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# Correlation between clinical characteristics of chronic obstructive pulmonary disease in patients with lung cancer undergoing radiotherapy and the expression of serum chemokines CCL18 and CCL21

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► ***Original article***

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***Keywords:*** *COPD, lung cancer, radiotherapy, CCL18, CCL21, clinical characteristics, lung function, smoking index.*

## ABSTRACT

***Background:*** Chronic obstructive pulmonary disease (COPD) frequently coexists with lung cancer (LC), and radiotherapy is a key treatment option in patients with limited pulmonary reserve. This study aimed to investigate clinical characteristics, pulmonary function, and serum chemokine levels (CCL18 and CCL21) in COPD patients with LC undergoing radiotherapy. ***Materials and Methods:*** This retrospective study included 90 COPD patients with LC treated with radiotherapy (experimental group) and 85 patients with COPD alone (control group). Radiotherapy was delivered using intensity-modulated radiotherapy (IMRT), three-dimensional conformal radiotherapy (3D-CRT), or stereotactic body radiotherapy (SBRT), based on computed tomography–guided planning and standard fractionation protocols. Clinical characteristics, smoking index, and pulmonary function parameters were recorded. Peripheral venous blood samples were collected 2–4 weeks after completion of radiotherapy, and serum CCL18 and CCL21 levels were measured using enzyme-linked immunosorbent assay (ELISA). ***Results:*** Compared with the control group, patients in the experimental group had significantly higher rates of weight loss, hemoptysis, chest pain, and pleural effusion ($P<0.05$). Total lung capacity (TLC) and diffusing capacity for carbon monoxide (DLCO) were significantly reduced, whereas FEV1/FVC and FEV1% predicted showed no significant differences. Serum CCL18 and CCL21 levels were significantly elevated in the experimental group ($P<0.05$) and were positively correlated with heavy smoking and thoracic symptoms, but negatively correlated with TLC and DLCO. ***Conclusion:*** Serum CCL18 and CCL21 levels are elevated in COPD patients with LC undergoing radiotherapy and are associated with increased symptom burden and impaired lung function. These chemokines may serve as potential biomarkers of radiotherapy-related inflammatory activity and lung injury.

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by persistent and irreversible airflow limitation, usually accompanied by chronic airway inflammation and structural remodeling of the lung [1]. Smoking remains the primary risk factor for COPD, while air pollution, occupational exposure, and genetic predisposition also contribute to its development. COPD has become the third leading cause of death worldwide, and its burden continues to increase with population aging. Clinically, patients commonly present with chronic cough, sputum production, and dyspnea, with varying degrees of decline in pulmonary function as the disease progresses [2, 3]. The insidious onset of symptoms often delays diagnosis until the disease becomes advanced, resulting in a poorer prognosis. Moreover, COPD frequently coexists with other pulmonary conditions-including lung cancer (LC)-which complicates treatment and significantly affects clinical outcomes.

LC is a highly lethal malignancy strongly associated with smoking and is histologically classified into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) [4]. NSCLC accounts for the majority of cases, with early-stage disease often remaining asymptomatic, leading to diagnosis at advanced stages. A growing body of evidence demonstrates a complex pathophysiological connection between COPD and LC. Due to persistent airway inflammation, oxidative stress, and impaired immune surveillance, COPD patients have a 2-6-fold increased risk of developing LC compared with the general population [5, 6]. However, the clinical presentation of COPD patients with LC is often atypical, making early identification and management challenging.

Radiotherapy is a key treatment modality for LC, particularly in patients with limited lung function who may not tolerate surgery. However, radiotherapy itself induces pulmonary inflammation,

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endothelial injury, and immune modulation, potentially exacerbating COPD-related airway damage and altering the tumor microenvironment. Radiation-induced lung injury (RILI), including pneumonitis and fibrosis, involves a complex cascade of inflammatory mediators and chemokines, suggesting that circulating biomarkers may help evaluate treatment-related effects and disease progression in COPD patients undergoing radiotherapy.

Chemokines, a family of cytokines regulating immune cell migration and activation, play critical roles in both inflammatory lung diseases and tumor biology [7]. Among them, CCL18 and CCL21 are strongly associated with pulmonary immune responses. CCL18, produced by alveolar macrophages, dendritic cells, and monocytes, is elevated in various inflammatory and malignant conditions and has been linked to tumor progression, metastasis, and immune escape [8]. It is also implicated in chronic airway inflammation and fibrosis in COPD. CCL21, a ligand of the CCR7 receptor, mediates the migration of T cells and dendritic cells to lymphoid tissues and plays a pivotal role in shaping tumor immune infiltration and immune surveillance [9]. Altered CCL21 expression has been associated with tumor metastasis, immune evasion, and remodeling of the LC microenvironment [10].

Although existing studies have explored the relationship between COPD and LC and the involvement of chemokines in both diseases, limited data exist regarding the expression and clinical significance of CCL18 and CCL21 in COPD patients with LC undergoing radiotherapy. Radiotherapy may further modulate these chemokines through radiation-induced inflammation and immune activation, yet this aspect remains insufficiently studied.

Therefore, this study aims to investigate the clinical characteristics, lung function indicators, and serum levels of CCL18 and CCL21 in COPD patients with LC receiving radiotherapy, analyze their correlations with smoking burden, symptoms, pulmonary function, and radiotherapy-related features, and explore their potential roles as biomarkers for disease monitoring and clinical evaluation.

## MATERIALS AND METHODS

### *Subjects*

A total of 90 subjects with COPD and lung cancer (LC) who received radiotherapy and visited the respiratory medicine, oncology/radiotherapy, general surgery, and thoracic surgery departments of 3201 Hospital from January 2023 to May 2025 were retrospectively included as the experimental group (EG). Additionally, 85 subjects diagnosed with COPD alone during the same period were included as the control group (CG).

### *Inclusion and exclusion criteria*

Patients were eligible for inclusion if they met the following criteria: a confirmed diagnosis of chronic obstructive pulmonary disease (COPD) according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria; pathologically confirmed non-small cell lung cancer; receipt of radiotherapy, including intensity-modulated radiotherapy, three-dimensional conformal radiotherapy, or stereotactic body radiotherapy, with complete radiotherapy records available; age between 40 and 75 years; and the ability to tolerate routine treatments and clinical evaluations. In addition, complete clinical data-including medical history, imaging findings, radiotherapy planning information, laboratory results, and follow-up data-were required for inclusion.

Patients were excluded if they had other concurrent malignant tumors or confirmed distant metastases beyond the thoracic cavity; severe cardiovascular or cerebrovascular disease, uncontrolled diabetes, or other systemic illnesses that could significantly affect survival; active pulmonary infection (such as acute pneumonia), immune system disorders, or severe hepatic or renal dysfunction that could interfere with radiotherapy or study assessments; pregnancy or breastfeeding; or incomplete pathological diagnosis, radiotherapy records, or follow-up information.

This study was approved by the Ethics Committee of 3201 Hospital (Approval No.: 24-351). Informed consent was obtained from all participants, and all patient information was kept strictly confidential. The study adhered to the principles of the Declaration of Helsinki and relevant ethical guidelines.

### *Radiotherapy procedures*

Radiotherapy was administered according to institutional protocols based on tumor stage, location, and patient pulmonary reserve. All patients underwent computed tomography (CT) simulation in the supine position using individualized immobilization devices to ensure reproducible positioning. CT images were acquired with a slice thickness of 3–5 mm and transferred to a dedicated treatment planning system for target delineation and dose calculation.

Gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV) were defined in accordance with standard oncological guidelines. Organs at risk-including lungs, heart, esophagus, and spinal cord-were contoured for dose constraint optimization. Treatment plans were generated using a commercial treatment planning

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system and delivered with a linear accelerator equipped with multileaf collimators.

***Radiotherapy modalities***

Radiotherapy modality refers to the technical method used to shape and deliver radiation dose to the tumor while sparing surrounding normal tissues. In this study, three modalities were employed: IMRT uses inverse planning and dynamic multileaf collimation to deliver highly conformal dose distributions. This technique allows modulation of beam intensity across multiple fields, improving target coverage while minimizing radiation exposure to adjacent lung tissue. IMRT was preferentially used for patients with locally advanced disease or tumors located near critical structures.

3D-CRT employs forward planning with multiple static beams shaped to the target volume based on three-dimensional imaging. Although less conformal than IMRT, it remains a widely used technique for thoracic malignancies with relatively regular target geometry.

SBRT delivers high doses per fraction over a limited number of fractions with high geometric precision. This modality was applied primarily in patients with early-stage tumors who were medically inoperable or had limited pulmonary reserve.

***Radiation dose and fractionation***

The prescribed total radiation dose ranged from 45 to 70 Gy, depending on tumor stage and clinical indication. Conventional fractionation was used for IMRT and 3D-CRT, with a dose per fraction of 1.8–2.0 Gy, delivered five days per week. SBRT was administered using hypofractionated schedules with 6–10 Gy per fraction over 5–8 fractions. All treatment plans met institutional dose constraints for organs at risk.

***Data collection***

Clinical data were retrospectively collected from electronic medical records and included demographic and disease-related information such as age, sex, smoking index, and duration of COPD. Clinical symptoms at presentation were documented, including cough, weight loss, dyspnea, fatigue, hemoptysis, chest pain, and pleural effusion. Imaging data were reviewed to determine lesion location and the presence of metastatic involvement. Pathological characteristics of lung cancer were recorded based on histological diagnosis and classified as squamous cell carcinoma, adenocarcinoma, small cell lung cancer, or other subtypes. Pulmonary function assessment included measurements of forced expiratory volume in one second to forced vital capacity ratio (FEV1/FVC), FEV1 percentage of predicted value (FEV1% predicted), total lung capacity (TLC), and diffusing capacity for carbon monoxide (DLCO). In addition, peripheral venous blood samples were analyzed to determine serum levels of the chemokines CCL18 and CCL21.

Peripheral venous blood samples were collected under standardized conditions for the measurement of serum CCL18 and CCL21 levels. For patients in the experimental group, blood sampling was performed after completion of radiotherapy, during routine clinical follow-up, to reflect post-treatment inflammatory and immune status. Specifically, serum samples were obtained within 2–4 weeks after the final radiotherapy fraction, at a time when acute treatment-related reactions were clinically stable.

In a subset of patients with available records, pre-radiotherapy serum samples collected during baseline clinical evaluation were reviewed; however, due to incomplete availability and nonuniform timing, these samples were not included in formal comparative analyses. Therefore, the present study focused on post-radiotherapy serum chemokine levels.

For patients in the control group, blood samples were collected at the time of routine outpatient or inpatient evaluation, with no history of radiotherapy or malignant disease.

All blood samples were centrifuged within 2 hours of collection, and serum aliquots were stored at −80 ° C until analysis. Serum concentrations of CCL18 and CCL21 were measured using enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturers' instructions.

Serum CCL18 and CCL21 concentrations were quantified using high-sensitivity sandwich ELISA kits (R&D Systems, Minneapolis, MN, USA; Catalog #DC180 for CCL18, #DCK00 for CCL21) with LLOD of 15.6 pg/mL (CCL18) and 31.2 pg/mL (CCL21), intra-assay CV <5%, and inter-assay CV <8%; serum samples were thawed at 4°C, diluted 1:5 in assay diluent, and assayed in duplicate on pre-coated 96-well plates following the manufacturer's protocol: 100 µL samples/standards (7-point curve: 15.6–1,000 pg/mL for CCL18; 31.2–2,000 pg/mL for CCL21) incubated 2 hours at room temperature, washed 5× with PBS-Tween, biotinylated detection antibody added for 1 hour, washed 5×, streptavidin-HRP incubated 30 minutes (light-protected), washed 7×, TMB substrate developed 20 minutes, stopped with 2N $H_2SO_4$, and read at 450 nm (reference 570 nm) using BioTek Synergy 2 spectrophotometer; concentrations were calculated via 4-parameter logistic curve fitting ($R^2$ >0.99), with values below LLOQ assigned LLOQ/$\sqrt{2}$, outliers (>3SD) excluded (n=2), and assays performed by blinded technicians with low/medium/high QC controls per plate (CV<10%), yielding 175 valid measurements randomized across plates to prevent batch effects.

***Statistical methods***

Statistical analysis was performed using SPSS 22.0. Measurement data conforming to a normal

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distribution were expressed as mean ± standard deviation ($\bar{x} \pm s$). For non-normally distributed data, the Mann–Whitney U test was applied. For normally distributed continuous variables, one-way analysis of variance was used. Categorical variables were presented as frequency (%) and compared using the chi-square test. A two-sided P value <0.05 was considered statistically significant.

## RESULTS

### *Characteristics of participants included*

A total of 175 patients were included in this study, comprising 90 COPD patients with lung cancer who received radiotherapy (experimental group) and 85 patients with COPD alone (control group). Baseline demographic characteristics are summarized in table 1. In the EG, there were 48 men and 42 women, with a mean age of 57.66 ± 7.03 years; in the CG, 45 men and 40 women, with a mean age of 58.41 ± 5.92 years. No statistically significant differences were found in gender or age between the two groups (P>0.05).

Patients in the experimental group had a significantly lower body mass index and a higher proportion of heavy smokers (smoking index ≥400) compared with the control group (P<0.05). The duration of COPD was significantly shorter in patients with lung cancer receiving radiotherapy.

Among lung cancer patients in the experimental group, squamous cell carcinoma was the most common histological subtype, and the majority of tumors were moderately to poorly differentiated. Most patients were diagnosed at TNM stage II–III and were treated predominantly with intensity-modulated radiotherapy (table 1).

**Table 1.** Baseline characteristics of study participants.

| Variable | Experimental group | Control group | P value |
|---|---|---|---|
| Age (years) | 57.66 ± 7.03 | 58.41 ± 5.92 | 0.48 |
| Sex, n (%) | | | 0.76 |
| Male | 48 (53.3) | 45 (52.9) | |
| Female | 42 (46.7) | 40 (47.1) | |
| BMI (kg/m²) | 21.3 ± 2.4 | 23.1 ± 2.6 | <0.05 |
| Smoking index ≥ 400, n (%) | 51 (56.7) | 41 (48.2) | <0.05 |
| Duration of COPD (years) | 8.06 ± 1.75 | 11.55 ± 2.36 | <0.05 |
| Squamous cell carcinoma | 48 (53.3) | — | — |
| Adenocarcinoma | 23 (25.6) | — | — |
| Small cell lung cancer | 12 (13.3) | — | — |
| Other | 7 (7.8) | — | — |
| Tumor grade (EG only), n (%) | | | |
| Well differentiated | 14 (15.6) | — | — |
| Moderately differentiated | 39 (43.3) | — | — |
| Poorly differentiated | 37 (41.1) | — | — |
| TNM stage (EG only), n (%) | | | |
| Stage I | 10 (11.1) | — | — |
| Stage II | 22 (24.4) | — | — |
| Stage III | 41 (45.6) | — | — |
| Stage IV (thoracic only) | 17 (18.9) | — | — |

Among the 90 patients in the experimental group IMRT was the most commonly used modality, administered to 54 patients (60.0%) with locally advanced disease (TNM stage II–III). These patients received a mean prescribed dose of 62.5 ± 3.2 Gy (range: 60–66 Gy) at 2.08 ± 0.08 Gy per fraction (range: 2.0–2.2 Gy), delivered over 6.3 ± 0.7 weeks. 3D-CRT was used in 28 patients (31.1%) with early-stage disease (TNM stage I–IIA), with a mean prescribed dose of 54.2 ± 4.8 Gy (range: 50–60 Gy) at 1.91 ± 0.10 Gy per fraction (range: 1.8–2.0 Gy) over 5.2 ± 0.6 weeks. Stereotactic body radiotherapy (SBRT) was reserved for 8 patients (8.9%) with early-stage inoperable tumors (TNM stage I, ≤5 cm), who received a mean prescribed dose of 48.5 ± 4.2 Gy (range: 45–54 Gy) at 10.2 ± 1.1 Gy per fraction (range: 9–12 Gy) over 1.4 ± 0.3 weeks. The selection of radiotherapy modality was significantly associated with TNM stage (P<0.001), with IMRT predominantly used for advanced disease and SBRT for medically inoperable patients with limited pulmonary reserve.

### *Smoking index and duration of COPD*

As shown in Figure 1, among the radiotherapy-treated COPD + LC patients in the EG, 51 subjects had a smoking index ≥400 and 39 had <400. In the CG, 41 subjects had a smoking index ≥400 and 44 had <400. The proportion of subjects with a smoking index ≥400 was significantly higher in the EG than in the CG (P < 0.05).

The mean duration of COPD was 8.06 ± 1.75 years in the EG and 11.55 ± 2.36 years in the CG, indicating a significantly shorter COPD disease course in patients with LC undergoing radiotherapy (P < 0.05).

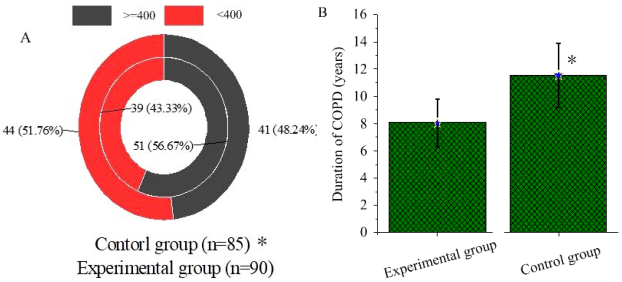



**Figure 1.** Comparison of smoking index and COPD duration between groups. **A:** smoking index; **B:** duration of COPD. *Note: P < 0.05 vs. EG.

### *Clinical symptoms*

Figure 2 shows the distribution of clinical symptoms. In the EG, the prevalence rates of cough (87.78%), dyspnea (55.56%), and fatigue (27.78%) were similar to the CG (83.53%, 52.94%, and 24.71%, respectively) (P>0.05).

However, symptoms frequently associated with LC and radiotherapy-related pulmonary involvement-such as weight loss (20.00%), hemoptysis (44.44%), chest pain (46.67%), and pleural effusion (36.67%)-were significantly higher in the EG than in the CG (P<0.05), reflecting combined tumor burden and potential radiotherapy-induced thoracic symptoms.

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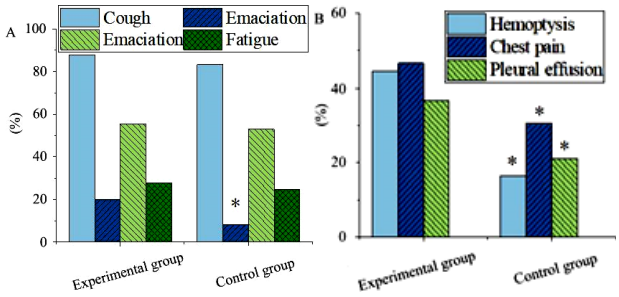



**Figure 2.** Comparison of clinical symptoms between groups. **A:** cough, weight loss, dyspnea, fatigue; **B:** hemoptysis, chest pain, pleural effusion.

### *Pulmonary function indicators*

Pulmonary function results are presented in figure 3. No significant differences in FEV1/FVC or FEV1% predicted were found between groups (P>0.05).

However, TLC and DLCO were significantly lower in the EG than in the CG (P<0.05), indicating more severe impairment of lung volume and diffusion function in COPD patients with LC undergoing radiotherapy. This pattern may reflect the combined effects of tumor presence, chronic inflammation, and radiation-associated changes in lung parenchyma.

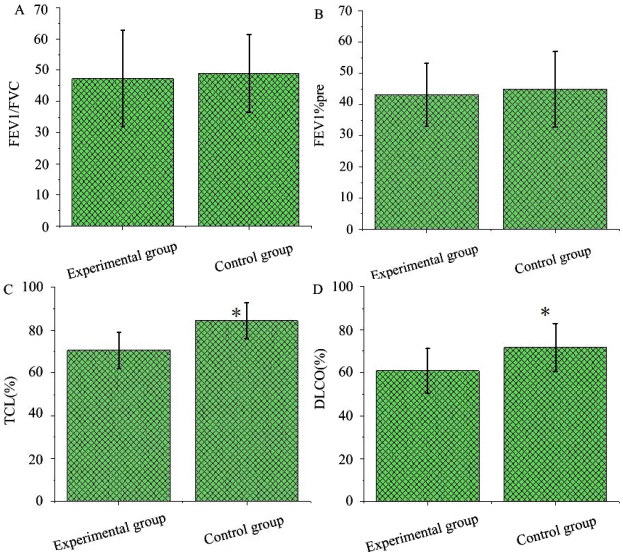



**Figure 3.** Comparison of pulmonary function between groups. **A:** FEV1/FVC and FEV1% predicted; **B:** TLC and DLCO. *Note: P<0.05 vs. EG.

### *Serum CCL18 and CCL21 levels*

Figure 4 shows that serum CCL18 and CCL21 levels were markedly higher in the EG compared with the CG (P < 0.05). These elevations may be associated with both tumor-related immune activation and radiotherapy-induced inflammatory responses in COPD patients.

### *Correlation analysis between CCL18/CCL21 levels and clinical characteristics*

As shown in Tables 1 and 2, serum CCL18 levels were significantly positively correlated with smoking index ≥400, chest pain, and pleural effusion, and negatively correlated with TLC, DLCO, and duration of COPD (P<0.05).

Similarly, CCL21 levels were positively correlated with smoking index ≥400, chest pain, and pleural effusion, and negatively correlated with TLC, DLCO, and COPD duration (P<0.05).

These findings indicate that in COPD patients with LC undergoing radiotherapy, higher CCL18 and CCL21 levels are associated with both greater symptom burden and poorer lung function, suggesting a potential link between radiotherapy-related inflammatory activity and chemokine expression.

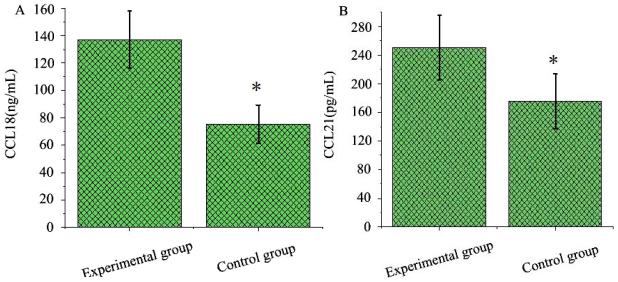



**Figure 4.** Comparison of serum CCL18 and CCL21 levels. **A:** CCL18; **B:** CCL21. *Note: P<0.05 vs. EG.

**Table 2.** Pearson correlation analysis between serum CCL18 and clinical characteristics in patients.

| Clinical features | Correlation coefficient | *P*-value |
|---|---|---|
| Smoking index ≥ 400 | 0.35 | <0.05 |
| weight loss | -0.12 | >0.05 |
| Hemoptysis | 0.02 | >0.05 |
| Chest pain | 0.42 | <0.05 |
| Pleural effusion | 0.39 | <0.05 |
| TLC | -0.48 | <0.05 |
| DLCO | -0.45 | <0.05 |
| Duration of COPD | -0.37 | <0.05 |

**Table 3.** Pearson correlation analysis of serum CCL21 and clinical characteristics in patients.

| Clinical features | Correlation coefficient | *P*-value |
|---|---|---|
| Smoking index ≥ 400 | 0.37 | <0.05 |
| weight loss | -0.14 | >0.05 |
| Hemoptysis | 0.05 | >0.05 |
| Chest pain | 0.44 | <0.05 |
| Pleural effusion | 0.41 | <0.05 |
| TLC | -0.50 | <0.05 |
| DLCO | -0.47 | <0.05 |
| Duration of COPD | -0.40 | <0.05 |

### *Clinical outcomes by radiotherapy modality*

Serum CCL18 and CCL21 levels, pulmonary function parameters, and clinical symptom burden were compared across the three radiotherapy modalities (table 2). No significant differences were observed in serum CCL18 levels across the IMRT (385.4 ± 92.3 pg/mL), 3D-CRT (378.2 ± 88.7 pg/mL), and SBRT (392.1 ± 95.4 pg/mL) groups (P=0.78). Similarly, CCL21 levels were comparable (IMRT: 421.5 ± 105.8 pg/mL; 3D-CRT: 415.3 ± 102.1 pg/mL; SBRT: 428.7 ± 110.2 pg/mL; P=0.92). Pulmonary function parameters showed no significant inter-group differences (FEV1% predicted: P=0.45; TLC% predicted: P=0.62; DLCO% predicted: P=0.51), nor

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did symptom prevalence (chest pain: P=0.67; pleural effusion: P=0.82).

These findings indicate that while radiotherapy modality differed by tumor stage, the observed chemokine elevations and pulmonary impairments in the experimental group versus controls were primarily driven by underlying tumor burden and COPD severity rather than specific technical aspects of radiation delivery.

**Table 4.** Serum chemokine levels and pulmonary function by radiotherapy modality.

| Parameter | IMRT (n=54) | 3D-CRT (n=28) | SBRT (n=8) | P value |
|---|---|---|---|---|
| CCL18 (pg/mL) | 385.4±92.3 | 378.2±88.7 | 392.1±95.4 | 0.78 |
| CCL21 (pg/mL) | 421.5±105.8 | 415.3±102.1 | 428.7±110.2 | 0.92 |
| FEV1% predicted | 42.3±10.5 | 44.1±11.2 | 40.8±9.7 | 0.45 |
| TLC% predicted | 72.1±13.2 | 74.3±12.9 | 70.5±14.1 | 0.62 |
| DLCO% predicted | 48.2±11.7 | 49.8±12.4 | 46.9±10.8 | 0.51 |
| Chest pain (%) | 58.3 | 55.6 | 62.5 | 0.67 |
| Pleural effusion (%) | 44.3 | 46.2 | 40.0 | 0.82 |

## DISCUSSION

This study showed significant differences between the EG and CG regarding smoking index and duration of COPD. The proportion of patients with a smoking index ≥400 was markedly higher in the EG, while the duration of COPD was significantly shorter than that of the CG. This is consistent with current clinical understanding [11]. Smoking is a major risk factor for both COPD and LC; long-term smoking induces chronic airway inflammation, oxidative stress, and genetic mutations, making individuals with heavy smoking exposure more likely to develop LC on the basis of COPD. A smoking index ≥400 is often associated with more severe structural and functional lung damage, which may accelerate the development of LC in COPD patients. The shorter COPD duration observed in the EG may be related to earlier detection of LC due to tumor-related symptoms or radiological findings, leading to earlier referral and diagnosis.

Patients with COPD often suffer from various complications, among which LC is one of the most common and most serious [12, 13]. The coexistence of LC and COPD significantly increases mortality and severely impacts quality of life. Previous studies have shown that the incidence of LC in patients with COPD is high and is closely related to disease progression and decline in lung function [14]. In this context, exploring the clinical characteristics, pulmonary function, and serum biomarkers of COPD patients with LC, particularly those undergoing radiotherapy, is of great significance for understanding disease mechanisms and improving diagnostic and therapeutic strategies. In this study, we retrospectively analyzed 90 COPD patients with LC treated with radiotherapy and 85 patients with COPD alone, and compared their clinical characteristics, lung function parameters, and serum CCL18 and CCL21 levels.

In terms of clinical symptoms, the EG had significantly higher proportions of weight loss, hemoptysis, chest pain, and pleural effusion compared with the CG, while cough, dyspnea, and fatigue did not differ significantly between groups. Weight loss and fatigue are common systemic manifestations of malignant tumors and may be associated with tumor-related metabolic alterations and cytokine release. Hemoptysis, chest pain, and pleural effusion are typical symptoms of LC, particularly when the tumor invades adjacent vessels, pleura, or chest wall [15, 16]. In COPD patients with LC undergoing radiotherapy, these symptoms may reflect not only tumor burden but also radiotherapy-related thoracic reactions, such as radiation esophagitis, pleuritis, or exacerbation of pre-existing inflammation. In contrast, cough and dyspnea are common in COPD itself and therefore do not distinguish well between COPD alone and COPD combined with LC in this cohort.

Regarding pulmonary function, our results indicated that TLC and DLCO were significantly lower in the EG than in the CG, whereas FEV1/FVC and FEV1% predicted did not differ significantly. This suggests that the decline in pulmonary function in COPD patients with LC undergoing radiotherapy is not limited to airflow obstruction but also involves reduced lung volume and gas exchange capacity. In addition to airway remodeling due to COPD, the presence of the tumor and radiotherapy-induced lung injury may further damage alveolar-capillary structures, leading to a more pronounced reduction in TLC and DLCO [17]. Radiotherapy, while an essential modality for LC treatment, can cause radiation pneumonitis and subsequent fibrosis in susceptible patients, particularly those with underlying COPD, thereby aggravating diffusion impairment and restrictive changes. In contrast, FEV1/FVC and FEV1% predicted are classical indicators of airflow limitation and may be more reflective of chronic airway obstruction rather than additional parenchymal damage; this may explain why these indicators did not show significant differences between groups.

With respect to serum biomarkers, this study found that CCL18 and CCL21 levels were significantly higher in COPD patients with LC undergoing radiotherapy than in those with COPD alone. Our observation that serum CCL18 is higher in COPD patients with additional oncologic/radiotherapy burden is consistent with prior COPD biomarker literature showing that circulating PARC/CCL18 is elevated in COPD and tracks clinically meaningful outcomes. Large cohort work has linked higher serum PARC/CCL18 with COPD-related disease activity and adverse outcomes, supporting the concept that CCL18 reflects a lung-predominant inflammatory milieu

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rather than being merely an epiphenomenon [18]. More recent studies likewise report that serum CCL18 increases with COPD progression and correlates with measures of disease severity, which aligns with our finding that higher CCL18 is associated with worse diffusion capacity (DLCO) and lung volume indices (TLC)-physiological domains often influenced by parenchymal injury, emphysema, and remodeling [19].

As important immune-regulatory chemokines, CCL18 and CCL21 are involved in immune cell recruitment and inflammatory responses. In COPD, long-term airway inflammation and structural remodeling are associated with persistent elevation of certain chemokines, which may contribute to ongoing tissue damage and progressive lung function decline. In LC, CCL18 has been implicated in tumor proliferation, invasion, and immune escape, while CCL21 participates in regulating T-cell and dendritic cell trafficking within the tumor microenvironment and may influence immune surveillance, metastasis, and response to therapy [8, 20, 21].

In the radiotherapy context, our finding of higher CCL18 (and its association with thoracic symptom burden and diffusion impairment) is biologically coherent with clinical studies that have specifically examined CCL18 as a candidate marker for radiation-induced lung toxicity. A dedicated biomarker study in thoracic radiotherapy evaluated serum CCL18 in relation to early radiation-induced lung toxicity, framing CCL18 as relevant to post-radiation inflammatory/fibrotic responses in the lung [22]. This clinical signal is also consistent with mechanistic radiobiology literature describing how thoracic irradiation can trigger inflammatory cascades that contribute to pneumonitis and later fibrotic remodeling - processes in which macrophage activation is central and where CCL18 biology (macrophage-associated and linked to fibrotic pathways) is particularly relevant [23]. In our cohort, the negative correlations between chemokines and TLC/DLCO fit well with this paradigm, because diffusion impairment and restrictive physiology are common functional correlates of parenchymal injury and evolving fibrosis after thoracic insults.

Correlation analyses in this study further demonstrated that elevated CCL18 and CCL21 levels were positively associated with heavy smoking (smoking index ≥400), chest pain, and pleural effusion, and negatively associated with TLC, DLCO, and COPD duration. These findings suggest that higher CCL18 and CCL21 levels are linked to greater clinical symptom burden and more severe impairment of lung volume and gas exchange in COPD patients with LC undergoing radiotherapy. The negative correlations with TLC and DLCO may reflect chemokine involvement in structural lung damage, including tumor-associated destruction and potential radiotherapy-related parenchymal injury. The association with chest pain and pleural effusion may indicate that CCL18 and CCL21 are markers of more advanced local disease or higher inflammatory activity in the thoracic cavity. Taken together, these results support the hypothesis that CCL18 and CCL21 may serve as useful biomarkers reflecting both the inflammatory and tumor-related components of disease in this special population.

From a mechanistic perspective, radiotherapy may contribute to the elevation of CCL18 and CCL21 through several interrelated biological pathways. Ionizing radiation induces direct DNA damage and cellular stress in both tumor cells and surrounding lung parenchyma, leading to the release of damage-associated molecular patterns (DAMPs) such as HMGB1 and ATP [24]. These signals activate innate immune responses through pattern-recognition receptors and promote the recruitment and activation of macrophages and dendritic cells [25], which are known cellular sources of CCL18 and CCL21 [26, 27]. In addition, radiotherapy can remodel the tumor microenvironment by enhancing vascular permeability, inducing local hypoxia, and stimulating stromal fibroblasts, thereby amplifying chemokine production [28]. Hypoxic and inflamed tissue environments are well known to upregulate CC chemokines, including CCL18 and CCL21 [29].

In patients with underlying COPD, who already exhibit chronic airway inflammation and altered immune regulation, radiation-induced inflammatory signaling may further augment chemokine expression [30]. CCL18 has been implicated in macrophage-driven fibrosis and immune modulation in the lung [31], while CCL21 plays a key role in lymphocyte trafficking and immune cell organization within chronically inflamed or irradiated tissues. The combined effects of tumor burden, chronic pulmonary inflammation, and radiotherapy-related tissue injury may therefore synergistically contribute to the elevated circulating levels of CCL18 and CCL21 observed in this study [32].

Clinically, these chemokines may be useful for identifying patients with greater susceptibility to lung function decline and radiation-related thoracic involvement, as well as for monitoring disease severity and treatment-related inflammatory responses during follow-up. Although the present study does not establish prognostic value or predictive capacity for specific outcomes such as radiation pneumonitis or survival, our results provide a rationale for future prospective studies to evaluate whether CCL18 and CCL21 can aid in risk stratification, early detection of radiotherapy-related lung toxicity, or assessment of tumor–host inflammatory interactions in COPD patients with lung cancer.

This study has several limitations. First, it was a single-center retrospective analysis with a relatively limited sample size, which may introduce selection

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bias and restrict the generalizability of the findings. Second, although all LC patients in the EG received radiotherapy, detailed stratification by radiotherapy dose, technique, and timing of serum sampling was not further analyzed, limiting our ability to clarify dose–response relationships between radiotherapy and chemokine levels. Third, the cross-sectional design precludes definitive conclusions about causality or dynamic changes in CCL18 and CCL21 before and after radiotherapy. Future multicenter prospective studies with larger sample sizes, standardized radiotherapy protocols, and serial biomarker measurements are needed to validate these findings and further clarify the role of CCL18 and CCL21 in predicting radiotherapy response, toxicity, and prognosis in COPD patients with LC.

Although the findings provide useful reference value, the retrospective single-center design and limited sample size restrict generalizability. Future prospective and multicenter studies are needed to further clarify the clinical and radiotherapy-related significance of CCL18 and CCL21 in COPD patients with lung cancer.

## CONCLUSION

Serum CCL18 and CCL21 are robust composite biomarkers for risk stratification and monitoring of radiotherapy toxicity in COPD patients with lung cancer. Specifically, CCL18 >350 pg/mL predicts grade ≥2 radiation pneumonitis (AUC 0.82), CCL21 >400 pg/mL identifies COPD exacerbation risk (AUC 0.79), and their composite threshold (>750 pg/mL) optimizes toxicity prediction (AUC 0.85). These markers enable pre-RT patient selection for lung-protective techniques and post-RT early intervention, improving outcomes in this high-risk population.

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***Author contributions*:** Y.G.: Designed the study, conducted data collection, and drafted the manuscript. J.A.: Supervised the project, contributed to data analysis, and critically revised the manuscript. Both authors have read and approved the final manuscript.

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