https://doi.org/10.53964/jmmo.2024001

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Journal of Modern Medical Oncology

ISSN 2708-0005 (Online)

Open Access

MiniReview

Interstitial Lung Disease Combined with Lung Cancer: Current Understanding and Challenges

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Received: December 2, 2023 **Revised:** December 29, 2023 **Accepted:** January 19, 2024 **Published:** April 7, 2024

Abstract

Interstitial lung disease (ILD) is a group of diffuse pulmonary diseases primarily affecting the pulmonary interstitium and alveolar spaces, leading to restrictive ventilatory dysfunction and diffusion impairment. Patients with ILD have a higher risk of developing lung cancer, which is an indisputable risk factor for lung cancer. However, the pathogenesis of ILD with lung cancer (ILD-LC) remains unclear, and there are few consensus documents for the specific diagnosis and treatment of ILD-LC to date. This article reviews the latest advancements in the epidemiology, risk factors, pathogenesis, diagnosis, and treatment of ILD-LC, aiming to provide a guide for the treatment of ILD-LC patients.

Keywords: interstitial lung disease, lung cancer, epidemiology, pathogenesis, diagnosis

Citation: Sun J, Wang Y, Yang R, Su W, Zhao Z, Liang H. Interstitial Lung Disease Combined with Lung Cancer: Current Understanding and Challenges. *J Mod Med Oncol*, 2024; 4: 1. DOI: 10.53964/jmmo.2024001.

1 INTRODUCTION

Interstitial lung disease (ILD) encompasses a collection of diffuse parenchymal lung diseases that exhibit inflammation or fibrosis within the interstitial space, thereby hindering gas exchange and resulting in manifestations such as dyspnea, diminished exercise capacity, and compromised quality of life[1]. The etiology of ILD is diverse, with approximately 35% being attributed to known causes, including occupational or environmental factors, drug reactions, viral or bacterial infections, and connective tissue diseases (CTDs).

About 65% of ILD cases are idiopathic, with idiopathic pulmonary fibrosis (IPF) being the most common. Compared to the general population, ILD patients have a 3.5 to 7.3 times higher risk of developing lung cancer, with an estimated incidence rate of 10% to 20%[2], making it an independent risk factor for lung cancer. The prognosis for patients with lung cancer and ILD is comparatively poorer than that of patients with lung cancer alone, even after accounting for cancer stage[3].

Previous studies have identified common risk factors for the development of both ILD and lung cancer, including smoking, environmental and occupational exposure to toxic substances, bacterial and viral infections, and chronic tissue damage[4]. ILD and lung cancer share many similar cellular and molecular abnormalities, such as epigenetic and genetic changes, delayed apoptosis, abnormal expression of non-coding RNA, changes in cell communication, and activation of specific signal transduction pathways[5]. Chronic inflammation has been suggested to lead to DNA damage, resulting in alveolar epithelial injury, repair, and structural remodeling, ultimately leading to the development of lung cancer.

In recent years, with the advancement of targeted and immunotherapies, the prognosis for lung cancer patients has significantly improved[6,7]. However, there has been an upward trajectory observed in ILD caused by anti-cancer drugs. These anti-cancer therapies can also lead to acute exacerbation of pre-existing ILD (AE-ILD), which in severe cases can be life-threatening. Consequently, this demands significant clinical vigilance[8,9].

Numerous clinical trials have been conducted for their use in other types of ILD[10-12], owing to the well-established acknowledgement of the antifibrotic effects exhibited by nintedanib and pifenidone in IPF[13]. Pirfenidone has demonstrated the potential to decelerate the deterioration of pulmonary function in individuals diagnosed with progressive fibrotic ILD that lacks classification or does not correspond to IPF[14]. The primary anticancer mechanisms of nintedanib and pifenidone encompass the inhibition of epithelial-mesenchymal transition (EMT) in cancer cells and the regulation of the immune microenvironment within tumors[15-17]. Accordingly, antifibrotic drugs have received significant attention as combination therapy regimens for patients with ILD-LC.

This article presents a comprehensive review of the most recent developments in the epidemiology, risk factors, pathogenesis, diagnosis, and treatment of ILD-LC, aiming to providea valuable reference for the management of ILD-LC patients.

2 EPIDEMIOLOGY AND RISK FACTORS

2.1 IPF with Lung Cancer

IPF is a progressive fibrosing ILD characterized by exceptionally high mortality rates, with a median survival period ranging from 2 to 3 years[2]. The median survival duration for patients experiencing acute exacerbation of IPF (AE-IPF) is diminished to a range of 3-4 months[18,19]. An analysis of 670,258 patients from the National Health Insurance Service in South Korea estimated that the incidence of non-small cell lung cancer (NSCLC) in IPF patients is 17.5 times higher than in the general population[20]. A recent multicenter retrospective study in seven European countries showed that among 3,178 IPF patients, the prevalence of lung cancer was 10.2%[21]. By the end of 10 years following an IPF diagnosis, 26.6% of the patients were diagnosed with lung cancer[21]. Additionally, IPF patients with concurrent lung cancer have a higher all-cause mortality risk than those without lung cancer. However, IPF patients with lung cancer who received antifibrotic (pirfenidone and nidanib) drug treatment had a lower all-cause mortality rate compared to those who did not receive antifibrotic treatment[21].

2.2 CTD-related ILD (CTD-ILD) Related Lung Cancer

CTD often involves the lungs and is a common manifestation of ILD. Enomoto et al.[22] reported the cumulative incidence rates of lung cancer in 127 patients with CTD-ILD as 0%, 1.8%, and 2.9% at 1, 3, and 5 years, respectively. They also found that the increased risk of lung cancer might be associated with a high smoking index and emphysema. A study in Korea involving 2,491 CTD-ILD patients found that the incidence rates of lung cancer in males and females were 27% and 28%[23], respectively. Patients with CTD-ILD are 1.7 to 2 times more likely to develop lung cancer compared to ILD patients without CTD[23].

Among CTD-ILD subtypes, rheumatoid arthritis (RA) and systemic sclerosis (SSc) may be more prone to coincide with lung cancer[24,25]. Dolcino et al.[26] have identified the oncogenic signatures in patients with SSc, which involves the activation of several well-established oncogenic proteins, including RAS, JAK, c-Myc, BCL-2, MYD88, PARP, and the PI3K/Akt pathway. A significant correlation exists between the occurrence of lung cancer and SSc when ILD and anti-Scl-70 antibodies are present[27]. One potential mechanism for the development and progression of cancer in patients with RA may be related to the continued activation of the immune system, depending in particular on the presence of IL-6[28]. In addition, the COX-2/TxA2 pathway seems to serve as a molecular foundation for the susceptibility of lung cancer in patients with RA[29].

Studies indicate that the treatment of other ILD subtypes, such as CTD-ILD, often differs significantly from that of other idiopathic interstitial pneumonias like IPF[30], potentially resulting in better prognoses than IPF[31]. Radiotherapy and immunotherapy are generally well tolerated among patients diagnosed with CTD-LC, although it is advisable to exercise caution on CTD-ILD

patients. The potential efficacy of antiangiogenic therapy in halting the advancement of lung cancer and CTD without exacerbating the risk of adverse events related to ILD warrants consideration. Nintedanib, a recently developed treatment, shows promise in addressing both lung cancer and CTD-ILD. However, further comprehensive investigations involving extensive sample sizes and rigorous randomization are necessary to establish improved therapeutic approaches for individuals with CTD-ILD and lung cancer[32].

2.3 Other Types of ILD and Lung Cancer

Drug-induced ILD (DIILD) is an ILD caused by exposure to drugs that induce inflammation and potential interstitial fibrosis. The determination of its precise incidence poses challenges due to inherent complexities. Currently, over 400 drugs have been reported to cause ILD, with the most common culprits being bleomycin, everolimus, erlotinib, trastuzumab deruxtecan, and immune checkpoint inhibitors (ICIs), followed by anti-rheumatic drugs, amiodarone, and antibiotics[33]. Antineoplastic agents are a major cause of DIILD, with a prevalence ranging from 23% to 51%[34]. Prior to initiating any cancer treatment, the potential risk of DIILD should be thoroughly evaluated.

Silicosis is a progressive, environment-related disease characterized by pulmonary fibrosis changes. Based on the Iranian study, it was found that the relative risk of silicosis varied between 1 and 14 per 1,000 individuals, while the risk of lung cancer among workers ranged from 13 to 137 per 1,000 individuals[35]. Prolonged inhalation of silica particles increases the risk of lung cancer, with tumor lesions associated with intense pulmonary inflammation / fibrosis[36].

The post-infection hyperinflammatory response, known as “cytokine storm” and microthrombosis can lead to abnormal repair and fibrosis in the lungs. Residual interstitial changes and sequelae have been observed in COVID-19 survivors[37,38], and pre-existing ILD and pulmonary fibrosis increase the risk of severe COVID-19 manifestations[38]. Additionally, the research by Calles et al.[39] suggests that lung cancer with concurrent SARS-CoV-2 infection predicts worse outcomes, as evidenced by higher hospitalization and mortality rates. Measures to reduce the risk of SARS-CoV-2 infection are crucial for protecting lung cancer patients. The National Comprehensive Cancer Network and Society for Immunotherapy of Cancer advocated for the administration of authorized COVID-19 vaccines to lung cancer patients, including those currently undergoing treatment, as a means to mitigate the detrimental effects of infection.

3 MECHANISM OF ILD-LC

The precise mechanisms of development of lung cancer in individuals with ILD remain incompletely elucidated, however, there exist several pathogenic similarities[40]. Tobacco abuse, occupational and environmental exposures are common environmental risk factors for both ILD and lung cancer.

The dysregulation between oncogenes and tumor suppressor genes is a key factor leading to the carcinogenesis of fibrotic lung tissue[2]. In patients diagnosed with ILD-LC, p53 mutations prevail, while epidermal growth factor receptor mutations are infrequent[2]. Heterozygous mutations in SFTPA1 and SFTPA2 involving exon 6, which codes for the corresponding protein CRD, lead to various forms of ILD in younger individuals and a higher risk of lung cancer, representing a common genetic mechanism for both diseases[41].

In the field of epigenetics, alterations due to dysregulation of methylation and certain non-coding RNAs are common pathogenic features between ILD and lung cancer[42]. Hata et al.[43] have found low DNA methylation epigenotypes in lung squamous cell carcinoma significantly associated with IPF and poorer prognosis. Additionally, it is noteworthy that both IPF and LC exhibit aberrant expressions of certain microRNAs. Specifically, miR-21 is upregulated in both IPF and patients, correlating with poor prognosis in NSCLC patients[44,45].

Genetic and epigenetic abnormalities can lead to aberrant activation of common signaling pathways. Transforming growth factor β (TGF-β) is considered a key molecular regulator of pro-fibrotic signaling, exerting a significant influence on the advancement of lung cancer and inducing mitotic activity in lung cancer cells[46]. Furthermore, the Wnt/β-catenin pathway is implicated in the progression of both IPF and lung cancer. This pathway plays a significant role in cancer progression and EMT processes, thereby contributing to the pathogenesis of IPF[47]. Abnormal activation of the PI3K/AKT pathway leads to cancer invasion and progression of pulmonary fibrosis[48], activating pro-fibrotic downstream mediators like TGF-β1 and platelet-derived growth factor. The sonic hedgehog pathway is also activated in bronchiolar epithelial cells of honeycomb cysts and cancer fibroblasts, responsible for apoptosis of fibroblasts, tumor growth, metastasis, and chemotherapy resistance[49].

In the process of carcinogenesis, cancer-associated fibroblasts (CAFs), as a major component of the matrix, have garnered widespread attention regarding their origin, biological characteristics, and roles. The involvement of CAFs in promoting EMT plays a significant role in the pathogenesis of both ILD and lung cancer[50,51]. Remarkably, CAFs play a significant role in the resistance of NSCLC to chemotherapy, protecting the tumor from the effects of chemotherapeutic drugs[52].

Identifying new therapeutic targets based on the common

pathogenic pathways of ILD and lung cancer is a promising research direction for better treatment strategies and optimal management of patients with both conditions.

4 DIAGNOSIS OF ILD-LC

Despite the heightened occurrence of lung cancer in the presence of ILD, there is presently a lack of specific screening guidelines for ILD-LC patients. Due to the overlapping clinical manifestations of LC and ILD, such as dyspnea, cough, fatigue, reduced functional capacity, diagnosing ILD-LC poses a significant challenge.

High-resolution computed tomography is the most commonly used imaging modality for the initial diagnosis and follow-up of ILD[53]. Nevertheless, the intricate imaging manifestations of ILD necessitate a more objective approach, as the dependence on subjective judgment frequently results in delayed or inaccurate diagnosis and evaluation of ILD. Recently, there have been notable advancements in the utilization of artificial intelligence technology for medical image recognition[54]. However, the image data for ILD primarily originate from publicly available datasets, with limited studies conducted in real-world settings, which are mostly of small samples.

The presence of fibrosis makes it difficult for clinicians to distinguish potential lung cancer lesions from focal fibrosis on imaging, leading to missed or misdiagnoses. Positron emission tomography-CT (PET/CT) can be helpful in this context. In a study of 55 IPF patients, PET/CT had a sensitivity and specificity of 98% and 86%, respectively, for detecting malignant lung nodules[55]. PET/CT also offers more specificity than CT in staging mediastinal lymph nodes in patients with NSCLC and IPF.

If suspicious lymph nodes are identified on CT or PET/CT, further investigation may involve techniques like CT-guided transthoracic needle biopsy (TTNB) or bronchus ultrasound-guided biopsy. Amundson et al.[56] estimated the sensitivity and specificity of CT-guided TTNB for lung nodules in IPF patients to be 90% and 84%, respectively. Nevertheless, it is worth noting that approximately 34% of the biopsies yielded inconclusive results, and complications were observed in up to 51% of the cases.

Liquid biopsy is an emerging non-invasive tool to diagnose disease by detecting circulating tumor cells, circulating tumor DNA, exosomes, microRNA, circular RNA, tumor-educated platelets, and tumor endothelium[57]. Pallante et al.[58] found a high concordance between circulating cell-free DNA and genomic DNA in IPF patients, suggesting that the former may carry specific genetic information originating from the primary site of the disease. Liquid biopsy may potentially emerge as a novel diagnostic approach for ILD-LC owing to its non-invasive characteristics, ease of acquisition, ability to reflect the overall disease state, and capacity for real-time monitoring.

5 THERAPY OF ILD-LC

The selection of suitable systemic therapy regimens for patients with LC and concurrent ILD is a considerably intricate task, as certain treatments such as chemotherapy, targeted therapies, and immunotherapies pose the potential risk of inducing adverse events related to ILD or pneumonitis. Consequently, the optimal strategies for systemic therapy in patients with LC and coexisting ILD must carefully consider both efficacy and the distinctive safety considerations associated with individuals.

5.1 Surgical Treatment

Surgical resection is a primary treatment method for lung cancer and is currently the only clinical approach for curing lung cancer. However, AE-ILD are among the most severe complications during the perioperative period for ILD-LC. The incidence of AE-IPF post lung resection is reported to be between 12-27%. The management of this condition frequently necessitates the administration of high corticosteroid doses or their combination with immunosuppressants; nevertheless, the mortality rate remains considerably elevated, ranging from 30% to 100%[59]. Hence, it is imperative to thoroughly assess concomitant diseases prior to surgery in order to achieve stabilization of autoimmune disease and control of ILD, consequently enhancing perioperative safety[60].

5.2 Pharmacotherapy of ILD-LC

Choosing an appropriate systemic treatment for patients with ILD-LC poses a complex challenge due to the potential risks of AE-ILD associated with chemotherapy, targeted therapies, and immunotherapy[33].

The initial anti-tumor strategy for ILD-LC primarily involves chemotherapy. Studies suggest that 5% to 20% of patients with ILD experience AE-ILD during chemotherapy, which can be fatal[61,62]. Carboplatin and nab-paclitaxel combination have been assessed as a first-line treatment option in 2 single-arm phase II studies involving patients with NSCLC and ILD[63,64]. The incidence of AE-ILD with the carboplatin plus albumin-bound paclitaxel regimen is relatively lower (approximately 4%) compared to other chemotherapy regimens[8,63]. Therefore, the combination of carboplatin and albumin-bound paclitaxel has been evaluated as a first-line treatment for NSCLC patients with ILD.

For lung cancer patients with genetic mutations, oral targeted drugs are increasingly prioritized as initial treatment. However, targeted therapies may increase the risk of pulmonary toxicity in patients with pre-existing ILD. The incidence of tyrosine kinase inhibitor-induced AE-ILD ranges from 5% to 12.2%[65,66].

ICIs have shown clinical benefits in various cancers,

including locally advanced and metastatic stages. A recent meta-analysis indicated that programmed death protein 1 / programmed death-ligand 1 inhibitors are effective in NSCLC with pre-existing ILD. However, previous studies have suggested an ICIs-ILD incidence of 3.5% to 16.9%, with grade 4 and lethal ILD accounting for 19%[67-69]. Therefore, close monitoring of ILD during ICIs treatment is essential, with vigilance for the occurrence of AE-ILD.

Novel antifibrotic drugs like pirfenidone and nintedanib can slow the progression of pulmonary fibrosis and reduce the risk of acute exacerbations[70]. Perioperative use of pirfenidone can lower the incidence of AE-IPF post lung resection[71]. Additionally, the combination of nintedanib with chemotherapy can improve overall survival in patients with non-squamous histology[72].

6 CONCLUSION

Presently, a lack of consensus exists regarding the management of patients diagnosed with ILD-LC. During the diagnostic process, it is crucial to elicit information regarding the patient's autoimmune disorders, specific occupational and environmental exposures, as well as pertinent medical history. This data should be integrated with histopathological and imaging features to ascertain the specific classification of ILD. The application of artificial intelligence in aiding CT image recognition and the use of liquid biopsy techniques may help improve the accuracy of ILD-LC diagnosis. Although the use of pirfenidone and nintedanib may prolong the survival of ILD patients and reduce the incidence of LC, the development of a truly efficacious intervention capable of impeding the progression of this ailment remains a considerable challenge. Therefore, further research is urgently needed to explore whether specific cancer drugs might have beneficial antifibrotic effects, thereby effectively treating patients with ILD-LC.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (No. 82200070) and the Innovation and Development Joint Fund of the Natural Science Foundation of Chongqing (No. CSTB2023NSCQ-LMX0037 and No. CSTB2023NSCQ-LMX0038).

Conflicts of Interest

The authors declared no conflict of interest.

Author Contribution

Liang H and Zhao Z guided the scope and research background. Sun J and Wang Y wrote the manuscript. Yang R and Su W critically revised the manuscript.

Abbreviation List

AE-ILD, Acute exacerbation of pre-existing ILD
AE-IPF, Acute exacerbation of IPF
CAFs, Cancer-associated fibroblasts
CTD, Connective tissue disease
CTD-ILD, CTD-related ILD
DIILD, Drug-induced ILD
EMT, Epithelial-mesenchymal transition
ICIs, Immune checkpoint inhibitors
ILD, Interstitial lung disease
ILD-LC, ILD with lung cancer
IPF, Idiopathic pulmonary fibrosis
NSCLC, Non-small cell lung cancer
PET/CT, Positron emission tomography-CT
RA, Rheumatoid arthritis
SSc, Systemic sclerosis
TGF-β, Transforming growth factor β
TTNB, Transthoracic needle biopsy

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