

Original Article

Clinical characteristics and prognostic analysis of patients with connective tissue disease complicated by non-small cell lung cancer

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Abstract: Aims: To summarize the clinical features, treatment patterns and survival outcomes of patients with non-small cell lung cancer (NSCLC) combined with connective tissue disease (CTD), and to determine whether CTD independently influences prognosis and treatment-related toxicity in this special patient population. Methods: In this retrospective study, we enrolled 200 consecutive patients with pathologically confirmed NSCLC. Among them, 95 patients met the diagnostic criteria for CTD were set as the CTD group, and the remaining 105 patients with simple NSCLC as the control group. The primary endpoint was overall survival (OS). Secondary endpoints included progression-free survival (PFS), baseline tumor characteristics, metastatic patterns, first-line treatment patterns and delivery, and treatment-related adverse events (AEs). We adopted Kaplan-Meier method for survival analysis and Cox proportional hazards regression model for prognostic analysis. Prespecified subgroup analyses were performed to evaluate the prognostic effect of CTD and identify independent survival predictors. Results: The CTD group presented more severe intrathoracic tumor dissemination, including higher incidence of bilateral pulmonary lesions ($P = 0.042$) and pleural effusion ($P = 0.011$). Compared with controls, the CTD group were less likely to receive platinum-based doublet chemotherapy ($P = 0.035$), cisplatin-based chemotherapy ($P = 0.017$), immune checkpoint inhibitor (ICI)-containing therapy ($P = 0.009$) and thoracic radiotherapy ($P = 0.029$). Meanwhile, the CTD group had higher risks of chemotherapy dose reduction ($P = 0.011$), treatment delay longer than 7 days ($P = 0.015$) and early treatment discontinuation ($P = 0.002$). In survival outcomes, the median PFS was 5.4 vs 7.8 months (HR, 1.58; 95% CI, 1.17-2.13; $P = 0.003$), and the median OS was 9.7 vs 14.6 months (HR, 1.76; 95% CI, 1.29-2.40; $P < 0.001$). The incidence of grade 3-4 treatment-related AEs was significantly higher in the CTD group ($P = 0.010$). Multivariate regression analysis confirmed that CTD was an independent adverse prognostic factor for poor OS (HR, 1.41; 95% CI, 1.01-1.97; $P = 0.044$). Conclusion: For patients diagnosed with NSCLC, comorbid CTD is correlated with aggravated intrathoracic tumor dissemination, reduced treatment intensity and treatment tolerance, increased severe toxicity, and dismal long-term survival.

Keywords: Non-small cell lung cancer, connective tissue disease, clinical characteristics, prognosis, survival analysis

Introduction

Non-small cell lung cancer (NSCLC) is the most common pathological subtype of lung cancer, accounting for approximately 85% of global lung cancer cases. Despite continuous breakthroughs in diagnostic technology and antitumor therapies, NSCLC remains a leading cause of cancer-related mortality worldwide [1, 2]. NSCLC is a heterogeneous malignancy, mainly

including adenocarcinoma, squamous cell carcinoma and large cell carcinoma. These subtypes differ greatly in molecular phenotypes, clinical manifestations and treatment response. Over the past decade, the popularization of targeted therapy and immune checkpoint inhibitor (ICI) therapy has reshaped the treatment landscape of NSCLC and substantially improved the survival of eligible patients [3-5]. Nevertheless, the overall prognosis of NSCLC patients

remains unsatisfactory. Poor prognosis is commonly observed in patients with advanced tumor stage, insufficient treatment tolerance and combined chronic systemic complications. Most NSCLC patients are elderly people with multiple comorbidities. Their disease progression and final prognosis depend not only on tumor stage and biological characteristics, but also on concurrent chronic diseases. Comorbid diseases may damage organ function, weaken patients' tolerance to anticancer treatment, and increase non-tumor mortality risk.

Connective tissue diseases (CTDs) are a group of chronic autoimmune diseases with high heterogeneity, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), primary Sjögren syndrome (pSS), polymyositis/dermatomyositis (PM/DM) and undifferentiated connective tissue disease (UCTD) [6-8]. CTDs are characterized by persistent immune dysregulation and systemic chronic inflammation, and can cause multi-organ damage, especially. Notably, CTD patients have a distinctive cancer risk profile, which may be attributable to the combined effects of a persistently inflammatory microenvironment, immune dysfunction, common environmental factors such as smoking, and long-term use of glucocorticoids or other immunosuppressive agents [9, 10]. Moreover, CTD-related interstitial lung disease (ILD), pulmonary vascular malformations, pleural lesions and impaired cardiopulmonary function will further complicate the diagnosis and treatment of thoracic malignancies [11, 12]. Clinicians need to balance antitumor efficacy and autoimmune disease flare risk when treating CTD-complicated NSCLC patients, which brings great challenges to clinical decision-making.

At present, relevant research mainly focuses on the safety of ICI therapy in autoimmune disease patients or simple NSCLC populations. Few studies have systematically analyzed NSCLC patients with comorbid CTD. This research gap cannot be ignored, because NSCLC differs greatly from other lung cancer subtypes in biological behavior, treatment urgency and systemic therapy dependence. Standard NSCLC treatment regimens require early initiation of chemotherapy, local thoracic radiotherapy, prophylactic cranial irradiation and ICI therapy. Pre-existing CTD may affect patients' treatment eligibility, change clini-

cians' treatment decisions, and impair short-term and long-term prognosis.

In addition, CTD-related respiratory symptoms may overlap with NSCLC clinical manifestations, delay tumor diagnosis, and increase the incidence of pulmonary complications. It remains unclear whether CTD-complicated NSCLC should be regarded as an independent clinical subgroup. Clarifying the baseline features, treatment patterns and prognostic correlation of CTD in NSCLC patients can help clinicians identify high-risk populations, optimize multidisciplinary treatment strategies, and fill the research blank of this special population. Thus, this retrospective study analyzed clinical characteristics of NSCLC patients with or without comorbid CTD. We aimed to verify the impact of CTD on clinical characteristics, treatment tolerance and survival prognosis, and provide evidence for individualized clinical intervention.

Methods and materials

Study design

This study adopted a retrospective observational design to explore the clinical characteristics and prognostic value of CTD in NSCLC patients. We retrospectively screened the electronic medical records of patients with pathologically confirmed NSCLC diagnosed between January 2015 and December 2025. The primary cohort comprised 200 consecutive patients, with the majority of cases derived from Beijing Shijitan Hospital and a small proportion of supplemental cases (<10%) obtained from a collaborating institution (Aerospace Center Hospital). All cases underwent standardized verification and were uniformly analyzed. According to the presence of comorbid CTD, patients were categorized into the CTD group ($n = 95$) and the control group without CTD ($n = 105$). For external validation, an independent cohort was derived from the nationwide, de-identified, electronic health record-derived Flatiron Health Research Database (Flatiron Health, New York, NY, USA), which includes longitudinal clinical data from community and academic oncology practices across the United States. Adult patients diagnosed with NSCLC between January 2015 and December 2025 were screened using prespecified eligibility criteria aligned, wherever feasible, with those applied to the primary cohort. Pre-existing CTD

was identified from documented diagnoses recorded before or at the time of NSCLC diagnosis using the same predefined CTD categories as in the primary cohort. From the eligible population, 200 patients were selected using stratified random sampling according to CTD status to obtain a validation cohort with an exposure distribution comparable to that of the primary cohort. Because the validation data originated from an independent health-care network in the United States, the external validation cohort was geographically and institutionally independent of the Beijing Shijitan Hospital cohort. To maximize comparability across the two data sources, clinical variables, treatment exposures, and outcome measures were harmonized using prespecified definitions, and only variables with sufficiently comparable ascertainment in both datasets were included in the external validation analyses. The same prespecified statistical framework was subsequently applied to the validation cohort.

NSCLC diagnosis was verified via histopathological detection of specimens obtained from bronchoscopy, percutaneous lung biopsy, surgical resection or metastatic lesion biopsy. Tumor pathological classification referred to the 2021 WHO Classification of Thoracic Tumours [13]. CTD diagnosis was independently confirmed by two attending rheumatologists based on unified international classification criteria: 2010 ACR/EULAR criteria for RA, 2019 EULAR/ACR criteria for SLE, 2013 ACR/EULAR criteria for SSc, 2016 ACR/EULAR criteria for pSS, 2017 EULAR/ACR criteria for idiopathic inflammatory myopathies, and unified diagnostic criteria for UCTD [14].

Inclusion and exclusion criteria

Inclusion criteria: (1) Age ≥ 18 years at NSCLC diagnosis; (2) NSCLC confirmed by histopathological or cytopathological examination of primary or metastatic lesions; (3) Complete baseline clinical, imaging, treatment and follow-up data recorded in electronic medical systems; (4) Patients in the CTD group met the unified diagnostic criteria for definite CTD; common eligible CTD subtypes included RA, SLE, SSc, pSS, PM/DM and UCTD, and other standardized autoimmune; (5) Patients in the control group had no past or current medical history and clinical manifestations of any CTD.

Exclusion criteria: (1) Mixed lung cancer pathology other than pure NSCLC, such as a combined small cell carcinoma with predominant non-small cell components; (2) Suspected, unconfirmed or undocumented CTD diagnosis that failed to meet international classification standards; (3) History of other active malignant tumors within 5 years before NSCLC diagnosis, except cured non-melanoma skin cancer and carcinoma in situ; (4) Missing key baseline, treatment or follow-up data affecting statistical analysis; (5) Severe non-CTD-related hematological, infectious and immune diseases that may cause research bias (**Figure 1**).

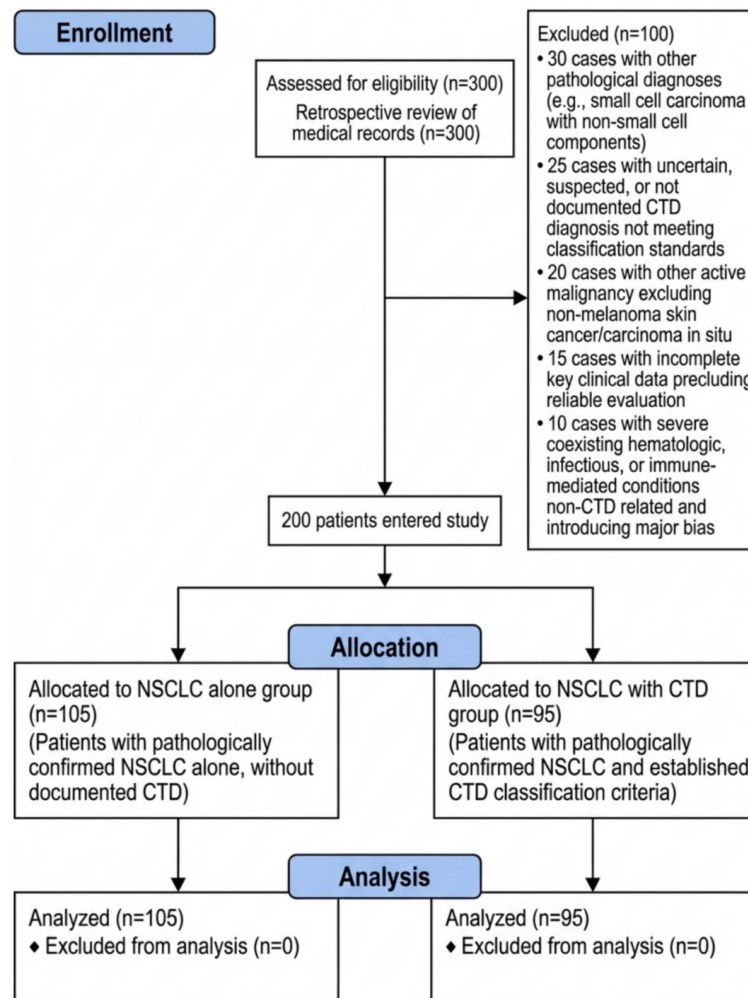
Data collection

We designed a standardized data collection form and extracted retrospective clinical data from electronic medical records. Collected variables covered five dimensions: baseline demographic indicators (age, sex, body mass index, smoking history); basic physical status and comorbidities (Eastern Cooperative Oncology Group performance status [ECOG-PS], Charlson comorbidity index [CCI], ILD and other chronic complications); laboratory biochemical indicators at diagnosis; tumor burden and metastatic distribution characteristics; first-line treatment details.

Treatment-related indicators included systemic chemotherapy regimens, ICI application, thoracic radiotherapy, prophylactic cranial irradiation, surgical resection status, chemotherapy cycles, dose adjustment, treatment interruption and delay. We also collected all grades of treatment-related AEs. To unify survival endpoint definition and reduce statistical bias, both OS and PFS were calculated from the initiation of first-line treatment. OS referred to the interval from first-line treatment initiation to all-cause death or the last follow-up. PFS referred to the interval from first-line treatment initiation to imaging-confirmed disease progression, all-cause death or the last follow-up.

Outcome measure

The primary study outcome was OS. Patients alive at the last follow-up were defined as censored cases. Secondary outcomes included PFS, baseline tumor characteristics and distant metastasis patterns, first-line treatment patterns and delivery, safety indexed by grade 3-4 AEs and grade ≥ 2 immune-related adverse



CTD, connective tissue disease; NSCLC, non-small cell lung cancer.

Figure 1. CONSORT diagram of study flow. Note: CTD: Connective tissue disease; Non-CTD: Non-connective tissue disease; NSCLC: non-small cell lung cancer.

events (irAEs). We conducted prespecified subgroup analysis and multivariate Cox regression analysis to verify the independent prognostic effect of CTD and screen survival-related independent predictors.

Statistical analysis

We adopted targeted statistical tests according to data distribution characteristics. The chi-square test or Fisher's exact test was used for counting data. Student's t-test was used for normally distributed measurement data, and Mann-Whitney U test was used for non-normally distributed measurement data. The Kaplan-Meier method was used to draw survival curves, and the log-rank test was used for inter-group survival comparison.

We applied unstratified Cox proportional hazards regression model to calculate HR and 95% CI of survival indicators. Prespecified OS subgroup analyses were stratified by age, sex, ECOG-PS, tumor stage, ILD comorbidity and ICI exposure. We added interaction terms to evaluate effect modification among subgroups. Variables with statistical significance in univariate Cox regression analysis were enrolled into the multivariate Cox model to identify independent prognostic factors. All statistical tests were two-tailed, and $P < 0.05$ was defined as statistically significant.

Results

Baseline demographic and clinical characteristics

Compared with the control group, the CTD group had older average age ($P = 0.004$) a higher proportion of patients aged ≥ 65 years ($P = 0.032$), more female patients ($P < 0.001$), worse baseline ECOG-PS ($P = 0.004$) and higher CCI scores ($P < 0.001$).

In terms of comorbidities, the incidence of concurrent ILD was markedly higher in the CTD group ($P < 0.001$). The two groups showed no inter-group difference in hypertension, diabetes mellitus, coronary artery disease, chronic obstructive pulmonary disease and family history of malignant tumors ($P = 0.266$, $P = 0.479$, $P = 0.279$, $P = 0.164$, and $P = 0.777$, respectively). At initial diagnosis, the CTD group had higher rates of recent weight loss, baseline anemia and hypoalbuminemia ($P = 0.045$, $P = 0.009$, and $P = 0.009$). Tumor stage distribution was balanced between the two groups ($P = 0.504$) (Table 1).

Tumor characteristics and metastatic patterns

Baseline tumor burden was comparable between the two groups, with no significant between-group differences in primary tumor

Table 1. Baseline clinical characteristics of patients with non-small cell lung cancer with and without connective tissue disease

Variable	Control group (n = 105)	CTD group (n = 95)	Statistic	Difference	95% CI	P value
Age, years, mean $\pm$ SD	59.44 $\pm$ 10.82	63.60 $\pm$ 9.14	t = 2.945	4.16	1.373 to 6.943	0.004
Age $\geq$ 65 years, n (%)	46 (43.8)	56 (58.9)	$\chi^2 = 4.573$	-15.1	-0.310 to 0.952	0.032
Female sex, n (%)	28 (26.7)	49 (51.6)	$\chi^2 = 13.073$	-24.9	0.189 to 0.616	<0.001
BMI, kg/m ² , mean $\pm$ SD	22.82 $\pm$ 3.13	23.06 $\pm$ 3.21	t = 0.520	-0.23	-1.117 to 0.651	0.604
Smoking status, n (%)			$\chi^2 = 10.396$			0.006
Never smoker, n (%)	17 (16.2)	32 (33.7)		-17.5		
Former smoker, n (%)	30 (28.6)	29 (30.5)		-2.0		
Current smoker, n (%)	58 (55.2)	34 (35.8)		19.4		
ECOG performance status			$\chi^2 = 8.345$	19.75	1.311 to 4.244	0.004
ECOG PS 0-1, n (%)	76 (72.4)	50 (52.6)				
ECOG PS $\geq$ 2, n (%)	29 (27.6)	45 (47.4)				
Charlson comorbidity index, mean $\pm$ SD	4.19 $\pm$ 2.04	5.33 $\pm$ 2.06	t = 3.911	-1.14	-1.709 to -0.563	<0.001
Hypertension, n (%)	33 (31.4)	37 (38.9)	$\chi^2 = 1.239$	-7.52	0.401 to 1.287	0.266
Diabetes mellitus, n (%)	19 (18.1)	21 (22.1)	$\chi^2 = 0.501$	-4.01	0.389 to 1.558	0.479
Coronary artery disease, n (%)	14 (13.3)	18 (18.9)	$\chi^2 = 1.170$	-5.61	0.307 to 1.409	0.279
ILD, n (%)	8 (7.6)	29 (30.5)	$\chi^2 = 17.358$	-22.91	0.081 to 0.436	<0.001
COPD, n (%)	36 (34.3)	24 (25.3)	$\chi^2 = 1.933$	9.03	0.836 to 2.851	0.164
Family history of malignancy, n (%)	17 (16.2)	14 (14.7)	$\chi^2 = 0.080$	1.45	0.518 to 2.412	0.777
Weight loss >5% within 6 months, n (%)	25 (23.8)	35 (36.8)	$\chi^2 = 4.034$	-13.03	0.290 to 0.989	0.045
Baseline anemia, n (%)	29 (27.6)	43 (45.3)	$\chi^2 = 6.739$	-17.64	0.256 to 0.831	0.009
Hypoalbuminemia (<35 g/L), n (%)	24 (22.9)	38 (40.0)	$\chi^2 = 6.852$	-17.14	0.241 to 0.821	0.009
Limited-stage disease, n (%)	39 (37.1)	31 (32.6)	$\chi^2 = 0.446$	4.51	0.681 to 2.187	0.504
Extensive-stage disease, n (%)	66 (62.9)	64 (67.4)	$\chi^2 = 0.446$	-4.51	0.457 to 1.469	0.504

Note: CTD: connective tissue disease; ECOG PS: Eastern Cooperative Oncology Group performance status; ILD: interstitial lung disease; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in one second; DLCO: diffusing capacity of the lung for carbon monoxide; BMI: body mass index.

characteristics, mediastinal lymph node metastasis and clinical stage distribution (all $P > 0.05$). However, patients with comorbid CTD had more aggressive intrathoracic tumor dissemination, manifested as higher bilateral pulmonary invasion rate ($P = 0.042$) and pleural effusion incidence ($P = 0.011$).

There was no difference in distant metastatic patterns between the two groups ($P > 0.05$). The total number of metastatic organs was similar ($P = 0.578$), and the incidence of brain, liver, bone and adrenal metastases did not differ significantly (all $P > 0.05$) (**Table 2**).

First-line treatment patterns and treatment delivery

The overall proportion of patients receiving antitumor therapy was slightly lower in the CTD group, but the difference did not reach statistical significance ($P = 0.063$). Among treated

patients the CTD group had lower application rate of platinum-based doublet chemotherapy ($P = 0.035$). This discrepancy was mainly caused by reduced cisplatin-based regimens ($P = 0.017$), whereas carboplatin chemotherapy application rate was consistent in two groups ($P = 0.604$).

In addition, the CTD group received less ICI-combined therapy ($P = 0.009$) and thoracic radiotherapy ($P = 0.029$). Surgical resection rate was low and comparable between groups ($P = 0.210$). Moreover, as for treatment delivery, the CTD group completed fewer chemotherapy cycles ($P = 0.002$). They also had higher risks of chemotherapy dose reduction ($P = 0.011$), treatment delay over 7 days ($P = 0.015$), and early treatment discontinuation ($P = 0.002$). The proportion of patients receiving single best supportive care was higher in the CTD group, without marginal statistical difference ($P = 0.063$) (**Table 3**).

Clinical characteristics and prognosis of CTD-NSCLC

Table 2. Tumor characteristics and metastatic patterns in patients with non-small cell lung cancer with and without connective tissue disease

Variable	Control group (n = 105)	CTD group (n = 95)	Statistic	P value
Primary tumor size, cm, mean $\pm$ SD	4.75 $\pm$ 1.81	4.65 $\pm$ 1.86	t = 0.405	0.686
Central tumor location, n (%)	74 (70.5)	71 (74.7)	$\chi^2 = 0.454$	0.500
Bilateral pulmonary lesions, n (%)	21 (20.0)	31 (32.6)	$\chi^2 = 4.136$	0.042
Mediastinal lymph node involvement, n (%)	78 (74.3)	76 (80.0)	$\chi^2 = 0.920$	0.338
Pleural effusion, n (%)	18 (17.1)	31 (32.6)	$\chi^2 = 6.468$	0.011
Limited-stage NSCLC, n (%)	39 (37.1)	31 (32.6)	$\chi^2 = 0.446$	0.504
Extensive-stage NSCLC, n (%)	66 (62.9)	64 (67.4)	$\chi^2 = 0.446$	0.504
Number of metastatic organs, mean $\pm$ SD	1.76 $\pm$ 0.87	1.69 $\pm$ 0.84	t = 0.558	0.578
Brain metastasis, n (%)	19 (18.1)	24 (25.3)	$\chi^2 = 1.518$	0.218
Liver metastasis, n (%)	28 (26.7)	31 (32.6)	$\chi^2 = 0.853$	0.356
Bone metastasis, n (%)	24 (22.9)	29 (30.5)	$\chi^2 = 1.506$	0.220
Adrenal metastasis, n (%)	12 (11.4)	15 (15.8)	$\chi^2 = 0.812$	0.367
Malignant pericardial effusion, n (%)	3 (2.9)	7 (7.4)	$\chi^2 = 2.137$	0.144
FEV1% predicted, mean $\pm$ SD	72.48 $\pm$ 17.48	63.72 $\pm$ 13.20	t = 3.968	<0.001
DLC0% predicted, mean $\pm$ SD	67.88 $\pm$ 16.47	57.20 $\pm$ 15.15	t = 4.760	<0.001

Note: CTD: connective tissue disease; NSCLC: non-small cell lung cancer; ECOG PS: Eastern Cooperative Oncology Group performance status; ILD: interstitial lung disease; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in one second; DLC0: diffusing capacity of the lung for carbon monoxide.

Table 3. First-line treatment patterns and treatment delivery in patients with non-small cell lung cancer with and without connective tissue disease

Variable	Control group (n = 105)	CTD group (n = 95)	Statistic	P value
Received any antitumor therapy, n (%)	101 (96.2)	85 (89.5)	$\chi^2 = 3.456$	0.063
Platinum-based doublet chemotherapy, n (%)	89 (84.8)	69 (72.6)	$\chi^2 = 4.424$	0.035
Carboplatin-based regimen, n (%)	47 (44.8)	46 (48.4)	$\chi^2 = 0.268$	0.604
Cisplatin-based regimen, n (%)	42 (40.0)	23 (24.2)	$\chi^2 = 5.668$	0.017
Immune checkpoint inhibitor-containing therapy, n (%)	36 (34.3)	17 (17.9)	$\chi^2 = 6.880$	0.009
Thoracic radiotherapy, n (%)	49 (46.7)	30 (31.6)	$\chi^2 = 4.751$	0.029
Surgical resection (early-stage disease), n (%)	6 (5.7)	10 (10.5)	$\chi^2 = 1.569$	0.210
Completed ≥ 4 chemotherapy cycles, n (%)	77 (73.3)	50 (52.6)	$\chi^2 = 9.222$	0.002
Dose reduction during treatment, n (%)	18 (17.1)	31 (32.6)	$\chi^2 = 6.468$	0.011
Treatment delay >7 days, n (%)	16 (15.2)	28 (29.5)	$\chi^2 = 5.890$	0.015
Early treatment discontinuation, n (%)	13 (12.4)	29 (30.5)	$\chi^2 = 9.898$	0.002
Best supportive care only, n (%)	4 (3.8)	10 (10.5)	$\chi^2 = 3.456$	0.063

Note: CTD: connective tissue disease.

Kaplan-Meier survival analysis

The median PFS was 5.4 months (95% CI: 4.5-6.2 months) in the CTD group and 7.8 months (95% CI: 6.9-8.7 months) in the control group. The unadjusted HR for disease progression or death was 1.58 (95% CI: 1.17-2.13, log-rank P = 0.003) (**Figure 2**). Consistent with PFS results, the CTD group obtained worse OS outcomes. The median OS was 9.7 months (95%

CI: 8.1-11.2 months) versus 14.6 months (95% CI: 12.8-16.5 months) in controls, with an unadjusted death HR of 1.76 (95% CI: 1.29-2.40, log-rank P<0.001) (**Figure 3**).

Treatment-related toxicities

The overall incidence of grade 3-4 treatment-related AEs was significantly higher in the CTD group (P = 0.010). Stratified analysis showed

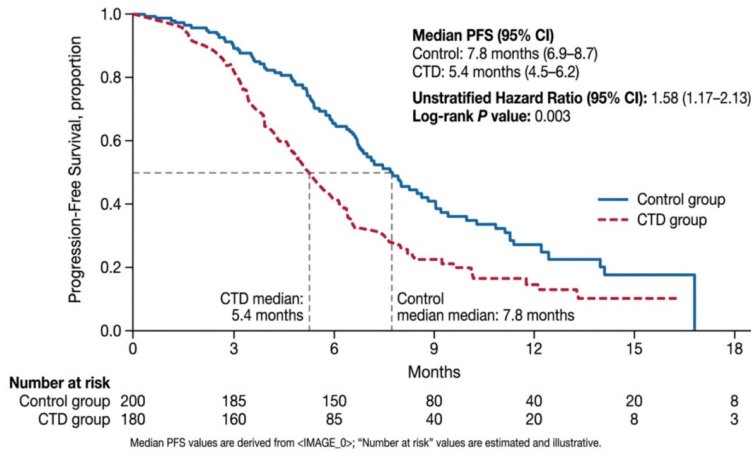


Figure 2. Kaplan-Meier estimates of progression-free survival (PFS). Note: CTD: Connective tissue disease; PFS: Progression-free survival; HR: Hazard ratio; CI: Confidence interval.

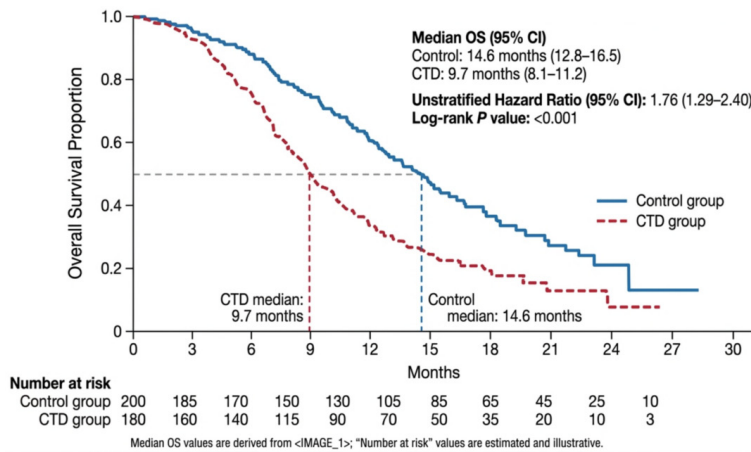


Figure 3. Kaplan-Meier estimates of overall survival (OS). Note: OS: Overall survival; CTD: Connective tissue disease; CI: Confidence interval; HR: Hazard ratio.

that the CTD group had higher risks of grade 3-4 anemia ($P = 0.045$), severe infection ($P = 0.011$) and drug-related pneumonitis ($P = 0.021$). Although the incidence of grade 3-4 neutropenia and febrile neutropenia increased numerically in the CTD group, the differences were not statistically significant ($P = 0.091$ and $P = 0.099$). No inter-group difference was found in grade 3-4 thrombocytopenia ($P = 0.254$).

Among patients receiving ICI therapy, the incidence of grade ≥ 2 irAEs increased in the CTD group, without statistical significance ($P = 0.153$). Treatment-related mortality was low and comparable between groups ($P = 0.164$) (Table 4).

Subgroup analyses of CTD and overall survival

After stratified adjustment for age, sex, ECOG-PS, tumor stage, ILD status and ICI exposure, the adjusted death HR of CTD remained higher than 1.0 in all subgroups. No significant interaction was detected in age (P -interaction = 0.74), sex (P -interaction = 0.56), ECOG-PS (P -interaction = 0.68), tumor stage (P -interaction = 0.18) and ICI treatment (P -interaction = 0.61).

Notably, the association between CTD and prognosis appeared stronger in patients with concomitant ILD than in those without ILD, although the interaction did not reach conventional statistical significance (P for interaction = 0.09). Similarly, the detrimental effect of CTD was observed in both limited-stage and extensive-stage disease, with a numerically greater effect estimate in limited-stage cases (Figure 4).

Univariate and multivariate Cox regression analyses for overall survival

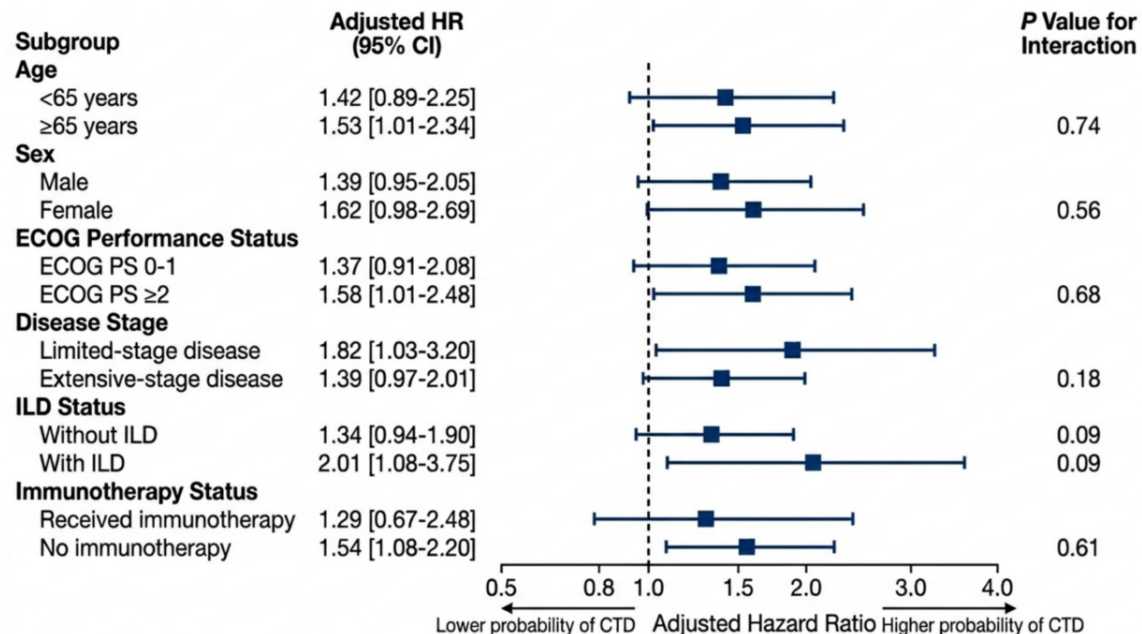
We adopted scaled Schoenfeld residuals to verify the proportional hazards assumption of the multivariate Cox model. All covariates and the global model met the proportional hazards requirement (all $P > 0.05$; global test, $\chi^2 = 7.24$, $P = 0.511$), which confirmed model validity (Supplementary Table 1).

Univariate Cox regression analysis screened out 11 adverse prognostic factors for OS: age ≥ 65 years (HR = 1.39, 95% CI: 1.02-1.90, $P = 0.038$), ECOG-PS ≥ 2 (HR = 2.07, 95% CI: 1.50-2.86, $P < 0.001$), CCI ≥ 5 (HR = 1.44, 95% CI: 1.05-1.98, $P = 0.023$), comorbid CTD (HR = 1.76, 95% CI: 1.29-2.40, $P < 0.001$), comorbid ILD (HR = 1.83, 95% CI: 1.23-2.71, $P = 0.003$), hypoalbuminemia (HR = 1.51, 95% CI: 1.10-

Table 4. Treatment-related toxicities in patients with non-small cell lung cancer with and without connective tissue disease

Variable	Control group (n = 101 treated)	CTD group (n = 85 treated)	Statistic	P value
Any grade 3-4 adverse event, n (%)	29 (28.7)	40 (47.1)	$\chi^2 = 6.657$	0.010
Grade 3-4 neutropenia, n (%)	18 (17.8)	24 (28.2)	$\chi^2 = 2.863$	0.091
Febrile neutropenia, n (%)	6 (5.9)	11 (12.9)	$\chi^2 = 2.724$	0.099
Grade 3-4 anemia, n (%)	8 (7.9)	15 (17.6)	$\chi^2 = 4.029$	0.045
Grade 3-4 thrombocytopenia, n (%)	7 (6.9)	10 (11.8)	$\chi^2 = 1.299$	0.254
Severe infection, n (%)	9 (8.9)	19 (22.4)	$\chi^2 = 6.522$	0.011
Drug-related pneumonitis, n (%)	5 (5.0)	16 (18.8)	$\chi^2 = 5.298$	0.021
Immune-related adverse events, n (%)	8/36 (22.2)	7/17 (41.2)	$\chi^2 = 2.044$	0.153
Treatment-related death, n (%)	2 (2.0)	5 (5.9)	$\chi^2 = 1.940$	0.164

Note: CTD: connective tissue disease.

**Figure 4.** Subgroup analyses of the association between CTD and overall survival. Note: CTD: Connective tissue disease; ILD: Interstitial lung disease; ECOG PS: Eastern Cooperative Oncology Group performance status; HR: Hazard ratio; CI: Confidence interval.

2.08, $P = 0.010$), advanced tumor stage (HR = 2.41, 95% CI: 1.70-3.43, $P < 0.001$), liver metastasis (HR = 1.58, 95% CI: 1.13-2.21, $P = 0.008$), elevated lactate dehydrogenase (LDH) (HR = 1.71, 95% CI: 1.24-2.36, $P = 0.001$), FEV1% predicted $< 70\%$ (HR = 1.36, 95% CI: 1.01-1.84, $P = 0.045$) and DLC0% predicted $< 60\%$ (HR = 1.49, 95% CI: 1.10-2.02, $P = 0.010$). Completion of ≥ 4 chemotherapy cycles was an independent protective factor for OS (HR = 0.48, 95% CI: 0.35-0.67, $P < 0.001$).

Six-month weight loss $> 5\%$ showed a marginal trend of poor prognosis (HR = 1.32, 95% CI: 0.95-1.82, $P = 0.099$). Female gender and smoking history had no correlation with OS. After multivariate model, four indicators remained as independent adverse prognostic factors: ECOG-PS ≥ 2 (HR = 1.76, 95% CI: 1.23-2.52, $P = 0.002$), comorbid CTD (HR = 1.41, 95% CI: 1.01-1.97, $P = 0.044$), advanced tumor stage (HR = 2.08, 95% CI: 1.44-3.00, $P < 0.001$) and elevated LDH (HR = 1.41, 95% CI: 1.00-

Table 5. Univariate and multivariate Cox regression analyses for overall survival

Variable	Univariate HR	95% CI	P value	Multivariate HR	95% CI	P value
Age ≥ 65 years	1.39	1.02-1.90	0.038	1.17	0.83-1.65	0.365
Female sex	0.91	0.65-1.28	0.591	0.95	0.65-1.40	0.803
Ever-smoker	1.18	0.80-1.76	0.403	1.12	0.74-1.69	0.584
ECOG PS ≥ 2	2.07	1.50-2.86	<0.001	1.76	1.23-2.52	0.002
Charlson comorbidity index ≥ 5	1.44	1.05-1.98	0.023	1.18	0.83-1.68	0.361
CTD presence	1.76	1.29-2.40	<0.001	1.41	1.01-1.97	0.044
ILD presence	1.83	1.23-2.71	0.003	1.28	0.82-1.98	0.273
Weight loss >5% within 6 months	1.32	0.95-1.82	0.099	1.14	0.80-1.61	0.466
Hypoalbuminemia (<35 g/L)	1.51	1.10-2.08	0.010	1.24	0.87-1.77	0.235
Advanced-stage disease	2.41	1.70-3.43	<0.001	2.08	1.44-3.00	<0.001
Liver metastasis	1.58	1.13-2.21	0.008	1.31	0.90-1.90	0.153
LDH above upper normal limit	1.71	1.24-2.36	0.001	1.41	1.00-1.99	0.047
Completed ≥ 4 chemotherapy cycles	0.48	0.35-0.67	<0.001	0.59	0.41-0.85	0.004
FEV1% predicted <70%	1.36	1.01-1.84	0.045	1.15	0.80-1.65	0.452
DLC0% predicted <60%	1.49	1.10-2.02	0.010	1.19	0.83-1.69	0.344

Note: CTD: Connective tissue disease; ECOG PS: Eastern Cooperative Oncology Group performance status; BMI: Body mass index; ILD: Interstitial lung disease; COPD: Chronic obstructive pulmonary disease.

1.99, $P = 0.047$). Completion of ≥ 4 chemotherapy cycles remained an independent protective factor (HR = 0.59, 95% CI: 0.41-0.85, $P = 0.004$) (Table 5). Other baseline indicators lost independent prognostic correlation after multivariate adjustment.

External validation

Baseline characteristics of the validation cohort are summarized in [Supplementary Table 2](#). Consistent with the primary cohort, tumor stage distribution was balanced between two groups ($P = 0.670$). The CTD group had reduced platinum-based chemotherapy utilization rate with marginal statistical difference ($P = 0.070$), and significantly lower cisplatin-based regimen application rate ($P = 0.026$).

In the validation cohort, CTD patients received fewer ICI-combined therapy ($P = 0.014$) and thoracic radiotherapy ($P = 0.034$), and were less likely to finish four-cycle standard chemotherapy ($P = 0.004$). They also had higher incidence of chemotherapy dose reduction ($P = 0.048$), treatment delay over 7 days ($P = 0.046$) and early treatment discontinuation ($P = 0.017$). Consistent with primary cohort outcomes, grade 3-4 AEs were more common in the CTD group (48.8% vs 29.2%, $P = 0.024$) (Table 6).

Discussion

This single-center retrospective study revealed that NSCLC patients with comorbid CTD formed a special high-risk clinical subgroup. Comorbid CTD aggravated intrathoracic tumor dissemination, reduced first-line antitumor treatment intensity and treatment adherence, increased severe treatment-related toxicity, and shortened PFS and OS. After adjusting traditional prognostic confounders including ECOG-PS, tumor stage and LDH level, CTD remained an independent adverse prognostic factor. This result indicated that CTD was not just a common comorbidity, but a core determinant of NSCLC survival outcomes.

Our study proved that CTD mainly affected intrathoracic tumor progression, rather than accelerating distant metastasis. The two groups had consistent primary tumor features, mediastinal lymph node metastasis status and tumor stage, but CTD patients presented higher bilateral pulmonary invasion and pleural effusion rates. Distant metastatic organ distribution showed no inter-group difference. Most previous CTD-oncology studies focused on immunotherapy safety and pulmonary comorbidity management, and rarely analyzed tumor anatomical dissemination patterns [15-17]. We proposed a potential mechanism: long-term

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Table 6. External validation of treatment patterns, toxicities, and survival outcomes in NSCLC patients with and without connective tissue disease

Variable	Non-CTD group (n = 106)	CTD group (n = 94)	Effect estimate/ Statistic	P value
Tumor stage			$\chi^2 = 0.182$	0.670
Stage I-III disease, n (%)	38 (35.8)	31 (33.0)		
Stage IV disease, n (%)	68 (64.2)	63 (67.0)		
Platinum-based doublet chemotherapy, n (%)	87 (82.1)	67 (71.3)	$\chi^2 = 3.281$	0.070
Cisplatin-based regimen, n (%)	39 (36.8)	21 (22.3)	$\chi^2 = 4.955$	0.026
Immune checkpoint inhibitor-containing therapy, n (%)	34 (32.1)	16 (17.0)	$\chi^2 = 6.022$	0.014
Thoracic radiotherapy, n (%)	47 (44.3)	28 (29.8)	$\chi^2 = 4.502$	0.034
Completed ≥ 4 chemotherapy cycles, n (%)	75 (70.8)	48 (51.1)	$\chi^2 = 8.158$	0.004
Dose reduction during treatment, n (%)	19 (17.9)	28 (29.8)	$\chi^2 = 3.900$	0.048
Treatment delay >7 days, n (%)	17 (16.0)	26 (27.7)	$\chi^2 = 3.987$	0.046
Early discontinuation, n (%)	14 (13.2)	25 (26.6)	$\chi^2 = 5.689$	0.017
Any grade 3-4 adverse event, n/N (%)	31/106 (29.2)	42/86 (48.8)	$\chi^2 = 5.121$	0.024

Note: CTD: Connective tissue disease; Non-CTD: Non-connective tissue disease; HR: Hazard ratio; CI: Confidence interval; PFS: Progression-free survival; OS: Overall survival.

CTD-related immune dysregulation, recurrent alveolar injury and abnormal pulmonary tissue remodeling reshape the thoracic microenvironment. Such pathological changes facilitate local tumor proliferation and intrathoracic invasion.

Clinically, this finding reminds radiologists and oncologists to distinguish CTD-related benign pulmonary lesions from tumor progressive lesions. Autoimmune pulmonary inflammation may overlap with NSCLC imaging manifestations, which can easily cause misdiagnosis and interfere with treatment evaluation. Our research also confirmed that CTD reduced clinical treatment intensity and treatment sustainability. CTD patients avoided cisplatin regimens but tolerated carboplatin-based chemotherapy equivalently. This discrepancy originated from stronger renal toxicity and gastrointestinal toxicity of cisplatin. Clinicians tended to abandon high-intensity cisplatin therapy to prevent CTD flare and organ damage.

Meanwhile, CTD patients had lower ICI and thoracic radiotherapy utilization rates. Except for treatment selection bias, the CTD group had poor treatment implementation quality, including insufficient chemotherapy cycles, frequent dose adjustment and treatment interruption. Multiple factors jointly caused this phenomenon: poor baseline physical condition, high ILD comorbidity rate, limited pulmonary reserve, clinicians' concerns about autoimmune disease

exacerbation and treatment-induced pneumonitis [18-20]. Different from previous studies focusing on treatment eligibility, we highlighted that CTD impaired whole-course treatment durability. Stable and standardized treatment delivery is the key to guarantee NSCLC survival benefit, so treatment interruption caused by CTD directly leads to poor prognosis.

Dual-cohort verification confirmed the adverse prognostic role of CTD. Both primary and validation groups yielded consistent results, which strengthened the external validity of our conclusion. Combined with existing oncology research, chronic systemic inflammation and immune imbalance can weaken antitumor treatment efficacy, restrict standard regimen application, and reduce patient treatment tolerance [21-23]. Our study further supplemented that sufficient chemotherapy cycles can partially offset the survival risk brought by CTD. Treatment continuity acts as the intermediate mediator linking CTD and dismal prognosis. Collectively, CTD affects NSCLC survival via two pathways: inherent biological vulnerability caused by autoimmune inflammation, and reduced clinical treatment intensity.

Treatment-related toxicity analysis provides targeted clinical safety suggestions. The CTD group had higher grade 3-4 hematological toxicity, severe infection and drug-induced pneumonitis risk. Although grade ≥ 2 irAEs did not reach statistical difference, the upward nume-

rical trend accorded with global clinical concerns of ICI application in autoimmune populations. The increased pulmonary toxicity risk was closely associated with baseline CTD-related pulmonary damage. Pre-existing occult interstitial lesions, persistent immune activation and impaired tissue repair ability jointly amplify pulmonary inflammatory injury induced by chemotherapy and radiotherapy [24, 25].

We suggest carrying out standardized multidisciplinary assessment before antitumor treatment for CTD-NSCLC patients. Baseline pulmonary function detection, rheumatology consultation and individualized toxicity monitoring can reduce severe adverse event risks. Subgroup analysis showed that patients combined with ILD were more vulnerable to CTD-related survival damage. We speculated that impaired pulmonary function was the key intermediate variable. CTD patients had lower FEV1% predicted and DLCO% predicted, which reflected decreased ventilatory function and gas exchange capacity. Pulmonary functional insufficiency narrows the therapeutic window, limits tolerance to platinum chemotherapy and radiotherapy, and increases treatment interruption risk.

Although pulmonary function indicators were not independent prognostic factors in multivariate regression, this result was caused by covariance overlap with ILD, ECOG-PS and systemic inflammation burden. Pulmonary function still serves as an intuitive risk stratification indicator for CTD-NSCLC patients.

Several study limitations need to be acknowledged. First, this was a single-center retrospective study, inevitably existing selection bias and residual confounding bias. Retrospective data cannot quantify CTD activity severity, baseline immunosuppressive treatment and clinician subjective risk judgment, which may interfere with treatment decision-making analysis. Second, CTD contains heterogeneous subtypes. Our sample size was insufficient to conduct subtype-stratified analysis and evaluate the impact of different immunosuppressive regimens on tumor prognosis. Third, mild and moderate adverse events may be underrecorded due to retrospective data collection. It is difficult to completely distinguish autoimmune flare, pulmonary infection, tumor progression and drug-induced pneumonitis via historical medical records. Fourth, the global NSCLC

treatment paradigm changed greatly from 2015 to 2025. The popularization of immunotherapy and multimodal therapy brought temporal heterogeneity. We adopted external validation to reduce such bias, but multicenter prospective cohorts are still required to verify our conclusions.

In conclusion, comorbid CTD is an independent high-risk factor for NSCLC patients. CTD aggravates intrathoracic tumor dissemination, reduces first-line treatment intensity and durability, increases severe treatment-related toxicity, and brings inferior survival outcomes. Beyond pulmonary function damage and comorbidity burden, CTD itself plays an adverse prognostic role. Clinicians should incorporate CTD screening into routine NSCLC risk evaluation, and optimize individualized treatment plans via multidisciplinary collaboration. Further research needs to screen high-risk CTD subtypes, clarify the interaction among underlying ILD, immunosuppressive medication and tumor prognosis, and build toxicity-prevention treatment strategies to balance antitumor efficacy and autoimmune safety.

Disclosure of conflict of interest

None.

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Supplementary Table 1. Proportional hazards

Variable	rho	Chi-square	P value
Age ≥65 years	-0.062	0.58	0.446
ECOG PS ≥2	0.094	1.21	0.271
CTD presence	0.108	1.96	0.161
ILD presence	0.131	2.86	0.091
Advanced-stage disease	-0.073	0.87	0.351
Liver metastasis	0.084	1.03	0.309
LDH above upper normal limit	-0.118	2.31	0.128
Completed ≥4 chemotherapy cycles	-0.097	1.72	0.190
Global test	-	7.24	0.511

Note: CTD: Connective tissue disease; ECOG PS: Eastern Cooperative Oncology Group performance status; ILD: Interstitial lung disease; LDH: Lactate dehydrogenase.

Supplementary Table 2. Baseline demographic and clinical characteristics of patients with and without connective tissue disease in the external validation cohort

Variable	Non-CTD group (n = 106)	CTD group (n = 94)	Statistic	Difference	95% CI	P value
Age, years, mean ± SD	63.56 ± 9.10	59.45 ± 10.88	t = 2.907	4.11	1.322 to 6.897	0.004
Age ≥65 years, n (%)	47 (44.3)	55 (58.5)	χ ² = 4.003	-14.20	0.322 to 0.990	0.045
Female sex, n (%)	31 (29.2)	46 (48.9)	χ ² = 8.158	-19.70	0.241 to 0.772	0.004
BMI, kg/m ² , mean ± SD	22.85 ± 3.13	23.03 ± 3.21	t = 0.385	0.71	-1.057 to -0.712	0.701
Smoking status, n (%)			χ ² = 7.747			0.021
Never smoker, n (%)	20 (18.9)	30 (31.9)				
Former smoker, n (%)	31 (29.2)	33 (35.1)				
Current smoker, n (%)	55 (51.9)	31 (33.0)				
ECOG performance status			χ ² = 4.489	-14.50	1.045 to 3.339	0.034
ECOG PS 0-1, n (%)	74 (69.8)	52 (55.3)				
ECOG PS ≥2, n (%)	32 (30.2)	42 (44.7)				
Charlson comorbidity index, mean ± SD	4.19 ± 2.03	5.34 ± 2.07	t = 3.967	-1.15	-1.724 to -0.579	<0.001
Hypertension, n (%)	35 (33.0)	34 (36.2)	χ ² = 0.219	-3.20	0.485 to 1.560	0.640
Diabetes mellitus, n (%)	18 (17.0)	20 (21.3)	χ ² = 0.597	-4.30	0.373 to 1.536	0.440
Coronary artery disease, n (%)	15 (14.2)	17 (18.1)	χ ² = 0.574	-3.90	0.350 to 1.593	0.449
ILD, n (%)	10 (9.4)	27 (28.7)	χ ² = 12.295	-19.30	0.117 to 0.569	<0.001
COPD, n (%)	34 (32.1)	23 (24.5)	χ ² = 1.415	7.60	0.782 to 2.717	0.234
Family history of malignancy, n (%)	16 (15.1)	13 (13.8)	χ ² = 0.064	1.30	0.502 to 2.443	0.800
Weight loss >5% within 6 months, n (%)	24 (22.6)	34 (36.2)	χ ² = 4.429	-13.50	0.278 to 0.960	0.035
Baseline anemia, n (%)	30 (28.3)	40 (42.6)	χ ² = 4.448	-14.30	0.296 to 0.959	0.035
Hypoalbuminemia (<35 g/L), n (%)	25 (23.6)	36 (38.3)	χ ² = 5.088	-14.70	0.270 to 0.917	0.024
FEV1% predicted, mean ± SD	72.29 ± 17.50	63.84 ± 13.22	t = 3.817	8.457	4.088 to 12.833	<0.001
DLC0% predicted, mean ± SD	67.85 ± 16.39	57.12 ± 15.21	t = 4.779	10.730	6.303 to 15.158	<0.001
Tumor stage			χ ² = 0.182	2.90	0.633 to 2.039	0.670
Stage I-III disease, n (%)	38 (35.8)	31 (33.0)				
Stage IV disease, n (%)	68 (64.2)	63 (67.0)				

Note: CTD: Connective tissue disease; Non-CTD: Non-connective tissue disease; ECOG PS: Eastern Cooperative Oncology Group performance status; BMI: Body mass index; ILD: Interstitial lung disease; COPD: Chronic obstructive pulmonary disease; FEV1: Forced expiratory volume in one second.