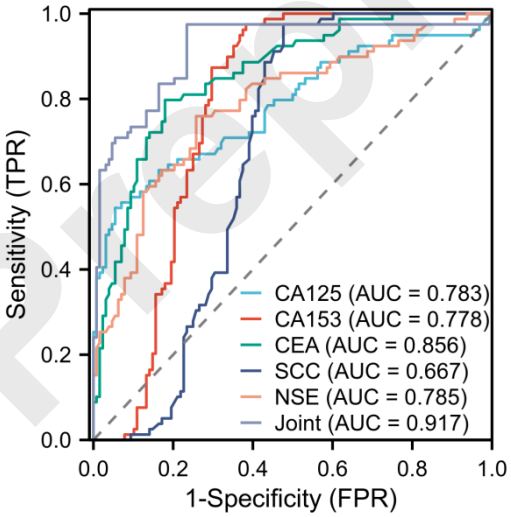
Indicators	AUC	Sensitivity	Specificity	Cutoff Value	P *Value*	Youden's Index	95%*CI*
CA125	0.783	54.43%	94.53%	30.51 U/mL	<0.05	0.490	0.715-0.852
CA153	0.778	97.47%	61.72%	19.17 U/mL	<0.05	0.592	0.713-0.843
CEA	0.856	79.75%	82.03%	4.28 ng/mL	<0.05	0.618	0.805-0.908
SCC	0.667	97.47%	52.34%	1.75 ng/mL	<0.05	0.498	0.593-0.741
NSE	0.785	75.95%	74.22%	15.69 ng/mL	<0.05	0.502	0.719-0.851
Combined detection	0.917	97.47%	76.56%	—	<0.05	0.740	0.874-0.960

Figures



384

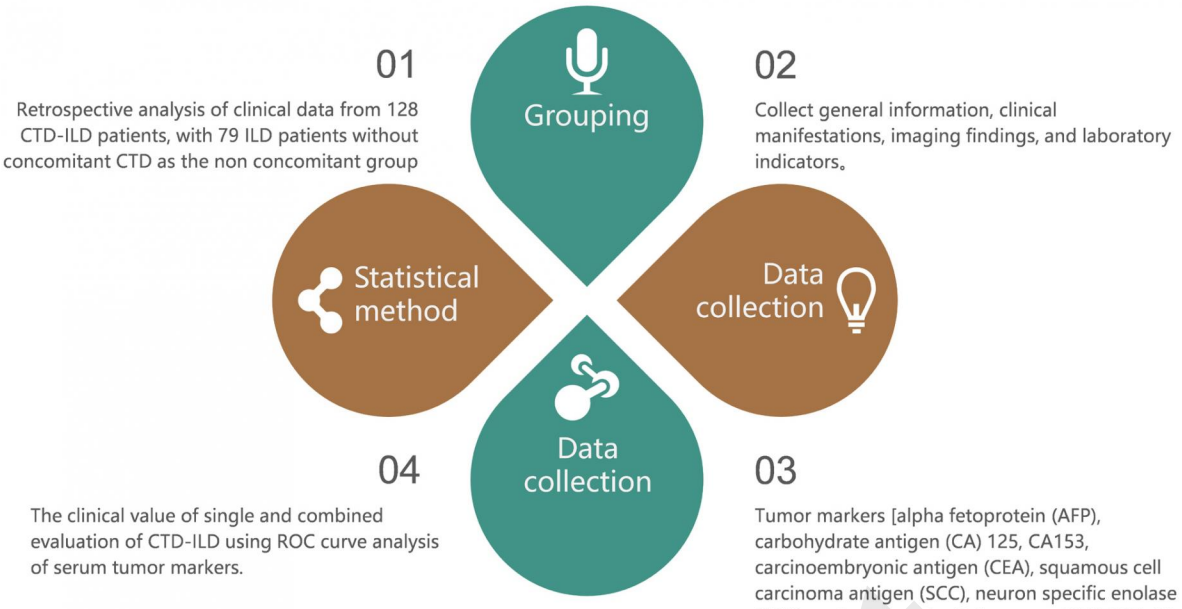
385 **Fig. (1): The process of general data selection.**



386

387 **Fig. (2): ROC curve analysis of the assisted diagnostic value of serum tumor markers for**

388 **CTD-ILD.**


01
Retrospective analysis of clinical data from 128 CTD-ILD patients, with 79 ILD patients without concomitant CTD as the non concomitant group
Grouping
02
Collect general information, clinical manifestations, imaging findings, and laboratory indicators。
Statistical method
Data collection
Data collection
04
The clinical value of single and combined evaluation of CTD-ILD using ROC curve analysis of serum tumor markers.
03
Tumor markers [alpha fetoprotein (AFP), carbohydrate antigen (CA) 125, CA153, carcinoembryonic antigen (CEA), squamous cell carcinoma antigen (SCC), neuron specific enolase (NSE), and cytokeratin 19 fragment (CYFRA21-1)]