Expert Consensus

Expert consensus on cancer treatment-related lung injury

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Background: Although advancements in cancer therapies have substantially improved the survival of cancer patients, these treatments may also result in acute or chronic lung injury. Cancer treatment-related lung injury (CTLI) presents with a diverse array of clinical manifestations and can involve multiple sites. Due to the lack of specific diagnostic protocols, CTLI can deteriorate rapidly and may be life-threatening if not promptly addressed. Unfortunately, there is no universally accepted consensus document on the diagnosis and management of CTLI.

Methods: A multidisciplinary panel comprising experts from respiratory and critical care medicine, oncology, radiation oncology, thoracic surgery, radiology, pathology, infectious diseases, pharmacy, and rehabilitation medicine participated in this consensus development. Through a systematic literature review and detailed panel discussions, the team formulated nine key recommendations.

Results: This consensus document addresses the concept, epidemiology, pathogenesis, risk factors, diagnostic approach, evaluation workflow, management strategies, differential diagnosis, type-specific management and clinical staging of CTLI. Emphasis is placed on raising awareness among clinicians and therapeutic practices through comprehensive guidelines.

Conclusions: The consensus provides a detailed diagnostic protocol for CTLI and introduces a structured management framework based on grading, typing, and staging. It highlights the critical role of multidisciplinary team (MDT) collaboration and emphasizes the need for individualized, whole-process patient care strategies to optimize clinical outcomes.

Keywords: Cancer; anti-tumor therapy; lung injury; diagnosis; treatment

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Introduction

Cancer poses a significant global health burden. While advancements in cancer treatment have substantially improved patient survival, these therapies may also lead to acute or chronic lung injuries. The lungs are particularly vulnerable due to their dual role in receiving systemic venous blood and their direct exposure to the external environment, making them susceptible to damage from various toxic agents. Chemotherapy, radiotherapy, targeted therapy, immunotherapy, and antibody-drug conjugates

(ADCs) have all been implicated in causing lung injury. As the number of cancer treatments increases and oncologic outcomes improve, reports of cancer treatment-related lung injury (CTLI) are becoming increasingly common. This trend may be partially attributed to the increase in clinical awareness. Anti-tumor agents are among the most prevalent drugs associated with drug-induced lung injury (1,2). Lung injury not only impairs quality of life but can also result in treatment discontinuation, disease progression, and even death. In an analysis of 53 cohorts, lung injury emerged as the commonest fatal toxicity in patients receiving epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) (3). A prospective study from the French Registre des Effets Indésirables Sévères des Anticorps Monoclonaux Immunomodulateurs en Cancérologie (REISAMIC) registry revealed that with increased vigilance towards immune-related adverse events (irAEs), the prognoses for most adverse events have improved, notably with a significant reduction in myocarditis-related mortality; however, the respiratory mortality rate has increased rather than decreased, reaching a high of 26.3% (4). Due to the respiratory system's direct interface with the external environment and its unique microenvironment and circulation, diagnosing and treating lung disorders is more complex compared to conditions in other organs. CTLI exhibits a diverse range of clinical presentations and involvement sites and can easily be misdiagnosed due to the lack of specific diagnostic protocols and broad differential diagnosis, including lower respiratory tract infection, pulmonary embolism, tumor progression, pseudo-tumor progression, exacerbation of pre-existing lung diseases, cardiogenic pulmonary edema, and acute coronary syndrome (ACS). Furthermore, definitive diagnosis often requires advanced imaging or invasive procedures (e.g., bronchoscopy with biopsy), which are primarily available in tertiary care settings. Diagnostic complexity is compounded in severe CTLI cases, where patients may be too critically ill to tolerate imaging or bronchoscopy examinations due to hypoxemia or hemodynamic instability, further delaying accurate identification. Delayed diagnosis or improper treatment of CTLI can lead to rapid disease progression and even death. Therefore, timely identification, diagnosis, and management are crucial to improving patient outcomes. In light of these challenges, there is a critical need to establish a dedicated consensus on CTLI to address the current lack of standardized diagnostic algorithms and limited high-quality evidence guiding therapeutic interventions. This consensus document not only reaffirms the existing grading system for CTLI but also introduces specific clinical types and stages to facilitate more precise and personalized treatment approaches. The consensus recommendations presented here were developed through extensive consultations with experts in the field.

Highlight box

Key recommendations

- We recommend that effective diagnosis and management of cancer treatment-related lung injury (CTLI) require a multidisciplinary team (MDT) approach alongside tailored, comprehensive patient care strategies.

What was recommended and what is new?

- Earlier expert consensus on drug-induced lung injury primarily emphasized its clinical symptoms, imaging findings, and pathological characteristics.
- This consensus updates previously highly focused areas and places emphasis on new management approaches based on specific typing and staging of CTLI.

What is the implication, and what should change now?

- This expert consensus implicates a CTLI management strategy utilizing grading, typing, and staging systems to guide personalized and comprehensive clinical care, with particular emphasis on implementing an MDT approach throughout the therapeutic continuum. Future clinical studies focusing on novel diagnostic biomarkers and innovative treatment modalities for CTLI.

Methods

The development of this consensus document involved an expert panel comprising a multidisciplinary team (MDT) with extensive experience and specialized knowledge in respiratory and critical care medicine, oncology, radiation oncology, thoracic surgery, radiology, pathology, infectious diseases, pharmacy, and rehabilitation medicine. Literature was retrieved from databases including PubMed, Embase, Web of Science, The Cochrane Library, Wanfang Medicine, and Chian National Knowledge Infrastructure (CNKI) up to 31 January 2024. The Boolean operators were used to construct a logical search, focusing on keywords related to cancer treatment and lung injury. The keywords were retrieved and intersected to identify relevant studies, among which the treatment-related keywords included "surgical treatment", "interventional therapy", "radiotherapy", "chemotherapy", "targeted therapy", "immunotherapy", and "antibody-drug conjugate (ADC)", whereas the lung injury-related keywords encompassed "lung injury", "pleural injury", "airway injury",

"pulmonary vascular injury", "pulmonary toxicity", "radiation pneumonitis", "treatment complications", "pulmonary function tests", "arterial blood gas analysis", and "interstitial pneumonia". The initial draft of this consensus document was authored by C.Z., X.L., W.Z., M.L., G.L., H.G., and Q.C. After a targeted literature review of CTLI, the diagnostic and treatment consensus were developed based on literature and professional expertise. Additionally, the levels of evidence and grades of recommendations were assigned in accordance with the 2009 edition of the Oxford Centre for Evidence-Based Medicine's criteria. The expert panel was divided into six subgroups, each comprising at least five representatives from the corresponding fields. These subgroups were tasked with reviewing and refining specific issues within the consensus document. To be included in the final manuscript, each recommendation required more than 70% agreement from the panel. After achieving subgroup consensus, experts who had not been involved in the initial drafting were invited to participate in further revisions (Appendix 1). The final version of this consensus document was achieved through multiple rounds of revisions and collective deliberation.

Concepts

Consensus 1 CTLI is an umbrella term encompassing a range of non-infectious physical, chemical, and immune-mediated pathophysiological responses in the respiratory system including the airways, lung parenchyma/interstitium, vasculature, and pleura compartments, resulting from anti-tumor drugs, surgical procedures, radiotherapy, and/or other localized treatments during cancer therapy. (Level of evidence: 1a)

Etiologies of CTLI

CTLI can be etiologically classified as either drug-related or non-drug-related. Drug-related CTLI primarily encompasses lung injuries caused by chemotherapy, targeted therapy, mammalian target of rapamycin (mTOR) inhibitors, immunotherapy, and ADCs, whereas non-drug-related lung injury includes those caused by surgery, radiotherapy, and other localized treatment modalities (*Table 1*).

Injury types

CTLI can manifest as various types of injuries depending on the site of damage within the respiratory system. Among them, airway injury may manifest as airway mucosal inflammation, edema, ulceration, scarring, airway stenosis, and tracheoesophageal fistula. Parenchymal/interstitial lesions can present as diffuse alveolar damage (DAD), pulmonary edema, pulmonary hemorrhage, interstitial lung disease (ILD), and pulmonary fibrosis. Pulmonary vascular injury can manifest as pulmonary embolism and vasculitis, whereas pleural injury may present as hemothorax, pneumothorax, pleural adhesions, and peritoneal irritation sign (*Table 1*). ILD resulting from parenchymal/interstitial injury is the most prevalent form of CTLI.

Epidemiology

Consensus 2 The incidence and mortality of lung injury resulting from different cancer treatment modalities vary significantly. Although CTLI due to a single factor does exist in clinical settings, it is more frequently a multifactorial condition. (Level of evidence: 1a)

CTLI has been reported across a spectrum of tumor types, and the incidence and mortality rates of lung injury associated with various cancer treatments vary widely, since CTLI is frequently not caused by a single factor but rather by a combination of multiple factors. Moreover, the combination of multiple anti-tumor drugs may increase the risk of pulmonary toxicity.

Chemotherapy-related lung injury (CRLI)

The incidence of CRLI varies depending on the specific drug and treatment regimen, with overall rates ranging from 1% to 40% (5). Specifically, the incidence of pulmonary toxicity associated with gemcitabine, pemetrexed, bleomycin, and mitomycin C ranges from 1.1% to 3.9%, 1.8%, 6.8% to 15%, and 2% to 12%, respectively (6). Manifestations of CRLI are diverse, mainly including ILD, acute respiratory distress syndrome (ARDS), bronchospasm, and thrombotic microangiopathy. Pulmonary veno-occlusive disease (PVOD) with pulmonary hypertension and exudative pleural effusions has also been reported (7). Nevertheless, ILD is the most common form of CRLI (7). The mortality rate of CRLI varies by drug. For example, bleomycin-associated interstitial pneumonitis (IP) has a mortality rate of 8.1–23% (6).

Radiotherapy-induced lung injury (RILI)

RILI can be categorized into an early acute phase known as radiation pneumonitis (RP; occurring usually within 6 months) and a late phase called

Table 1 Etiology, common sites, and types of CTLI

Etiologies of CTLI	Description	Common sites and types
Drug-related lung injury		
Chemotherapy	Chemotherapy-induced CTLI is typically characterized by pulmonary inflammation and fibrosis. The severity of such lung injuries may vary based on the specific chemotherapeutic agent (e.g., bleomycin, gemcitabine, methotrexate, etoposide, etc.), dosage, and patient-specific factors. The choice of specific treatment regimens can also impact the severity of chemotherapy-induced CTLI	Airway: inflammation and stenosis Lung parenchyma/interstitium: pneumonitis and pulmonary fibrosis Pulmonary vasculature: pulmonary hypertension, PVOD Pleura: pleural adhesions
Targeted therapy	Targeted therapy typically exhibits a lower incidence of side effects compared to conventional chemotherapy. However, it is crucial to recognize that some targeted agents, especially TKIs (e.g., EGFR-TKIs, ALK-TKIs, and other multitargeted TKIs) and anti-vascular agents (e.g., bevacizumab), can induce pulmonary toxicities such as pulmonary fibrosis	Airways: NA Lung parenchyma/interstitium: pneumonitis and alveolar hemorrhage Pulmonary vasculature: pulmonary embolism and pulmonary hypertension Pleura: pleural effusion
mTOR inhibitors	Pulmonary toxicity from mTOR inhibitors encompasses acute and chronic lung injuries that occur as adverse reactions during treatment. Acute lung injury may manifest with symptoms including dyspnea, cough, and chest pain, whereas chronic lung injury can result in severe outcomes such as pulmonary fibrosis and airway stenosis	Airway: inflammation and stenosis Lung parenchyma/interstitium: fibrosis, alveolitis, and emphysema Pulmonary vasculature: NA Pleura: NA
Immunotherapy	Immunotherapy-related lung injury involves more complex mechanisms, which primarily manifest as lung inflammation and fibrosis but may also present as bronchial asthma attacks. Immunotherapies associated with lung injury include immune checkpoint inhibitors, CAR-T cell therapy, and TCR-T cell therapy	Airways: inflammation and stenosis Lung parenchyma/interstitium: cryptogenic organizing pneumonitis, hypersensitivity pneumonitis, acute interstitial pneumonitis, nodular reactions/GGO nodules, and pulmonary fibrosis Pulmonary vasculature: vasculitis Pleura: pleuritis and pleural effusion
ADCs	ILD or pneumonitis is a major adverse event associated with ADC use. Drug-related ILD has been reported with ADC drugs such as T-DM1, T-DXd, and mirvetuximab soravtansine	Airway: NA Lung parenchyma/interstitium: pneumonitis and pulmonary fibrosis Pulmonary vasculature: NA Pleura: pleuritis and pleural effusion
Non-drug-related lung injury		
Surgery	Surgery for cancer can lead to lung injury, ranging from hypoxemia to ALI and ARDS, possibly caused by surgical trauma, stress response, anesthetic use, single-lung ventilation, ischemia-reperfusion injury, transfusion-related lung injury, and volume overload	Airway: NA Lung parenchyma/interstitium: pulmonary edema and pneumonitis Pulmonary vasculature: NA Pleura: hemothorax and pneumothorax

Table 1 (*continued*)

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Etiologies of CTLI	Description	Common sites and types
Radiotherapy	RILI refers to damage to normal lung tissue within the radiation field, which is caused by a specific dose of radiation. The injured site undergoes processes including immediate damage, formation of basement membrane peeling area, alveolar wall sclerosis, initiation of fibrosis, and development of elastic fibers in the alveolar septum. Factors influencing RILI include radiotherapy techniques, treatment approaches, and patient-specific characteristics	Airway: tracheitis/bronchitis Lung parenchyma/interstitium: pneumonitis, pulmonary fibrosis Pulmonary vasculature: narrowing or blockage of the pulmonary blood vessels Pleura: radiation-induced pleurisy
Other local therapeutic procedures	Local therapeutic procedures, including transbronchial intervention, thoracentesis, chest drainage, thoracoscopic surgery, and radiofrequency ablation, can lead to lung injury	Airways: mucosal inflammation, edema, ulceration, scarring, airway stenosis, and tracheoesophageal fistula Lung parenchyma/interstitium: pulmonary hemorrhage, infection, atelectasis, localized pneumonitis, or pulmonary fibrosis Pulmonary vasculature: pulmonary vascular injury Pleura: hemothorax, pneumothorax, and pleural adhesions

ADCs, antibody-drug conjugates; ALI, acute lung injury; ALK, anaplastic lymphoma kinase; ARDS, acute respiratory distress syndrome; CAR, chimeric antigen receptor; CTLI, cancer treatment-related lung injury; EGFR, epidermal growth factor receptor; GGO, ground-glass opacity; ILD, interstitial lung disease; mTOR, mammalian target of rapamycin; NA, not applicable; PVOD, pulmonary veno-occlusive disease; RILI, radiotherapy-induced lung injury; TCR, T cell receptor; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor.

radiation fibrosis (occurring after 6 months to several years) (8). In the RTOG 0617 study, the incidence of grade 3 or higher RP was up to 7.9% in the 74-Gy dose group undergoing concurrent chemoradiotherapy (CRT) (9). The incidence of pneumonitis increased notably subsequent to the administration of combined chemotherapy, immunotherapy, targeted therapy, and additional treatment modalities (10,11). A meta-analysis revealed that the mortality rate was 1–2% in patients with RP (12) but could reach 50% in those with severe RP (13).

TKI-related lung injury

ILD associated with TKIs has been observed across various tumor types. In clinical trials of TKIs, gefitinib, erlotinib, afatinib, and osimertinib were found to induce severe drug-related ILD (incidence: 0.4–5.3%; mortality: 0–0.9%) (14). The incidence of ILD associated with cyclin-dependent kinase 4/6 (CD4/6) inhibitors ranges from 0.5% to 5.2% (15). A retrospective study examining TKI-related toxicities in the treatment of chronic myelogenous leukemia (CML) revealed that a minority of CML patients treated with dasatinib (<10%) or imatinib (<1%) also developed TKI-related ILD (16). Anti-vascular endothelial growth factor (VEGF) drugs are frequently utilized as targeted therapy for tumors. The representative drug bevacizumab rarely causes grade 3 or higher toxicities, with the incidence of ILD being as low as 0.6% (17). ILD associated with other targeted therapies is more infrequent. In a clinical trial involving sorafenib, a multi-target TKI, no cases of ILD have been linked to its use (18); similarly, only a small number of cetuximab-related ILD cases have been reported (19).

mTOR inhibitor-related lung injury

mTOR inhibitor-related pneumonitis is a rare but potentially life-threatening side-effect, representing a specific type of ILD caused by mTOR inhibitors. The epidemiological data on mTOR inhibitor-related pneumonitis are incomplete, and various studies have reported differing rates of incidence and mortality. In general, mTOR inhibitor-related pneumonitis has an

incidence of 3–54% and a mortality of 0–50%, depending on the type of drug, dose, course of treatment, and concomitant medications (20). Meta-analysis of phase II/III randomized controlled trials investigating mTOR inhibitor therapies revealed a 10.4% cumulative incidence of pulmonary toxicity across severity grades, with severe adverse events (grade ≥3) accounting for 2.4% of reported cases (21).

Immunotherapy-related lung injury

Immunotherapy encompasses the use of immune checkpoint inhibitors (ICIs), tumor vaccines, cellular immunotherapy, and non-specific immunomodulators. The most commonly reported immunotherapy-related lung injury involves ICIs and cell therapy, with checkpoint inhibitor pneumonitis (CIP) being one of the most frequent fatal irAEs. The incidence of CIP varies depending on the tumor type, the specific ICIs used, and the different combinations of these agents. A meta-analysis of 4,496 patients revealed a higher incidence of pneumonitis in non-small cell lung cancer (NSCLC) patients (4.1%) and renal cell carcinoma patients (4.1%) compared to that in melanoma patients (1.6%) (22). Data from a previous clinical study have demonstrated that the incidence of any grade of CIP following treatment with programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) monoclonal antibodies was approximately 5%, with the incidence of CIP above grade 3 being approximately 1% (23). Among these, the incidence of CIP with PD-1 treatment was slightly higher than that with PD-L1, at 3.6% and 1.3% respectively (24). Compared to PD-1/PD-L1, cytotoxic T-lymphocyte antigen-4 (CTLA-4) inhibitors are associated with a lower incidence (<1%) of CIP (25). In addition, a meta-analysis of 613 fatal irAEs found that the fatality rate of CIP was as high as 35%, which was particularly common in patients receiving immunotherapy and PD-1/PD-L1 monoclonal antibodies (26). In several real-world studies, the incidence of CIP was found to be significantly higher than that reported in clinical trials. It ranged approximately from 10% to 20% in NSCLC patients (27-30), with the proportion of severe CIP being 35.4% and the mortality rate among these patients being 6.1%. Steroid-refractory CIP (SRCIP) is a distinct subset of CIP that demonstrates poor response to glucocorticoid (GC) therapy, with a real-world incidence of approximately 18–40% (31,32). Management of SRCIP often necessitates the use of alternative immunosuppressive agents (e.g., infliximab), which was associated with a particularly poor prognosis and a mortality rate exceeding 70% (31,32). Only a limited number of studies have described the incidence of lung injury associated with cell therapy. In a study that aggregated data on chimeric antigen receptor T-cell (CAR-T) therapy from 2,657 patients in the USA Food and Drug Administration Adverse Event Reporting System (FAERS), cardiovascular and pulmonary adverse events were identified in 546 patients (20.5%). When compared to the entire database, CAR-T therapy was found to be associated with an increased incidence of pleural disease [n=46, 1.7%; odds ratio (OR) =3.91; 95% confidence interval (CI): 2.92–5.23; after adjusting for age and sex] (33).

ADC-related lung injury

A large-scale meta-analysis encompassing 7,732 patients across 39 studies evaluated the incidence of ADC-related pneumonitis (34). The pooled analysis demonstrated an all-grade pneumonitis incidence of 5.86% (grade ≥3: 0.68%) in solid tumor populations. With ADC monotherapy, these rates were marginally lower at 5.08% for all-grade events and 0.57% for grade ≥3 pulmonary complications. ADC combination therapies demonstrated an overall all-grade pneumonitis incidence of 10.58%, with grade ≥3 events occurring in 1.29%. Substantial variations in pneumonitis prevalence were observed across different ADCs, with trastuzumab deruxtecan (T-DXd) exhibiting the most pronounced pulmonary toxicity profile (all-grade: 13.58%; grade ≥3: 2.19%), marking the highest rates reported among ADC therapies. Among the 11 analyzed studies, pneumonitis-related mortality ranged from 0.1% to 2.6%.

Other categories of lung injury

Non-pharmacological factors are also significant contributors to CTLI. In addition to radiation therapy, surgery and other localized therapeutic procedures can also induce lung injury. Postoperative pneumonia (POP), one of the most frequent postoperative complications, exhibits a variable incidence that is influenced by the type of surgery and the surgical site. More specifically, the incidence of POP is higher after major surgeries in the upper abdomen, heart, lungs, esophagus, oral cavity, and head and neck, reaching up to 39% (35). A long-term follow-up study conducted by Simonsen *et al.* revealed that the mortality rates for patients with POP *vs.* those without POP were 21.6% *vs.* 16.8% within 31–365 days after surgery [hazard ratio (HR) =1.31; 95% CI: 1.00–1.73] and 62.2% *vs.* 53.0% at 1–5 years post-surgery (HR =1.22; 95% CI: 0.98–1.53) (36).

Lung surgery for early-stage lung cancer can also induce lung injury (37,38). This is related to a combination of ventilation-induced lung injury (i.e., to the contralateral lung being ventilated during lung surgery) and operative injury (to the lung being operated upon); this injury occurs most commonly in patients with poor pulmonary function, ILD and after immunotherapy (37-39). This is an area of active research to try to identify biomarkers and methods to circumvent or reduce such CTLI (40). Compared with surgery, local therapeutic procedures, such as lung tumor ablation and tracheal stenting, offer the benefits of reduced invasiveness, maximal preservation of lung function, and a mortality rate of less than 1% (41). However, these procedures can still be associated with thoracic complications (41), with pneumothorax being the most prevalent complication (12–62%), although other complications such as pleural effusion, pulmonary infection, pulmonary hemorrhage, and bronchopleural fistula have also been described (42,43).

Pathogenesis

Consensus 3 The pathogenesis of CTLI remains incompletely elucidated. The possible mechanisms may include direct physical damage, cytotoxic chemical injury, lung injury secondary to immune responses, and interactions among various mechanisms. (Level of evidence: 3b)

Direct cellular damage by physical or chemical factors results in lung injury through several mechanisms: (I) it induces the generation of reactive oxygen species (ROS) and excessive free radicals, which that disrupt the repair mechanisms of alveolar injury (44-47); (II) it stimulates the secretion of inflammatory cytokines and chemokines including tumor necrosis factor-α (TNF-α), monocyte chemoattractant protein-1 (MCP-1), and transforming growth factor-β (TGF-β) (48,49); (III) it activate apoptosis signals (e.g., Fas-Fas ligands and caspase) and enables the sequestration of redox-active metals (e.g., iron and copper) from cellular processes (50).The mechanism of lung injury associated with targeted therapy is target-dependent; for instance, targeting EGFR will inhibit the repair and regeneration of lung epithelial and endothelial cells, leading to cellular dysfunction (51). Furthermore, targeted therapy drugs, acting as potential antigens or haptens, can induce immune-mediated pulmonary toxicity (mostly mediated by T cells) (52). Additionally, these agents can mediate lung injury by eliciting phospholipid toxicity in alveolar macrophages and type II alveolar cells (52).

CIP is closely associated with immune system regulation. On the one hand, immunotherapy can induce epitope spreading, and the off-target effects of T cell-mediated immunity result in the destruction of normal tissues (53). On the other hand, the blockade of immune checkpoint signaling leads to the immune dysregulation of T cell subsets, including the release of immunosuppression by Th2 cells and Tregs and the excessive immune response and cytokine secretion by Th1 and Th17 cells, which culminate in autoimmune damage to normal tissues (54). Additionally, rise in autoantibodies, imbalance among inflammatory factors, alterations in microbial diversity, and regulation of the immune microenvironment by the "gut-lung axis" may contribute to the increased incidence of lung injury (55-58). The primary mechanism underlying ADC-induced lung injury is the target-independent uptake of ADCs by lung tissue. In addition, the bystander effect (i.e., the cytotoxic payload released by cancer cells) and the entry of payload into the bloodstream following the dissociation of ADCs may play a role in ADC-related lung injury (59).The precise mechanism by which the risk of combination therapy-mediated pneumonitis is elevated remains unclear. For instance, radiation recall pneumonitis (RRP) is an acute inflammatory response that arises in pre-irradiated lung tissue following the administration of systemic anti-tumor agents (60). This phenomenon is primarily attributed to DNA oxidative damage mediated by radiotherapy, which markedly upregulates the expression of major histocompatibility complex class I (MHC-I) in tumor cells, thereby rendering them more susceptible to enhanced immune recognition following systemic therapies, such as PD-1/PD-L1 inhibitors (61). Overall, the harm associated with combination therapy may stem from the cumulative toxicities and the alterations in immune microenvironment subsequent to treatments. The specific mechanisms involved require further elucidation through additional preclinical investigations.

Risk factors

Consensus 4 The common clinical risk factors for CTLI include advanced age, ethnicity and genetic predisposition, underlying lung diseases, and use of combination therapy. (Level of evidence: 2a)

Advanced age

Age may be a factor contributing to CTLI onset. A

prospective, multicenter study indicated a strong association between being over 60 years old and the development of RP in lung cancer patients (62). The incidence of EGFR-TKI-related ILD was elevated in patients over 55 years of age (63). The proportion of patients over 70 years of age in the CIP cohort significantly higher than that in the non-CIP cohort (54.5% *vs.* 30.3%, P=0.025) (64). However, this observed association may be confounded by factors such as smoking history, pre-existing lung diseases [e.g., chronic obstructive pulmonary disease (COPD) or fibrosis], and socioeconomic disparities. A recent study investigating T-DXd revealed an inverse association, with younger patients (<65 years) exhibiting a significantly higher incidence of CTLI (65). A study has indicated that the overall safety profile of ICIs is comparable between elderly and younger patients (66). These discrepancies highlight the need for multivariate analyses to disentangle age-specific effects from coexisting risk factors. Further studies are warranted to validate age as an independent risk factor for CTLI

Ethnicity and genetic predisposition

Variations in drug metabolism and response among different ethnic groups result in diverse toxicities experienced by patients of different ethnic backgrounds when administered the same anti-tumor drugs. A large-scale meta-analysis revealed that Asian patients exhibited a lower tolerance to lung radiation, with Asian patients diagnosed with locally advanced NSCLC experiencing a higher incidence of pneumonitis following CRT compared to non-Asian patients (67). The incidence of lung injury associated with EGFR-TKI or anaplastic lymphoma kinase (ALK) inhibitors was notably higher in Japanese cohorts (68,69). The incidence of CIP following concurrent CRT and subsequent immunotherapy was similar in another Japanese cohort, which may be associated with racial disparities in driver mutations (e.g., *EGFR* and *BRAF* mutations as well as *ALK* and *ROS1* translocations) and immunology (70). Another study indicated that Caucasian patients carrying the TGF-β allele were at a reduced risk of RP (71). However, such an association was not confirmed in a Chinese patient cohort, suggesting that disparities in human genetic backgrounds may partially account for these conflicting findings (72). Thus, ethnicity and genetic background are critical factors in CTLI.

Underlying lung diseases

Underlying lung diseases that are regarded as possible risk factors for CTLI include COPD, ILD, asthma, and pleural effusion (73). Due to the impaired lung function in these individuals, they are at a higher risk of developing lung injury during cancer treatment. Emphysema may be a risk factor for RP following thoracic radiotherapy in patients with locally advanced NSCLC, particularly those with squamous cell carcinoma of the lung. The severity of emphysema is positively correlated with the incidence of RP after radiotherapy (74). COPD patients typically exhibit compromised lung function, diminished lung elasticity, and constricted airways, rendering them more vulnerable to radiation-induced lung injury. Patients with ILD demonstrated a significantly elevated incidence of RP compared to those without ILD (grade ≥2, 20.5% *vs.* 5.8%; P<0.01; grade ≥3, 10.3% *vs.* 1.0%; P<0.01) (75). Another study showed that the incidence of concurrent CRT-related death increases in patients with pre-existing pulmonary fibrosis (76). Preexisting interstitial lung abnormalities may be a risk factor associated with CIP (77). Pre-existing pulmonary fibrosis may increase the risk of pneumonitis related to gefitinib and erlotinib (75-80). It is important to note that pre-existing lung diseases are associated with factors such as smoking, age, and socioeconomic status; thus, they may not act as independent risk factors for CTLI.

Combination therapy

Although the therapeutic benefits of combination therapies are significant, drugs from different classes may elicit similar patterns of pulmonary toxicity, thereby augmenting the risk of CTLI (81). For instance, while the combination of radiation therapy with other treatments raises the locoregional control rate in lung cancer patients, it may also increase the incidence of radiation-induced lung injury (82). Escalating the dose of cancer therapy, using combinations of various treatments, and adjusting the order in which the treatment combination is administered may elevate the incidence of ILD (83).In a retrospective study, a significantly greater proportion of patients experiencing lung injury was observed among those treated with a combination of cytotoxic medications and molecularly targeted agents compared to those receiving monotherapy (84). The combination of thoracic radiotherapy with EGFR-

TKIs elevated the overall risk of severe treatment-related pneumonitis in NSCLC patients. Additionally, this combination therapy was less tolerable compared to sequential treatment approaches (85). The combination of PD-L1 inhibitors with thoracic radiotherapy significantly increased the incidence and severity of treatment-related pneumonitis in lung cancer patients, with 6.25% of these patients developing fatal pneumonitis (86). The combination of nivolumab with EGFR-TKIs was reported to be associated with a higher incidence of ILD than when either drug was used alone (87). Furthermore, the incidence of CIP differed among immunotherapy agents, with users of anti-PD-1 antibodies experiencing a higher rate of CIP compared to users of anti-PD-L1 antibodies (3.6% *vs.* 1.3%, P=0.001) (24). However, the addition of anti-CTLA4 drugs did not seem to exacerbate the severity of respiratory irAEs (4). Immunotherapy combined with chemotherapy was significantly associated with an increased risk of pulmonary toxicity compared to immunotherapy alone (88). Therefore, combination therapy in patients with potential risk factors should be used with particular caution, and close monitoring for the onset of CTLI is essential.

Other considerations

Smoking history and sex may be also linked to the incidence of CTLI (89). Male sex has been reported as a risk factor for CTLI following treatment with EFGR-TKIs, pemetrexed, and methotrexate (6), but one study showed that females appear to be more likely to develop CIP (30). Notably, this observed sex disparity could be confounded by smoking patterns, as males historically demonstrate higher smoking prevalence, and smoking itself is strongly linked to pre-existing lung diseases that may potentiate CTLI risk. The seasonal distribution of ICI/TKI-induced pneumonitis has also been documented, indicating that viral infections may play a role in the development of pulmonary toxicity (69,89). There has also been a significant correlation noted between tumor location and RP, with lung tumors located in the middle or lower lobes and those larger in size (>22.5 mm) demonstrating a higher likelihood of RP (90,91). Recent research has revealed that NSCLC patients are more prone to experiencing irAEs if they have pre-existing antibodies such as antithyroid peroxidase, antithyroglobulin, antinuclear, and antirheumatoid factor antibodies before initiating ICI treatment (92). Profiling of antibodies in melanoma patients developing irAEs following immunotherapy identified distinct pre-treatment serum antibody profiles associated with severe irAEs for each therapy group; in particular, a strong correlation was observed between autoantibodies and the severity of irAEs (93). However, a study has paradoxically found that lower baseline autoantibody levels are associated with the development of organ-specific irAEs (55).

Diagnosis and evaluation of lung injury

Consensus 5 CTLI lacks distinct clinical signs and symptoms. Whenever there are respiratory symptoms and signs during tumor treatment, the possibility of CTLI should be considered, and the diagnosis and evaluation should be based on appropriate examinations as advised by the attending physician and specialists. (Grade of recommendation: B; level of evidence: 2a)

Clinical manifestations

CTLI may present with an insidious onset, with mild cases exhibiting no clinical symptoms, or it can manifest acutely with symptoms such as cough, dyspnea, fatigue, fever, chest pain, and hemoptysis. CTLI can progress gradually but may also worsen suddenly, potentially leading to respiratory failure and even death. Its clinical signs are also nonspecific but may include shortness of breath and cyanosis of the lips. Lung auscultation may reveal normal breath sounds, although moist rales or Velcro rales may also be heard.

Accessory examinations

Laboratory tests

Although the results of blood tests alone are insufficient for the definitive diagnosis of CTLI, these tests can provide valuable supporting information for the diagnosis of CTLI (*Table 2*).

Imaging studies

A variety of imaging patterns have been observed. Notably, a single drug is capable of eliciting multiple patterns, and a given patient may exhibit a range of patterns. The common imaging patterns encompass nonspecific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP), organizing pneumonia (OP), DAD, hypersensitivity pneumonitis (HP), and uncomplicated eosinophilic pneumonia (EP) (*Table 3*). RRP, another distinct entity, may present with modifications to the lung interstitium characterized by enhanced lung texturing and with emphysema and increased lung volume secondary to gas

Table 2 Overview of blood markers for lung injury

Item	Description
KL-6	KL-6 is a highly sensitive marker for ILD, with a diagnostic threshold set at 500 U/mL (94,95). Persistent elevation of KL-6 levels is indicative of severe lung injury (96,97). An elevation in serum KL-6 levels by ≥1.435-fold was correlated with the occurrence of grade ≥2 radiation-induced lung injury in patients with lung cancer (98)
Cytokines	Elevated levels of serum interleukin IL-6 and IL-10 serve as biomarkers for anti-tumor drug-induced lung injury (51,57). Additionally, IL-1, IL-6, IL-10, among other cytokines, are utilized as markers for monitoring the onset of radiation pneumonitis (99)
Injury-related proteins	CRP, LDH, SP-D, and SP-A are implicated in the occurrence, progression, and severity of lung injury (57,100,101)
Autoantibodies	Serum IgG may be used in the accessory examination for hypersensitivity pneumonitis (102,103)
Routine blood test	CTLI is often associated with eosinophilia (89). Elevated NLR, higher PLR, increased PLR (57,89), and reduced ALC and ALB levels may be suggestive of early CTLI (57). Radiation-induced lung injury may be associated with an increased WBC and an elevated ESR (8)

ALB, albumin; ALC, absolute lymphocyte count; CRP, C-reactive protein; CTLI, cancer treatment-related lung injury; ESR, erythrocyte sedimentation rate; IgG, immunoglobulin G; IL-1, interleukin 1; IL-6, interleukin 6; IL-10, interleukin 10; ILD, interstitial lung disease; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SP-A, surfactant protein A; SP-D, surfactant protein D; WBC, white blood cell.

retention and expansion (117). The diagnosis of CTLI is primarily reliant on chest computed tomography (CT), especially high-resolution computed tomography (HRCT). Chest X-ray has low resolution, making it unsuitable for visualizing subtle interstitial changes such as fine interstitial fibrosis, alveolar wall thickening, and small nodules. Consequently, it cannot identify the characteristics and extent of the lesions. In contrast, HRCT offers superior spatial resolution, enabling the visualization of fine lesions including interstitial fibrosis, bronchiectasis, and small nodules. It plays a crucial role in accurately displaying anatomical structures and lesion extent, making it particularly suitable for CTLI assessment (118).

CRLI

The radiologic manifestations of CRLI are diverse, depending on the severity of the injury and the nature of the pathologic alterations. The common imaging findings include (5): (I) lung parenchymal changes: chemotherapy-induced lung injury frequently presents as inflammation and fibrosis of the lung parenchyma. On chest X-ray or CT scans, increased lung density, blurred lung contours, and patchy infiltrates may be visualized. (II) Pulmonary interstitial fibrosis: chemotherapy-induced pulmonary interstitial fibrosis is depicted on imaging as thickened lung septa, enhanced reticulation, and honeycombing alterations. (III) Pleural changes: chemotherapy agents may induce pleural inflammation and fibrosis, which are manifested as pleural thickening, effusions, calcifications, and adhesions on imaging. (IV) Bronchial stenosis: lung injury secondary to chemotherapy may result in bronchial narrowing and obstruction. On CT scans, bronchial wall thickening, luminal narrowing, and distal bronchial dilation are observed. (V) Obstructive lesions: chemotherapy agents can lead to the narrowing or obstruction of airways, presenting as obstructive patterns within the lungs. This can result in gas retention and expansion in lung parenchyma, which may be visualized on imaging as emphysema and increased lung volumes.

Radiation therapy-related lung injury

The typical imaging changes of RP include patchy consolidation shadows or streak shadows in the irradiated field or range. These changes are confined to the area of radiation exposure and do not align with the anatomical distribution of lung fields or segments. A very small proportion of patients may present with sporadic RP, wherein, in addition to changes within the irradiated field, imaging alterations outside the irradiated area can also occur, predominantly immune-mediated bilateral lymphocytic alveolitis (8). A study included 82 symptomatic RP patients, and the results showed that CT changes extended beyond the expected radiation field in 82% of RP patients (119).

The imaging alterations of RP can be divided into three phases: exudative, mixed, and fibrotic. The exudative phase (<3 months) is primarily characterized by ground-glass and patchy opacities, and patients in this phase often respond well to treatment and exhibit reversibility. In the mixed phase (3–6 months), patchy and streaky opacities are

Table 3 Imaging studies and pathology of CTLI

Lesion type	HRCT findings	Corresponding pathological findings
NSIP (104,105)	Homogeneous involvement of lung parenchyma, manifesting as bilateral, symmetrical pulmonary reticular opacities, primarily affecting the middle and inferior lobes, and subpleural areas, with or without traction bronchiectasis. A subpleural line may be observed in some cases	Variable degrees of alveolar wall inflammation or fibrosis; homogeneous distribution of fibroblast foci; characteristic lymphoplasmacytic infiltrates localized within alveolar septa and peribronchiolar regions
UIP (104-107)	Heterogeneous involvement of lung parenchyma, manifesting as "spider web" or honeycomb-like structures of reticular shadows, with associated bronchiectasis or bronchiolectasis. Ground-glass and fine reticular opacities may be observed	(I) Dense fibrosis; (II) fibroblast foci; (III) lesions are patchy throughout the lungs and subpleural regions, with areas of normal lung tissue interposed; and (IV) honeycombing
OP (108-112)	Bilateral, multilobar, or multifocal patchy or infiltrative opacities, with migratory characteristics, distributed lung bases, periphery, and peribronchial locations, with some cases exhibiting with "reversed halo sign"	Polypoid hyperplasia within alveolar spaces and respiratory bronchioles, with fibroblasts and a mucoid matrix
DAD (113,114)	Diffuse ground-glass opacities are evident during the exudative phase, traction bronchiectasis is observed in the fibrotic phase, and honeycombing cystic changes may be seen in the advanced stages	Featured by presence of hyaline membranes within the alveolar spaces, alveolar wall edema, type II alveolar epithelial hyperplasia, widening of alveolar septa, and proliferation of loose fibrous tissue, with hyaline membranes being a histological hallmark of DAD. However, histopathologically, it can be challenging to capture the acute or exudative phase with abundant hyaline membranes
HP (113,115)	Interstitial thickening and honeycombing can be seen in the chronic phase of the disease. Nodules are visible at the center of the lobules in some patients. Solid opacities are present in advanced stages	Cellular inflammation of the bronchioles and adjacent lung tissue, along with the presence of loose granulomatous nodules
Uncomplicated EP (114,116)	Diffuse pulmonary ground-glass opacities, with some cases exhibiting small, faint nodules or speckled shadows within the lungs	The condition primarily affects the inflammatory response and lesions of the alveoli and pulmonary interstitium, characterized by eosinophilic infiltration within the alveoli and interstitial spaces. In some cases, it may be accompanied by alveolar inflammation, alveolar wall thickening, alveolar exudation, and pulmonary interstitial fibrosis

CTLI, cancer treatment-related lung injury; DAD, diffuse alveolar damage; EP, eosinophilic pneumonia; HP, hypersensitivity pneumonitis; HRCT, high-resolution computed tomography; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; UIP, usual interstitial pneumonia.

observed. The fibrotic phase (>6 months) is featured by fibrous streak shadows and an air bronchogram.

Targeted therapy-related lung injury

Targeted therapy-induced ILD can be classified into six imaging patterns: hypersensitivity reaction (HR), IP, cryptogenic organizing pneumonia (COP), peribronchovascular bundle (PBVB), nodular pattern, and DAD. Chest X-ray or CT in most ILD patients can display diffuse opacities, which may present as reticular-streaky, diffuse ground-glass, nodular, multifocal, large patchy, or a combination of these patterns (120). A Japanese study described the imaging characteristics of each of these patterns as follows: (I) HR pattern manifests as diffuse homogeneous/widespread opacities predominantly characterized by ground-glass attenuation, and lacking in traction bronchiectasis and structural distortion; (II) IP pattern demonstrates ground-glass attenuation, irregular linear/reticular opacities, and concomitant bronchiectasis/bronchiolectasis; (III) PBVB pattern presents as patchy ground-glass opacity (GGO) with preferential distribution along bronchovascular bundles; (IV) COP pattern exhibits nonsegmental consolidation predominantly localized to

subpleural regions or peribronchovascular spaces; (V) nodular pattern displays diffuse bronchovascular bundle-distributed nodular opacities, occasionally co-occurring with patchy GGO; and (VI) DAD pattern was not described (121). Another case report described the radiological features of the DAD pattern in a patient with acute lung injury (ALI) with alveolar hemorrhage as an adverse drug reaction related to crizotinib, in whom chest X-ray revealed bilateral diffuse lung infiltration, whereas CT displayed bilateral diffuse GGO and butterfly shadow (122).

Immunotherapy-related lung injury

Imaging is the most frequently utilized auxiliary diagnostic tool for CIP. CIP has no specific radiologic features, primarily presenting as nodular shadows, reticular shadows, lung consolidation, GGOs, interlobular septal thickening, and ropy opacities. The GGOs and consolidation shadows, often asymmetrically distributed, are the most common findings (123,124). Some patients may also exhibit the "paving stone sign" or "reversed halo sign" (125). In addition to the typical presentation of pneumonitis, a small proportion of patients may also exhibit nodular granulomatous nodules (126). According to the American Thoracic Society/European Respiratory Society (ATS/ERS) classification of the idiopathic IPs, CIP comprise NSIP-like, COP-like, HP-like, and ARDS-like patterns. Among them, the COP-like pattern is the most prevalent, comprising approximately 65% of cases, followed by the NSIP-like pattern, which accounts for about 15% (23,127). Most SRCIP patients have lesions in bilateral lungs, with the predominant imaging pattern being DAD, although other patterns, such as OP, may also be seen in a small proportion of cases (31).

ADC-related lung injury

HRCT of the chest is a crucial modality for the evaluation and follow-up monitoring of ADC-related lung injury. The most common radiologic findings include widespread patchy consolidation or GGOs, with or without intralobular reticular thickening. However, these findings are not exclusive to ADC drug-related lung injury.

Other types and multifactorial lung injuries

Thoracic surgery is a primary cause of surgical lung injury. According to Puybasset *et al.* (128), surgical lung injuries deteriorate progressively from the anterior to the posterior aspects of the lung and from the apex to the base and are particularly evident when near the diaphragm at the lung base. This may be attributed to capillary endothelial cell damage in the alveolar walls caused by hypoxemia, which increases capillary permeability. Furthermore, for a bedridden patient during the perioperative period, gravity will result in greater blood flow in the posterior and lower aspects of the lungs, leading to blood components seeping into the alveolar spaces. Consequently, on CT scans, there is an increase in density in these corresponding areas, manifesting as patchy or large areas of GGO or consolidation.

Multifactorial lung injury is more prevalent in adverse reactions resulting from drug combinations. There are variations in the timing of lung injury onset, drug cumulative doses, and clinical manifestations among different patients using different drugs. The imaging manifestations of lung injury following multi-drug combinations are extremely complex, and a range of conditions such as ILD, pulmonary edema, pulmonary hemorrhage, ARDS, pulmonary embolism, and drug-induced pneumonitis may occur. Clinical judgments should consider symptoms, medication history, and imaging findings.

Pulmonary function

Local or systemic treatment of tumors may result in reversible or irreversible lung damage. Immunotherapy-related pulmonary toxicity can manifest as airflow obstruction and diffusion disorders, which may include a significant decrease in forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and diffusing capacity of the lung for carbon monoxide (DLCO) (129,130). Stereotactic body radiation therapy (SBRT) can lead to a decrease in FEV_1, FVC, and DLCO in some NSCLC patients, and these indicators may remain low for an extended period of time (131). The decline in DLCO caused by platinum-based chemotherapy is typically reversible (132). Tumor treatment-related pulmonary function impairments can be primarily categorized into ventilatory disorder and gas exchange disorder (*Table 4*). Obstructive ventilatory defect (OVD) is characterized by a reduction in FEV_1 and FEV_1/FVC ratio and an increase in residual volume (RV) and RV/total lung capacity (TLC) ratio; in contrast, restrictive lung disease can cause a decrease in TLC, RV, vital capacity (VC), and DLCO (133). The latter is a typical pattern of lung injury involving the interstitium. Lung function may be normal in cases of mild injury but will exhibit a significant decrease in VC and diffusion function in patients with more severe lung injury (134). Pulmonary function changes can precede the onset of symptoms and imaging features, and they are closely associated with the occurrence, progression, and prognosis of lung injury (130).

Table 4 Lung function indicators in CTLI

Lung function indicators
FEV_1, FVC, VC, RV, TLC, DLCO, among others
Indicators for ventilatory dysfunction
Obstructive: FEV_1, FEV_1/FVC, MEF↓
Restrictive: TLC, VC, RV↓, VC/TLC↑
Indicators for gas exchange dysfunction
Diffuse dysfunction: DLCO↓

↓, indicates a decrease in the parameter value; ↑, indicates an increase in the parameter value. CTLI, cancer treatment-related lung injury; DLCO, diffusion capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; MEF, maximal expiratory flow rate; RV, residual volume; TLC, total lung capacity; VC, vital capacity.

A prospective study has indicated that reduced VC before the initiation of treatment, as evidenced by diminished FVC and FEV_1, serves as a risk factor for CIP (130). Another retrospective study reported that a decrease in TLC prior to treatment was associated with an increased risk of CIP (135). In a prospective study with a follow-up period of up to 14 years, a reduction in DLCO was linked to a poorer prognosis in ILD patients (136). DLCO, along with spirometry, are also valuable in evaluating the efficacy of interstitial lung injury treatment (137). Given the prognostic and diagnostic significance of pulmonary function in lung injury, pulmonary function tests (PFTs) should be used as an indicator of baseline assessment prior to cancer treatment and in the regular monitoring of lung injury. PFTs (including those for ventilatory function and gas exchange function) should be conducted throughout the entire disease course, particularly in patients with underlying pulmonary diseases (e.g., COPD, ILD), with assessments recommended every 3 months.

Alveolar lavage and biopsy

Alveolar macrophages are the predominant cell type in normal bronchoalveolar lavage fluid (BALF), and their composition and number can alter in the presence of CTLI. BALF can provide insight into the type of lung injury and aid in the exclusion of alternative diagnoses, such as pneumocystis jirovecii pneumonia (PCP), lymphangitic carcinomatosis, tumor progression, and pseudo-tumor progression. For instance, there is a slight increase in lymphocytes (predominantly $CD4^+$ T and $CD8^+$ T cells) in BALF collected from patients with ICI-related pneumonitis, resulting in an inverted CD4/CD8 ratio and a reduction in macrophages (138-140). Most chemotherapy agents can cause medication-induced pulmonary injury (MIPI). A lymphocyte count >50%, a mast cell differential count >1%, and a neutrophil count >3% strongly indicate HP (141,142). Histopathology of lung biopsy specimens is indicated in patients with clinical and radiographic findings that cannot identify the specific pattern of a lung injury, or when the differential diagnosis necessitates a distinct treatment strategy (e.g., consider factors including drug toxicity, infections, or malignancy) (143). In addition, pathological findings can specify the type, phase, and stage of a lung injury (*Table 3*), thereby aiding in subsequent treatments (including response assessment). Lung injury can be classified into acute, subacute, and chronic phases, each with distinct pathological manifestations.

Acute phase: ≤5 weeks, the main pathological findings include fibrin-rich alveolar exudate, mild hyperplasia of the alveolar epithelium, pronounced type II epithelial atypia, accumulation of alveolar macrophages, interstitial edema, thickening of the alveolar septum, and lymphocytic infiltration. The main histological patterns include ALI, DAD, and OP (144-146).

Subacute phase: greater than 5 weeks and less than 13 weeks, this phase is characterized by diffuse organizing foci with or without cellulose in tissues; the alveolar septum of the epithelium is thickened, along with interstitial fibrosis and lymphocyte infiltration. The main histological patterns include COP and OP (146).

Chronic phase: ≥13 weeks, further alveolar epithelial cell loss and progressive collagen deposition occur, leading to profound damage to normal lung architecture, which is manifested as pulmonary fibrosis accompanied by vascular thickening and occlusion (146).

Other pathological changes such as alveolar epithelial hyperplasia, alveolar septal thickening, and lymphocyte infiltration exacerbate as lung injury progresses (146). However, there is no exclusivity in pathological findings among different types of lung injury, and various pathological manifestations can coexist in different lung injuries (146). The pathological results can indicate a specific stage of lung injury.

Diagnostic algorithms

Consensus 6 The clinical assessment of CTLI should integrate clinical manifestations, imaging findings, and laboratory test results. An MDT approach is recommended for the grade-specific

diagnosis and treatment of CTLI. (Grade of recommendation: B; level of evidence: 2a)

MDT

The diagnosis of CTLI is intricate due to the diversity of cancer treatments and the variations in the timing of lung injury onset, the cumulative drug doses, and the clinical manifestations across patients and treatments. Additionally, CTLI lacks specificity in symptoms and imaging studies. An MDT is pivotal in the management of CTLI, particularly for patients with a suspected CTLI diagnosis. Several studies have demonstrated that MDT involvement enhances confidence in diagnosing ILD and can lead to changes in ILD diagnoses (147-150). An ATS/ERS joint statement suggests that the diagnosis of ILD should involve consultation among respiratory physicians, radiologists, and pathologists to facilitate dynamic diagnosis (151). We recommend that the diagnosis, clinical management, and therapeutic intervention of CTLI established through coordinated multidisciplinary collaboration involving pulmonologists, oncologists, radiologists, pathologists, and clinical pharmacists. This interdisciplinary framework, systematically integrated with symptoms and findings from laboratory tests, imaging studies, and pathology, will enhance the accuracy of CTLI diagnosis and facilitate the formulation of a rational treatment strategy.

Diagnostic criteria

All cancer treatments can cause lung injury, occurring either during or after a specific treatment. Accordingly, the possibility of CTLI should be considered in the presence of a new lung injury. Diagnostic criteria for drug-related lung injury as proposed by a previous study (89) include: (I) a history of exposure to drugs known to cause lung injury; (II) clinical manifestations, radiological, and histopathologic features consistent with those previously observed for the same drug; (III) other lung diseases excluded; (IV) improvement of symptoms following discontinuation of the suspected drug; and (V) recurrence of symptoms upon resumption of treatment. However, discontinuation of a suspected treatment for severe CTLI may not lead to improvement, and in such cases, treatment will not be resumed. Accordingly, we propose new diagnostic criteria for CTLI: (I) a history of exposure to tumor therapy; (II) imaging studies revealing new lung lesions; and (III) other potential causes excluded.The diagnostic algorithm is depicted in *Figure 1*.

Grading of CTLI

No definitive clinical grading criteria exist for CTLI; instead, it is graded using the Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE v5.0; National Cancer Institute, Rockville, MD, USA), which considers the patient's clinical manifestations, imaging findings, and the level of treatment or medical intervention required (*Table 5*).

Management strategies

Consensus 7 Despite the varied etiologies of CTLI, the therapeutic approaches are largely consistent. Depending on the injury grade, a combination of glucocorticoid-based treatment measures following drug discontinuation is used. (Grade of recommendation: A; level of evidence: 2a)

Principles of treatment

Patients with CTLI should receive grade-specific management following the discontinuation of a suspected anti-tumor therapy (*Figure 2*). For grade 1 patients, the anti-tumor therapy may be suspended, to resume when the condition is improved. If the condition deteriorates or new symptoms arise, it should be managed as grade 2. Patients with grade 2 CTLI should discontinue the anti-tumor therapy and may be administered low-dose GCs. Patients with grade 3 or higher CTLI require permanent cessation of the anti-tumor therapy and receive GCs therapy, along with life support procedures; the MDT approach may be applied if necessary. The long-term management of CTLI should be individualized, incorporating factors such as tumor burden, efficacy of cancer treatment, CTLI grade, and response to GCs. There are subtle differences among CTLIs (*Table 6*).

GCs

Despite the lack of robust clinical evidence, GCs are the commonly utilized medications for most CTLIs. In an analysis of over 6,000 cases of drug-induced interstitial lung disease (DI-ILD) from 156 studies, the authors concluded that GCs were more frequently used in severe cases despite a lack of high-quality evidence (6). The dosage and duration of GC treatments exhibit considerable variability. For GC

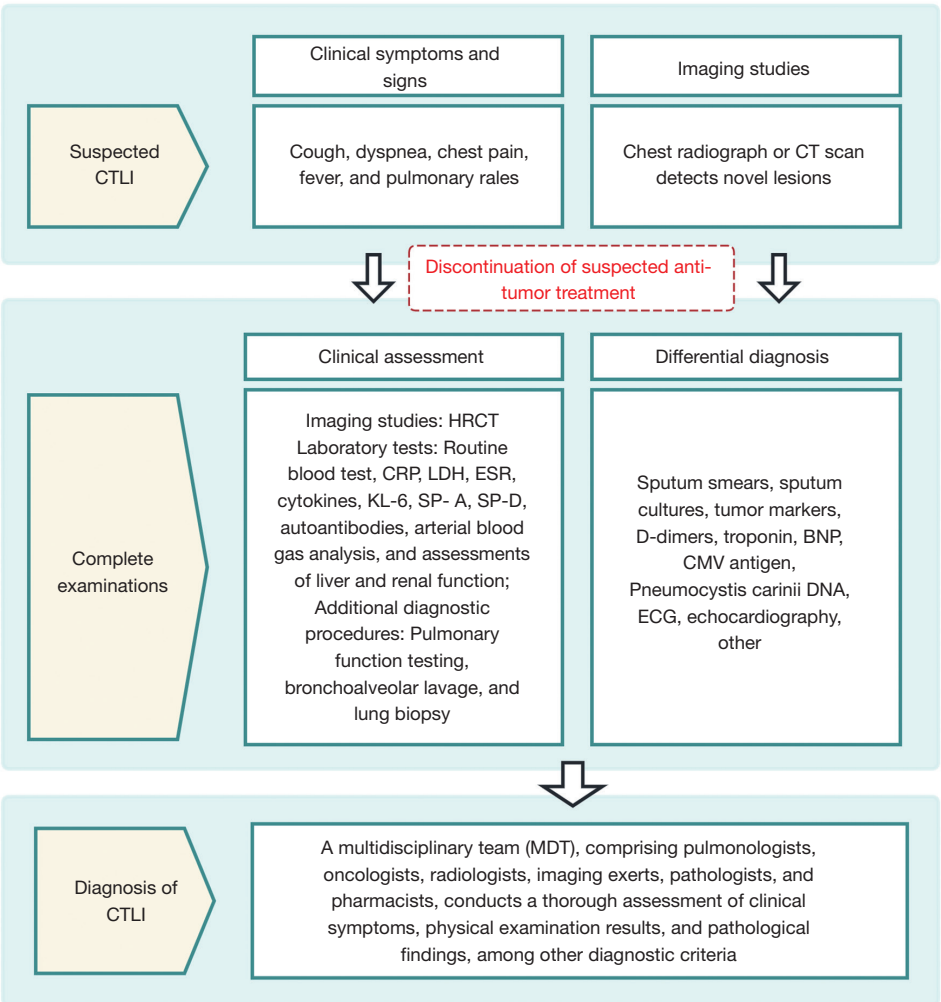

Figure 1 Diagnostic algorithm of cancer treatment-related lung injury. BNP, brain natriuretic peptide; CMV, cytomegalovirus; CRP, C-reactive protein; CTLI, cancer treatment-related lung injury; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; HRCT, high-resolution computed tomography; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; MDT, multidisciplinary team; SP-A, surfactant protein A; SP-D, surfactant protein.

therapies, a tiered management approach can be applied, as outlined in *Table 6*. The tapering of GC treatment should adhere to the principles of gradual reduction (over at least 4 weeks) and personalized management (59,152,153). Additionally, GC administration should include measures to prevent complications. For instance, proton pump inhibitors or H2 receptor antagonists can be co-prescribed to minimize gastric mucosal damage during high-dose GC therapy (154); for long-term GC treatment, calcium and vitamin D supplementation may be used to decrease the risk of osteoporosis (155). Attention should also be given to the risk of infectious diseases. A retrospective study revealed that 14.3% of patients undergoing GC therapy developed pneumonia, with three fatalities due to opportunistic infections; higher initial GC doses and prolonged duration of GC ≥30 mg/day were correlated with an increased risk of opportunistic infections (123). Thus, patients on long-term GC therapy should also receive prophylaxis for PCP (154). GC use should be tailored according to the underlying conditions, comorbidities, hormonal responsiveness, and GC tolerance. Previous research evidence has shown that both baseline and early use of GC can affect the efficacy

Table 5 Grading systems of CTLI severity

Grade	Clinical characteristics	Imaging features
1	Asymptomatic; clinical or diagnostic observations only; without the need for therapeutic intervention	Confined to a single lobe or less than 25% of lung parenchyma
2	Symptomatic; medical intervention indicated; limiting instrumental ADL	Involves more than one lung lobe or 25–50% of lung parenchyma
3	Severe symptoms; limiting self-care ADL; inpatient treatment; oxygen indicated	Involves all lung lobes or >50% of lung parenchyma
4	Life-threatening respiratory compromise; inpatient treatment; urgent intervention (e.g., tracheostomy or intubation) indicated	–
5	Death	–

ADL, activity of daily living; CTLI, cancer treatment-related lung injury.

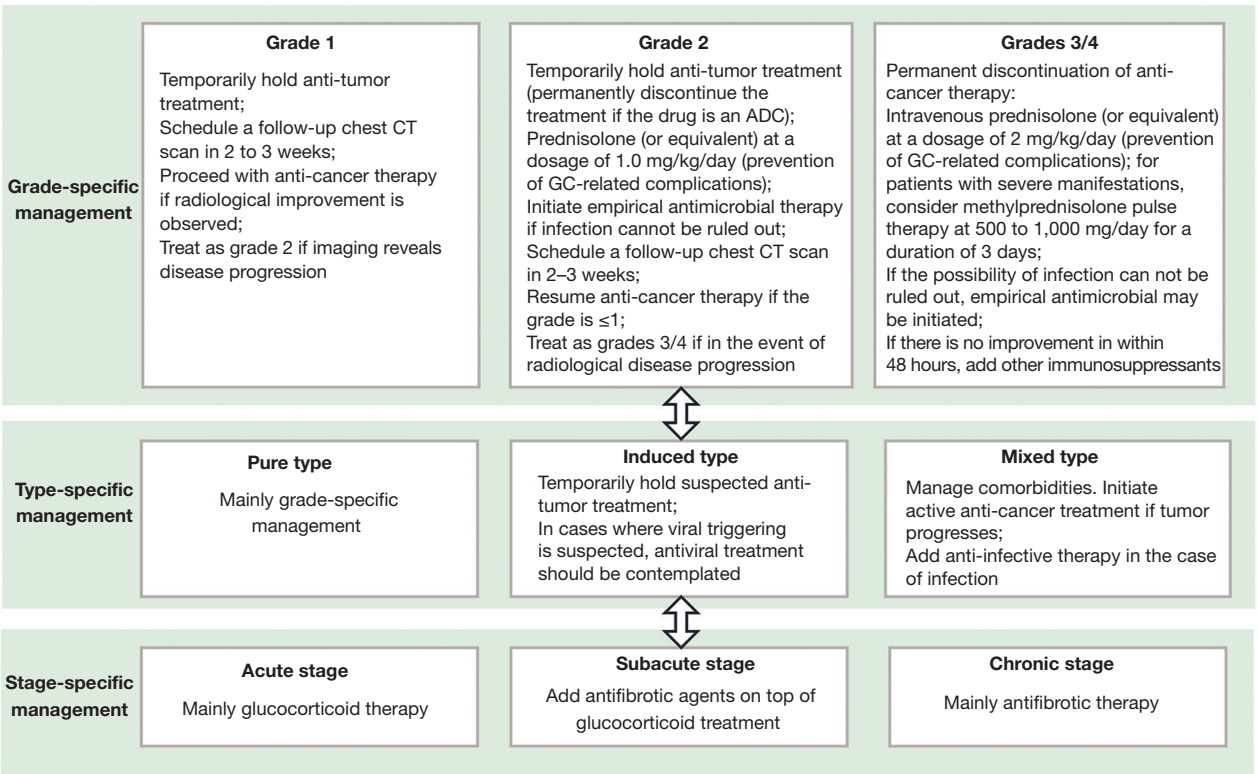

Figure 2 Principles for CTLI management. ADCs, antibody-drug conjugates; CT, computed tomography; CTLI, cancer treatment-related lung injury; GC, glucocorticoid.

of immunotherapy (156). Still, the use of GC in irAEs does not seem to reduce the response and efficacy of immunotherapy (156). However, the impact of GCs on immunotherapy outcomes remains controversial, and further research is warranted to clarify this relationship.

Immunosuppressants and biologics

Immunosuppressants or biologics, such as mycophenolate mofetil (MMF), infliximab, tocilizumab (IL-6 inhibitor), and immunoglobulins, may be considered as alternative treatments for steroid-refractory cases. However, there

Table 6 Grade-specific management of common CTLIs

Grade	TKI-LI	ICI-LI	ADC-LI[†]	RP
1	Close monitoring; treat as grade 2 or higher if the condition progresses	Postpone ICI therapy until resolution of symptoms and imaging findings; treat as grade 2 or higher in case of radiological progression	Temporarily pause ADC therapy until full recovery: if resolved within 28 days from date of onset, maintain the treatment; if resolved in >28 days from date of onset, reduce dose one level; if grade 1 occurs after the 22nd day of treatment and does not resolve within 49 days following the last infusion, discontinue the drug; corticosteroid therapy (e.g., ≥0.5 mg/kg/day prednisone) may be used until improvement and should be tapered over a minimum of 4 weeks. If symptoms deteriorate following hormone therapy, treat as grade 2	Close monitoring; treat as grade 2 or higher if the condition progresses
2	Temporarily hold TKIs; initiate prednisolone at 0.5–1.0 mg/kg/day; continue for 2–4 weeks followed by a gradual dose reduction upon symptom improvement, with a minimum total treatment duration of 6 weeks; consider oxygen therapy if necessary	Temporarily hold ICI until downgrading to grade 1 or lower; administer prednisolone at 1–2 mg/kg/day, with a reduction of 5–10 mg/week over 4–6 weeks; if no improvement is observed after 48–72 hours, treat as grade 3; empirical antimicrobial therapy may be considered	Permanent discontinuation of the drug; treat with prednisone at 1 mg/kg/day for at least 14 days until complete resolution of clinical symptoms and imaging findings, followed by a gradual dose reduction over at least 4 weeks; if there is no improvement within 5 days of corticosteroid therapy, consider increasing the corticosteroid dose (e.g., 2 mg/kg/day prednisone) and transitioning to intravenous administration	Oral prednisone at 0.5–1 mg/kg/day; if the condition progresses or if there is no improvement within 48–72 hours, treat as grade 3 or higher; in the presence of infection evidence, initiate antimicrobial therapy promptly
3	Permanent discontinuation of TKIs; administer prednisolone at 1.0–2.0 mg/kg/day for 2–4 weeks, followed by a gradual tapering of the dose after improvement of symptoms and signs, with a minimum total treatment duration of 8 weeks; empirical antimicrobial therapy may be considered; oxygen therapy, and assisted ventilation if necessary	Permanent discontinuation of ICI; initiate prednisolone at 1.0 to 2.0 mg/kg/day; if reassessment at 48 hours shows improvement, continue with corticosteroid therapy and taper over 4–6 weeks; if there is no improvement, consider infliximab (5 mg/kg), mycophenolate mofetil (1 g bid), or immunoglobulin; empirical antimicrobial therapy may be considered; use a ventilator as indicated	Permanent discontinuation of the drug; initiate high-dose intravenous methylprednisolone (e.g., 500–1,000 mg/day for 3 days), followed by a sequential dose of ≥1 mg/kg/day prednisone for at least 14 days or until complete resolution of clinical symptoms and chest CT findings, with subsequent tapering over a minimum of 4 weeks. If no improvement is observed within 3 to 5 days, reassess for other potential causes and conduct a comprehensive examination. Consider the use of other immunosuppressants such as infliximab, immunoglobulins, or cyclophosphamide	Intravenous administration of methylprednisolone (1–4 mg/kg/day) for 2–4 weeks, followed by tapering after 1 to 2 weeks of symptomatic and radiographic improvement; if no improvement is seen within 48–72 hours, the corticosteroid dosage can be increased; initiate empirical antimicrobial therapy if the possibility of infection cannot be ruled out
4	Permanent discontinuation of TKIs; initiate methylprednisolone pulse treatment at 500–1,000 mg/day for 3 days, followed by prednisolone at 1–2 mg/kg/day for 2–4 weeks, then gradually taper the dose after improvement of symptoms and signs, with a minimum total treatment duration of 8 weeks; empirical antimicrobial therapy may be considered; continuous oxygen therapy plus mechanically-assisted ventilation	Permanent discontinuation of ICI; initiate prednisolone at 2.0 mg/kg/day; if reassessment at 48 hours shows no improvement, consider infliximab (5 mg/kg), mycophenolate mofetil (1 g bid), or immunoglobulin; empirical antimicrobial therapy may be considered; non-invasive or invasive mechanical ventilation as needed		

[†], grade-specific management for ADC-LI was primarily applied to trastuzumab-deruxtecan-associated lung injury, which was extended to other ADC-LIs. ADC-LI, antibody-drug conjugate-related lung injury; CT, computed tomography; CTLI, cancer treatment-related lung injury; ICI-LI, immune checkpoint inhibitor-related lung injury; RP, radiation pneumonitis; TKI-LI, tyrosine kinase inhibitor-related lung injury.

is a lack of evidence from large-scale clinical studies regarding the use of these agents for CTLI, with only a limited amount of low-quality evidence available for the treatment of CIP. Beattie *et al.* (157) evaluated 26 patients with GC-refractory or -resistant CIP and observed clinical improvement in 5 of 6 patients who received MMF treatment. A study enrolled 26 patients with GC-refractory or -resistant CIP, wherein 20 patients were administered TNF-α inhibitors (infliximab in 19 cases and adalimumab in 1 case), among whom pneumonia was improved in five patients (157). Among 34 patients treated with tocilizumab for steroid-refractory irAEs, 27 (79.4%) demonstrated significant clinical symptom improvement (158). When using immunosuppressants and biologics, careful monitoring for potential adverse effects is essential. For instance, TNF inhibitors are associated with risks of hepatitis and myocarditis. IL-6 inhibitors may lead to gastrointestinal perforation and myelosuppression. Additionally, albumin administration has been linked to acute kidney injury and thromboembolic events (159).

Antifibrotic therapy

Fibrosis is a significant manifestation of CTLI during the chronic phase, and antifibrotic therapy may benefit CTLI management. Antifibrotic medications are known to slow the progression of idiopathic pulmonary fibrosis (IPF) (160). Animal research has demonstrated that pirfenidone can mitigate radiation-induced lung injury by decreasing the infiltration of M2 macrophages and suppressing activation of the TGF-β_1/Smad3 signaling pathway (161). A small-scale prospective study indicated that pirfenidone enhanced the range of motion in patients with radiation-induced pulmonary fibrosis (162). A phase II clinical trial suggested that nintedanib prevented the onset of RP in patients undergoing CRT (163). A phase II study (NCT02496585) assessing the combination of nintedanib with prednisone for the treatment of RP is currently in progress (164). Anecdotal evidence exists regarding the use of pirfenidone or nintedanib in the treatment of ILD caused by TKIs or ICIs (165-167). A phase II trial (NCT05280873) is currently underway to evaluate the combination of pirfenidone with prednisone for the treatment of CIP (168).

Antibiotic use

Patients with grade 2 or higher CTLI are at increased risk for pulmonary infections. In cases where an infectious etiology is suspected or cannot be ruled out, empirical antimicrobial therapy should be initiated promptly. The antimicrobial regimen should be adjusted based on sputum culture and susceptibility testing results, particularly in the event of pneumocystis and other fungal pulmonary infections.

Traditional Chinese medicine

Currently, animal studies and small-scale clinical trials have indicated that certain single traditional Chinese herbs (e.g., Radix et Rhizoma Glycyrrhizae, Radix Astragali, Radix Angelicae Sinensis, and Radix Salviae Miltiorrhizae) and compound formulations (e.g., Fei Tong Oral Liquid, Buqi Tongluo Decoction, and Feixiankang Granules) are useful in the treatment of ILD (169), possibly by inhibiting the release of inflammatory factors, mitigating oxidative stress, and interfering with collagen production (169).

Other adjunctive therapies

Patients with grade 2 and higher CTLI may have hypoxemia, which may be managed by controlled oxygen therapy, high-flow nasal cannula (HFNC), or non-invasive mechanical ventilation. Invasive mechanical ventilation may be considered in patients with severe hypoxemia, with considerations given to the potential for improvement, the patient's and family's preferences, and the availability of local medical resources.For patients exhibiting clinical symptoms, symptomatic treatments (e.g., use of cough suppressants and expectorants) can be indicated. For patients with underlying diseases and risk factors, active treatments should be offered to manage the underlying diseases and mitigate the risk factors (170).

Clinical differential diagnosis and type-specific management

Consensus 8 Although CTLI is an exclusive diagnosis, it is often complicated by infections and tumor progression and may be induced by viruses or other treatments. Categorizing CTLI into pure, mixed, and induced types is beneficial for clinical management. (Grade of recommendation: B; level of evidence: 2b)

Differential diagnosis

The differential diagnosis of CTLI encompasses a spectrum

of pathological alterations including infectious diseases (such as bacterial, fungal, viral, and tuberculous infections), non-infectious non-neoplastic conditions (e.g., pulmonary embolism, HP, and cardiogenic pulmonary edema), and tumor progression. However, clinical practitioners should also be aware of the co-existence of CTLI with these conditions.

Infectious diseases

Cancer patients are at extremely high risk for lung infections, including bacterial, fungal, viral, and tuberculous infections, due to the malignancy, the underlying chronic diseases, and the immunosuppression following anti-tumor therapy. Accordingly, when diagnosing CTLI, it is essential to conduct relevant etiological tests, such as sputum smears, cultures, respiratory viral nucleic acid or antigen detection, serum specific antibody tests, and, if necessary, alveolar lavage and next-generation sequencing (NGS) testing.

Non-infectious non-neoplastic conditions

CTLI should be distinguished from pulmonary embolism, HP, cardiogenic pulmonary edema, and ACS. Patients with pulmonary embolism frequently exhibit venous thrombosis in the lower extremities, sudden chest pain, hemoptysis, dyspnea, and elevated D-dimer levels. Pulmonary embolism can be diagnosed by pulmonary angiographic CT and treated with anticoagulation agents (171). HP presents with symptoms such as cough, dyspnea, and fatigue, often with a history of occupational or specific exposure, and HRCT may reveal a multitude of poorly defined centrilobular micronodules. Cardiogenic pulmonary edema may present with cough, pink frothy sputum, shortness of breath, orthopnea, vesicular breath sounds in both lungs, and elevated brain natriuretic peptide (BNP) levels, and imaging studies may reveal widened interlobular septa, forming of Kerley lines, and butterfly-shaped flaky blurred shadows near the hilum of both lungs (172). ACS presents with substernal chest pain (often radiating to the jaw, neck, or left arm), diaphoresis, elevated cardiac troponin levels, and dynamic electrocardiogram (ECG) changes (e.g., ST-segment elevation/depression or T-wave inversion) (173).

Tumor progression

Tumor progression, which involves primary lung cancer, pseudo-tumor progression, increased number of pulmonary metastases, and carcinomatous lymphangitis, may elicit symptoms such as fever, cough, and dyspnea, which can be analogous to CTLI. Differential diagnosis is based on tumor marker analysis and chest CT, whereas positron emission tomography (PET)-CT and lung histopathology may also be performed if indicated (174).

Type-specific management

The pulmonary system maintains direct anatomical continuity with the ambient atmosphere, serving as the primary site for gas and blood exchange in the human body. However, they are also a portal for microorganisms and other invasive agents to enter the body. Tumor patients are prone to primary or secondary pathogen infections due to the tumor itself, the underlying lung diseases, and the lung injury caused by physical and chemical factors during anti-tumor therapies. Lung infections complicated by or subsequent to lung injury caused by chemotherapy, TKIs, radiotherapy, and immunotherapy have been documented (175-178). A meta-analysis indicated that ICI therapy was correlated with a heightened risk of pulmonary infection (179). Recently, Lin *et al.* (180) introduced a classification system for immune-related pneumonitis, categorizing it into pure, mixed, and induced types, among which the mixed type denotes CIP complicated by concurrent lung infection and tumor progression. Hence, for mixed CTLI, the comorbidities including infections and tumors should also be addressed in addition to the grade-specific management of lung injury (*Figure 2*). Currently, multi-modal therapy is standard in cancer treatment. Various combinations of therapies may exert synergistic anti-tumor effects but can also potentially induce lung injury. Chemotherapy (181-183), targeted therapy (184-187), and ICIs (117,188-191) have been identified as causes of RRP. Case reports indicate that the coronavirus disease of 2019 (COVID-19) can also lead to RRP (192-194). A prior retrospective analysis suggested a potential association between cytomegalovirus (CMV) infection and CIP onset (195). Recently, Lin *et al.* (180) postulated that the induced type of CIP, such as that triggered by radiotherapy or viral reactivation, generates specific antigens that activate immune cells, and the strengthening of physical, chemical, and biological factors further activates these immune cells, leading to pneumonia and subsequently resulting in CIP. Therefore, for patients with inducted CTLI, the potential anti-tumor drug should be discontinued while treating the suspected inducing agents. Furthermore, patients suspected of having virus-induced CIP should receive antiviral treatment (*Figure 2*).

Table 7 Clinical staging and stage-specific management of CTLI

Stage	Phase	Clinical characteristics	Imaging features	Whose-process management
Acute stage	Initial phase of CTLI, characterized by acute onset of the disease, or, early stage of chronic CTLI exacerbation	It can present acutely and critically, necessitating immediate intervention, or, it exhibits clinical abnormalities but without severe symptoms	New multifocal radiographic findings	Pre-treatment baseline screening for high-risk populations; early diagnosis and prompt treatment according to CTCAE grades and CTLI types; comprehensive respiratory rehabilitation, psychological rehabilitation, and nutritional support
Subacute stage	Intermediate phase of CTLI	Symptoms stabilize, with a gradual reduction in CTCAE grade and treatment intensity	No new lesions appear; the existing lesions are gradually resorbed	Treatment efficacy should be closely assessed according to CTCAE grade and CTLI type; timely adjustment of the treatment strategy like the tapering of corticosteroids; comprehensive respiratory rehabilitation, psychological rehabilitation, and nutritional support
Chronic stage	Later phase of CTLI	Symptoms improve gradually or persist with recurrent episodes	Chronic fibrosis or ongoing progression of fibrosis, among others	Treatment based on CTCAE grade and CTLI type; comprehensive respiratory rehabilitation, psychological rehabilitation, and nutritional support; anti-fibrotic therapy if indicated; regular follow-up

CTCAE, Common Terminology Criteria for Adverse Events; CTLI, cancer treatment-related lung injury.

Clinical staging and whole-process management of lung injury

Consensus 9 CTLI in some cases can be fully resolved after timely diagnosis and prompt treatment but may recur or persist in many other patients. Clinical staging based on the disease course of CTLI, and stage-specific management are effective in improving the prognosis. (Grade of recommendation: B; level of evidence: 2b)

Clinical staging of CTLI

No standardized staging system for CTLI has been available. The disease course of CTLI varies due to the diverse mechanisms underlying lung injury. We propose a comprehensive staging system for CTLI, including the acute, subacute, and chronic stages, highlighting the necessity for tailored treatment strategies and management approaches at various stages of CTLI (196) (*Table 7*).

Acute stage: as the initial stage of CTLI, it is characterized by the acute symptoms or early exacerbations of chronic CTLI, usually occurring within 5–8 weeks following immune-related CTLI or radiotherapy-related CTLI (146,197). The acute phase represents the most symptomatic period in the course of lung injury, often presenting with persistent critical conditions such as respiratory failure. For CTCAE grade 2 or higher CTLI, respiratory support and use of GCs and/or immunosuppressants are essential for lower mortality, managing symptoms, and mitigating the risk of subsequent pulmonary fibrosis. Nutritional depletion and psychological distress are more pronounced during this stage. Focusing on early rehabilitation assessment and intervention can facilitate a shorter disease course, preserve lung function, and improve prognosis. Meanwhile, it is crucial to monitor and prevent adverse effects related to the use of corticosteroids and immunosuppressants.

Subacute stage: emerging following the acute phase, this stage typically occurs at a median of 5–13 weeks for immune-related CTLI, in contrast to 2–6 months for radiotherapy-related CTLI (146,197). In the subacute stage, the vital signs stabilize, the symptoms diminish progressively, and the CTCAE grade and treatment intensity are lowered. However, mild symptoms and lung imaging abnormalities may persist. During this stage, in addition to adjusting GCs and immunosuppressant therapies, the addition of anti-fibrotic drugs may be considered, with preliminary evidence supporting their use in RP and CIP (162,166,167). Respiratory and psychological rehabilitation play a vital role in CTLI management, aiding in the gradual recovery or restoration of lung function to pre-treatment levels.

Chronic stage: some patients may experience prolonged chronic lung injury, occurring beyond 13 weeks in immune-related CTLI and typically 6–24 months post-radiation in radiotherapy-related CTLI (146,197). This stage is marked by ongoing resorption of lesions and chronic pulmonary fibrosis. Some patients may endure recurrent and

prolonged illness, evidenced by the continued progression of pulmonary fibrosis. GC therapy demonstrates limited efficacy in patients at this stage, and prolonged use may lead to an increased risk of adverse effects. Fibrosis is a prominent feature at this stage, and patients in this stage may benefit from anti-fibrotic therapy (*Figure 2*) (73). In this stage, lung function may stabilize at a certain level, but full recovery to pre-treatment levels may not be achievable for some patients, for whom a gradual shift to antifibrotic therapy is warranted, along with enhanced respiratory rehabilitation and functional exercises to prevent re-exacerbations and mitigate the severity of any recurrence.

Respiratory rehabilitation, psychological rehabilitation, and nutritional support

Respiratory rehabilitation, psychological rehabilitation, and nutritional support are integral to the comprehensive treatment and rehabilitation of CTLI patients. Personalized plans and whole-process management should be implemented based on the individual's conditions and disease stage to enhance the patient's self-efficacy and quality of life.

Given the intricacies of tumors and comorbidities, a respiratory rehabilitation protocol should be tailored to individual patients, taking into account the degree of respiratory function impairment, exercise tolerance, comorbid conditions (particularly cardiac, musculoskeletal, and neurological disorders), as well as cognitive, psychological, and social factors. The protocol should encompass all CTLI stages throughout the entire clinical course, covering feasible respiratory support strategies, breathing exercises, respiratory muscle exercises, neuromuscular electrical stimulation, short-term postural adjustments, breathing technique instruction, patient education, and other interventions. Following stabilization of condition in the acute phase, early ambulation/bedside activities, abdominal breathing exercises, pursed-lip breathing exercises, cough training, postural drainage, balance training while sitting and standing, and respiratory control are recommended. Passive and active in-bed cycling may be arranged if condition allows. Patients can be instructed to engage in low-intensity integration exercises [e.g., walking, tai ji (a traditional Chinese mind-body exercise involving slow, deliberate movements and meditation), and Baduanjin (a classical Chinese health practice comprising eight gentle movements to improve flexibility and vitality)] at home and progressively incorporate breathing exercises and aerobic activities (e.g., moderate-intensity aerobic exercises and resistance training) (198,199). Neuromuscular electrical stimulation can be beneficial for individuals with severe lung and/or heart disease that impairs exercise tolerance (200-202). Furthermore, some patients and their families may be unaware of the potential benefits of pulmonary rehabilitation or show reluctance to initiate the relevant training; telerehabilitation and remote education using wearable devices and smartphone applications may offer a viable alternative. Physicians can remotely prescribe respiratory rehabilitation exercises and adjust protocols and settings based on data feedback. Patients can perform exercises at home under medical supervision, with devices such as pedometers encouraging spontaneous physical activity (203). Psychologically, early identification and management of symptoms (e.g., anxiety) resulting from CTLI can improve patients' emotional and physical well-being. Interventions include prompt and clear communication with patients and their families about critical information on diagnosis, treatment, and prognosis. This process encourages queries from both patients and their families, and ensures comprehensive disclosure regarding treatment options and the possible adverse effects associated with these interventions. Scales can be used to evaluate the patient's anxiety, depression, and other emotional states. Psychologists or psychiatrists may be consulted, if necessary, for cognitive-behavioral therapy, supportive interventions, and music therapy. Pharmacological interventions may be considered for patients with poor response to these supportive treatments. By encouraging patients to live with CTLI and foster a positive outlook on living, physicians can build trust with patients.

It is advisable to develop personalized nutritional support strategies tailored to the patient's condition, during which gastroenterologists, endocrinologists, and nutritionists can be consulted. Suitable nutritional support plans can be formulated by referring to guidelines and expert consensuses including the Chinese Expert Consensus on Nutritional Support for Respiratory Critical Care (204), the Expert Consensus on Nutritional Support for Lung Cancer Patients (205), and the Chinese Society of Clinical Oncology (CSCO) guidelines for Nutritional Support in Cancer Patients (206).

Conclusions

The diagnosis of suspected CTLI should integrate medical history, clinical symptoms, physical examination, laboratory

findings, imaging, and pathology, with input from an MDT. Our present consensus document outlines grade-, type-, and stage-specific management strategies for CTLI, underscoring the importance of MDT and personalized and whole-process care.

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Footnote

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