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# Radiation-induced lung injury in lung cancer patients with coexisting chronic obstructive pulmonary disease or asthma: Systematic review about mechanisms, risks, and management advances

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► ***Original article***

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## ABSTRACT

***Background:*** Thoracic irradiation for lung cancer (small cell and non-small cell) has one major dose-limiting effect: radiation-induced lung damage (RILI). For patients with lung cancer and chronic obstructive pulmonary disease (COPD) or asthma, this review compiles the latest research on RILI's causes, risk factors, and treatment options. ***Materials and Methods:*** A systematic literature search was conducted following PRISMA 2020 guidelines. Search MESH terms combined: "RILI," "radiation pneumonitis," "pulmonary fibrosis," "COPD," "asthma," "lung cancer," and "radiotherapy." Data extraction focused on patient characteristics, radiotherapy parameters, RILI incidence, underlying mechanisms, and management outcomes. ***Results:*** Out of 847 publications, 38 met the inclusion criteria and contained 12,847 patients, with 11,942 suffering from COPD and 905 with asthma. While no significant association was found with asthma (pooled OR 1.12, 95% CI 0.89-1.41, p=0.32), an analysis of 12 studies showed that individuals with COPD had a significantly higher risk of RILI (pooled OR 2.14, 95% CI 1.78-2.56, p<0.001). Lungs affected by COPD showed signs of a quick change from epithelial to mesenchymal cells, an imbalance in TGF-β signaling, heightened reactions to oxidative stress, and impaired capacity to repair DNA. Novel biomarkers for the early detection of RILI, lung density-guided radiation planning, statin medication, and inhibitors of the renin-angiotensin system are all part of the most recent advancements in treatments. ***Conclusion:*** Personalized radiotherapy planning incorporating baseline lung function, novel radioprotective agents, and early biomarker surveillance may optimize outcomes in this vulnerable population. Harmonized protocols for RILI assessment and management are urgently needed.

## INTRODUCTION

Despite the fact that lung cancer continues to be the greatest cause of death globally due to cancer, radiation continues to be an essential component of both curative and palliative treatment methods [1, 2]. Target conformality and normal tissue sparing have both been enhanced as a result of technological advancements in treatment delivery, such as intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT), and stereotactic body radiotherapy (SBRT) [3, 4]. Radiation-induced lung damage (RILI) remains a substantial dose-limiting toxicity that impairs treatment results and patient quality of life [5, 6]. This is despite the fact that these advances have been used. IMRT, VMAT, and SBRT are precision radiotherapy options for lung cancer: IMRT sculpts beam intensity to conform dose to irregular or centrally located tumors while sparing normal lung and nearby organs; VMAT achieves similar modulation by rotating the gantry in continuous arcs for faster delivery and efficient dose conformity; SBRT delivers very high, ablative doses in few fractions to small, early-stage, or oligometastatic lesions with strict immobilization and image guidance; all require CT-based planning, motion management, and individualized selection based on tumor size, location, and patient fitness.

RILI manifests through two distinct but interconnected phases: an early inflammatory phase (radiation pneumonitis) occurring weeks to months post-irradiation and a late fibrotic phase (radiation-

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induced pulmonary fibrosis) developing months to years later [7, 8]. The underlying pathophysiology involves complex interactions between alveolar epithelial cells, vascular endothelium, and recruited inflammatory cells, orchestrated by a cascade of cytokines including transforming growth factor-beta (TGF-β), tumor necrosis factor-alpha (TNF-α), and various interleukins [9,10]. The severity of RILI depends on multiple factors, including radiation dose, volume of irradiated lung, fractionation schedule, and, importantly, patient-specific characteristics [11, 12].

Chronic obstructive pulmonary disease (COPD) and asthma are the pre-existing respiratory disorders that are encountered the most often in patients who have lung cancer. This is due to the fact that smoking and chronic inflammation are risk factors that are shared by both disease types [13, 14]. As a result of the overlapping aetiology of tobacco smoke, chronic obstructive pulmonary disease (COPD) affects roughly 40–70% of lung cancer patients at the time of diagnosis [15]. The condition known as asthma, which is less common, affects between 5 and 10 percent of lung cancer patients and brings about a distinct set of inflammatory issues [16]. Due to the fact that these patients already have reduced pulmonary reserve and changed lung architecture [17, 18], the confluence of these disorders presents a unique set of problems for thoracic radiation.

Emerging evidence suggests that pre-existing COPD may potentiate RILI through several mechanistic pathways. The chronic inflammatory milieu characteristic of COPD amplifies radiation-induced cytokine cascades, while impaired antioxidant defenses in COPD-affected lungs exacerbate oxidative stress following irradiation [19, 20]. Furthermore, the structural alterations in COPD, including emphysematous destruction and small airways disease, may alter radiation dose distribution and create regions of heightened susceptibility [21]. Conversely, the relationship between asthma and RILI remains poorly characterized, with some studies suggesting potential protection through corticosteroid use and others indicating increased risk from airway hyperresponsiveness [22, 23].

The clinical management of lung cancer patients with COPD or asthma undergoing thoracic radiotherapy requires careful consideration of competing risks. While these patients may derive similar oncological benefits from radiotherapy as their counterparts with normal lung function, they face potentially higher risks of treatment-related pulmonary toxicity [24, 25]. This necessitates individualized treatment planning incorporating baseline pulmonary function tests, careful dosimetric optimization, and heightened surveillance for early RILI detection [26]. Recent advances in radiomics, biomarkers, and radioprotective agents offer promise for improving outcomes in this vulnerable population [27, 28].

There is a dearth of a complete synthesis of information about RILI in patients who have pre-existing COPD or asthma in the extant literature, despite the fact that this subject is clinically important. Previous studies have either focused on COPD as a risk factor or explored RILI mechanisms in general, but they have not systematically integrated mechanistic, epidemiological, and management data [29, 30]. There is also a lack of attention to the unique issues faced by those with asthma. To address these knowledge gaps, this systematic review will examine all current data on RILI, its risks, and recent therapeutic advances, with a focus on patients with lung cancer who also suffer from COPD or asthma.

The novel elements of this research include its comparative investigation of COPD and asthma as separate risk modifiers, its integration of molecular insights with clinical outcomes, and its systematic review of establishing treatment options that are suitable for this high-risk population. All of these aspects are new. These many characteristics all contribute to the creative quality of the study that is being conducted. Through a synthesis of research from a wide range of fields, our goal is to build a framework for customized risk categorization and therapeutic optimization. The treatment ratios and outcomes of patients with lung cancer who have a pre-existing respiratory problem may be improved with the use of this technique.

## MATERIALS AND METHODS

### *Search strategies and information sources*

PRISMA 2020 criteria were used to perform a systematic literature review [31]. PubMed/MEDLINE, WoS, and Scopus were searched extensively. The literature search included fundamental and contemporary studies published between January 2010 and December 2025.

Radiation-induced lung damage, lung cancer, COPD/asthma, and radiotherapy were the four major conceptual areas of the search strategy, which included MeSH terms and free-text keywords. The search string included: ("radiation-induced lung injury" OR "radiation pneumonitis" OR "radiation fibrosis" OR "radiation-induced pulmonary toxicity"), ("lung cancer" OR "non-small cell lung cancer" OR "NSCLC" OR "small cell lung cancer" OR "SCLC" OR "thoracic malignancy"), and ("chronic obstructive pulmonary disease" OR "COPD" OR "asthma" OR "airway disease" OR "obstructive lung disease").

### *Selection criteria*

Studies were considered eligible for inclusion if they met the following criteria: (1) original research articles (observational studies, clinical trials, or translational investigations); (2) included adult

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patients (≥18 years) with histologically confirmed lung cancer undergoing thoracic radiotherapy; (3) explicitly reported on patients with pre-existing COPD or asthma; (4) provided data on RILI outcomes (radiation pneumonitis or radiation-induced pulmonary fibrosis); and (5) published between January 2010 and December 2025.

Exclusion criteria comprised: (1) case reports, case series with <10 patients, conference abstracts, editorials, or narrative reviews without original data; (2) studies involving non-thoracic radiotherapy or non-lung primary tumors; (3) investigations of pediatric populations; (4) studies lacking clear definition or grading of RILI; (5) articles not available in English; and (6) duplicate publications or overlapping patient cohorts (where the most comprehensive or recent report was retained).

### *Data extraction and quality assessment*

Two independent reviewers performed title and abstract screening against eligibility criteria. Full-text articles of potentially relevant studies were retrieved and independently assessed by the same reviewers.

A standardized data extraction form was developed and piloted on five included studies. Extracted information encompassed: (1) study characteristics (author, year, country, study design, sample size); (2) patient demographics (age, sex, smoking status, COPD/asthma severity); (3) tumor characteristics (histology, stage); (4) radiotherapy parameters (technique, dose, fractionation, irradiated lung volume); (5) RILI outcomes (definition, grading scale, incidence, timing); (6) mechanistic findings (biomarkers, histopathology, imaging correlates); and (7) management strategies and outcomes.

Quality assessment of included studies was performed using appropriate tools based on study design. Randomized controlled trials were evaluated with the Cochrane Risk of Bias tool [32]. Cohort and case-control studies were assessed using the Newcastle-Ottawa Scale [33], with scores ≥7 considered high quality. Cross-sectional studies were evaluated using an adapted version of the Agency for Healthcare Research and Quality (AHRQ) methodology checklist [34]. Quality assessment was conducted independently by two reviewers, with discrepancies resolved through discussion.

### *Data synthesis and analysis*

Given the anticipated heterogeneity in study designs, patient populations, and outcome measures, a narrative synthesis approach was primarily employed. Studies were grouped according to their focus on: (1) epidemiological evidence of RILI risk; (2) mechanistic investigations; (3) risk factor analyses; and (4) management strategies. Within each category, findings were synthesised descriptively, with attention to patterns across studies and factors explaining heterogeneity. Where sufficient homogeneity existed in study design, patient population, and outcome definition, analysis was performed using random-effects models to account for between-study heterogeneity. Specifically, pooled odds ratios (OR) for RILI risk in COPD and asthma patients compared to non-COPD/non-asthma controls were calculated from studies reporting adjusted risk estimates.

## RESULTS

### *Literature search and study selection*

The systematic literature search yielded a total of 847 potentially relevant records across the three databases (PubMed: 312, Web of Science: 278, Scopus: 257). After removal of 189 duplicate records, 658 articles proceeded to title and abstract screening. Of these, 512 records were excluded based on irrelevance to the research question, leaving 146 full-text articles for detailed assessment. Following full-text review, 108 articles were excluded for reasons including no separate data for COPD/asthma patients (n=43), lack of RILI outcomes (n=28), overlapping patient cohorts (n=15), non-English language (n=12), and insufficient data quality (n=10). Ultimately, 38 studies met all inclusion criteria and were incorporated into this systematic review.

### *Characteristics of included studies*

The 38 included studies comprised a total of 12,847 patients with lung cancer and pre-existing COPD or asthma undergoing thoracic radiotherapy. Of these, 11,942 patients (93.0%) had COPD and 905 patients (7.0%) had asthma. The studies were published between 2010 and 2025, with increasing publication frequency in recent years (2010-2015: 9 studies; 2016-2020: 14 studies; 2021-2025: 15 studies). Geographically, studies originated from North America (n=14), Europe (n=12), Asia (n=10), and Australia (n=2). Study designs included prospective cohort studies (n=16), retrospective cohort studies (n=15), case-control studies (n=4), and secondary analyses of randomized controlled trials (n=3). Sample sizes ranged from 48 to 2,847 patients, with a median of 215 patients (IQR: 124-487). Radiotherapy techniques encompassed conventional fractionation (n=18), SBRT (n=12), IMRT/VMAT (n=6), and mixed techniques (n=2). RILI was primarily assessed using Common Terminology Criteria for Adverse Events (CTCAE) versions 3-5 (n=24), Radiation Therapy Oncology Group (RTOG) criteria (n=10), or study-specific definitions (n=4). Follow-up duration ranged from 3 months to 5 years, with median follow-up of 18 months.

### *Quality assessment results*

Quality assessment using the Newcastle-Ottawa Scale for cohort and case-control studies revealed that 27 studies (79%) were of high quality (score ≥

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7), while 7 studies (21%) were of moderate quality (score 5-6). No studies were rated as poor quality. Common strengths included representative patient selection, adequate follow-up duration, and appropriate adjustment for confounders. Common limitations included retrospective design, potential selection bias, and variable RILI definitions across studies.

### *Epidemiological evidence of RILI risk in COPD and asthma patients*

#### *Risk in COPD patients*

In 32 trials, lung cancer patients with and without COPD were examined for RILI risk. 26 studies found a higher prevalence of RILI in COPD patients (81%), 4 showed no connection (13%), and 2 revealed inconsistent findings (6%) across RILI grades or radiation approaches. Using consistent RILI criteria (CTCAE grade ≥2), 12 studies revealed a substantially greater incidence of RILI in COPD patients (pooled OR 2.14, 95% confidence range 1.78-2.56, $p < 0.001$). Research revealed differences in COPD severity, radiation approach, and RILI evaluation length ($I^2$ = 47%, p = 0.03). COPD severity increases mortality. Pooled odds ratio (OR) for mild to moderate COPD was 1.82 (95% CI 1.51-2.19), and for severe to very severe COPD, 2.91 (95% CI 2.23-3.79). Regardless of radiation method, risk was high, although the degree varied. Conventionally fractionated radiation with 60 Gy or more administered in 2 Gy segments had a pooled hazard ratio of 2.31 (95% CI 1.92-2.78). SBRT may lower relative risk for hypofractionated techniques (1.76 pooled OR, 95% CI 1.38-2.24), but absolute risk remains high. Egger's test was not significant (p=0.12); however, the funnel plot showed some asymmetry, which may suggest no publication bias.

#### *Risk in asthma patients*

11 studies provided data on RILI risk in lung cancer patients with asthma. In contrast to COPD findings, only 2 studies (18%) reported significantly increased RILI risk, while 8 studies (73%) found no significant association, and 1 study (9%) reported decreased risk potentially related to corticosteroid use. Analysis of 7 studies with available adjusted estimates showed no significant association between asthma and RILI risk (pooled OR 1.12, 95% CI 0.89–1.41, p=0.32). Heterogeneity was low ($I^2$ = 22%, p = 0.26). Subgroup analysis by asthma severity and treatment status was limited by insufficient data, though three studies suggested that patients with poorly controlled asthma or those not using inhaled corticosteroids may have modestly elevated risk. Two studies examining asthma with concomitant COPD (asthma-COPD overlap syndrome) reported significantly increased RILI risk (OR range 1.89-2.34), though sample sizes were small.

#### *Temporal patterns and severity distribution*

The temporal distribution of RILI differed between COPD and non-COPD patients. COPD patients developed radiation pneumonitis earlier (median 2.8 months vs. 3.9 months post-radiotherapy, p=0.008) and had higher rates of progression to radiation-induced pulmonary fibrosis (34% vs. 21% at 12 months, p=0.002). Severe (grade ≥3) RILI occurred more frequently in COPD patients (18% vs. 9%, p<0.001), with correspondingly higher rates of hospitalization, corticosteroid dependence, and respiratory failure.

### *Mechanistic insights into RILI in COPD and asthma*

#### *Pathophysiological pathways in COPD-associated RILI*

21 studies examined COPD patients' RILI susceptibility mechanisms. Table 1 shows numerous interrelated processes in COPD-associated radiation-induced lung damage. The oxidative stress amplification pathway was well-known. Chronic inflammation, smoking, and mitochondrial dysfunction increase oxidative stress in COPD lungs. Radiation damage to mitochondria and water radiolysis enhance reactive oxygen species, overwhelming antioxidant defenses. This "perfect storm" of DNA, protein, and lipid oxidative damage sustains inflammatory and fibrotic pathways. TGF-β dysregulation is crucial for fibrotic progression. TGF-β levels in COPD patients' bronchoalveolar lavage fluid and lung tissue dramatically rose and persisted following irradiation. Downstream Smad-dependent signaling increased fibroblast proliferation, extracellular matrix deposition, and epithelial-mesenchymal transition. Importantly, the TGF-β pathway interacts with oxidative stress, inflammation, and senescence pathways, causing self-reinforcing harm cycles. COPD's chronic inflammation prepares the lung for radiation overreactions. High amounts of pro-inflammatory cytokines (IL-6, IL-8, and TNF-α) and activated inflammatory cells create a radiation-sensitive milieu that intensifies and prolongs inflammatory processes. After irradiation, COPD patients' M2 macrophages polarized toward pro-fibrotic.

#### *Asthma-specific mechanistic considerations*

9 studies examined asthmatic RILI mechanisms, finding distinct patterns from COPD. Overall, well-controlled asthma with anti-inflammatory medicine did not enhance RILI risk. Found mechanisms that may impact RILI susceptibility. T2-high asthma's eosinophilic inflammation releases IL-4, IL-5, and IL-13. IL-13 promotes fibrosis and may alter radiation responses. The lack of RILI risk escalation may be due to inhaled corticosteroids blocking these pathways in most asthmatics. Histamine, tryptase, and pro-fibrotic mediators released by mast cell activation in asthma

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may influence radiation responses. Mast cells cluster in irradiated lungs and generate late fibrotic changes, although their role in asthma is uncertain. Asthma hyperresponsiveness may worsen radiation-induced airway damage and symptoms, such as pneumonitis. Systematic studies found no increased objective RILI by imaging or pulmonary function tests, suggesting asthmatics may overdiagnose owing to symptoms. The protective effect of corticosteroids returned. In asthmatics, regular inhaled corticosteroids lowered RILI rates, although not statistically. Two studies demonstrated systemic corticosteroids for asthma control during radiation may prevent RILI; however, confounding by indication limits causal inference.

### *Risk factors for RILI in COPD and asthma patients*

#### *Dosimetric risk factors*

Analysis of dosimetric parameters across 24 studies identified consistent predictors of RILI in COPD patients, with some differences from general lung cancer populations. Table 2 summarizes key dosimetric risk.

**Table 1.** Mechanistic pathways in COPD-associated radiation-induced lung injury.

| Mechanism | Key findings | Evidence strength | Therapeutic implications |
|---|---|---|---|
| Oxidative stress amplification | Elevated baseline reactive oxygen species (ROS) in COPD lungs; radiation exposure causes supra-additive ROS generation; depleted antioxidant reserves (glutathione, superoxide dismutase) | Strong (9 studies) | Antioxidant supplementation; N-acetylcysteine; superoxide dismutase mimetics |
| Dysregulated TGF-β signalling | Enhanced and prolonged TGF-β activation post-irradiation; Smad-dependent pathway overactivity; impaired negative feedback regulation | Strong (8 studies) | TGF-β inhibitors; angiotensin receptor blockers; pirfenidone |
| Accelerated epithelial -mesenchymal transition (EMT) | Synergistic induction of EMT by radiation and COPD-related chronic inflammation; increased expression of Snail, Twist, and vimentin; reduced E-cadherin | Moderate (5 studies) | EMT inhibitors; metformin; tyrosine kinase inhibitors |
| Impaired DNA damage repair | Reduced expression of DNA repair proteins (Ku70, Ku80, RAD51); prolonged γ-H2AX foci persistence; enhanced micronuclei formation | Moderate (4 studies) | DNA repair modulators; radio-protectors (amifostine) |
| Chronic inflammatory milieu | Elevated baseline IL-6, IL-8, TNF-α; exaggerated post-radiation cytokine surge; macrophage polarisation toward pro-fibrotic M2 phenotype | Strong (7 studies) | Anti-inflammatory agents; statins; cytokine inhibitors |
| Aberrant extracellular matrix remodelling | Increased matrix metalloproteinase (MMP-9, MMP-2) activity; disordered collagen deposition; elastin degradation from emphysema | Moderate (4 studies) | MMP inhibitors; anti-fibrotic agents; matrix modulators |
| Endothelial dysfunction | Enhanced vascular permeability; impaired thrombomodu-lin expression; endothelial-to-mesenchymal transition | Moderate (3 studies) | ACE inhibitors; endothelin receptor antagonists; statins |
| Cellular senescence | Accelerated radiation-induced senescence in alveolar epithelial cells; senescence-associated secretory phenotype (SASP) propagation | Emerging (2 studies) | Senolytics (dasatinib + quercetin); senomorphics |

**Table 2.** Dosimetric risk factors for RILI in COPD patients.

| Parameter | Threshold | Odds ratio (95% CI) | Evidence strength | Clinical application |
|---|---|---|---|---|
| Mean lung dose (MLD) | >15 Gy vs. ≤15 Gy | 2.84 (2.12–3.81) | Strong (18 studies) | Primary constraint; lower thresholds for COPD |
| V5 (volume receiving ≥5 Gy) | >55% vs. ≤55% | 1.92 (1.51–2.44) | Strong (15 studies) | Low-dose bath limitation |
| V10 | >40% vs. ≤40% | 2.23 (1.78–2.79) | Strong (14 studies) | Intermediate dose constraint |
| V20 | >25% vs. ≤25% | 3.12 (2.45–3.98) | Strong (20 studies) | Most widely used constraint |
| V30 | >18% vs. ≤18% | 2.56 (1.98–3.31) | Moderate (11 studies) | High-dose region control |
| Lung volume receiving >40 Gy | >15% vs. ≤15% | 2.18 (1.62–2.93) | Moderate (8 studies) | Very high-dose region |
| Contralateral lung V5 | >30% vs. ≤30% | 1.67 (1.23–2.27) | Moderate (6 studies) | Contralateral lung sparing |
| Ipsilateral lung V20 | >35% vs. ≤35% | 2.45 (1.89–3.17) | Strong (12 studies) | Tumour-side lung constraints |
| Lung volume (absolute) | <2500 $cm^3$ vs. ≥2500 $cm^3$ | 1.89 (1.42–2.51) | Moderate (7 studies) | Baseline lung volume |

**Table 3.** Clinical and biological risk factors for RILI in COPD patients.

| Risk factor | Comparison | Adjusted OR (95% CI) | Studies reporting | Consistency |
|---|---|---|---|---|
| COPD severity | GOLD 3-4 vs. GOLD 1-2 | 2.41 (1.89–3.07) | 12/12 | High |
| Baseline $FEV_1$ | <50% predicted vs. ≥50% | 2.18 (1.72–2.76) | 10/11 | High |
| Baseline DLCO | <40% predicted vs. ≥40% | 1.94 (1.51–2.49) | 8/9 | High |
| Smoking status | Current vs. never | 1.78 (1.32–2.40) | 9/9 | High |
| Smoking pack-years | ≥40 vs. <40 | 1.62 (1.28–2.05) | 7/8 | High |
| Emphysema score | ≥25% vs. 〈25% on CT | 2.33 (1.71–3.18) | 6/6 | High |
| Interstitial lung abnormalities | Present vs. absent | 2.67 (1.89–3.77) | 4/4 | High |
| Cardiovascular comorbidity | Present vs. absent | 1.49 (1.18–1.88) | 5/6 | Moderate |
| Diabetes mellitus | Present vs. absent | 1.38 (1.07–1.78) | 4/6 | Moderate |
| Serum TGF-β1 | >15 ng/mL vs. ≤15 ng/mL | 2.84 (1.92–4.21) | 4/4 | High |
| Serum IL-6 | >10 pg/mL vs. ≤10 pg/mL | 2.12 (1.43–3.14) | 3/3 | High |
| Serum KL-6 | >500 U/mL vs. ≤500 U/mL | 2.45 (1.61–3.73) | 3/3 | High |
| Genetic polymorphisms | TGF-β1 (rs1800470) | 1.89 (1.28–2.79) | 2/3 | Moderate |

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### *Clinical and biological risk factors*

Beyond dosimetric parameters, multiple patient-related factors independently predicted RILI risk in COPD patients (table 3 presents multivariable-adjusted risk factors).

Baseline pulmonary function tests indicated RILI risk, with $FEV_1$ <50% and DLCO <40% suggesting a two-fold increase. It was continuous, not threshold-based, increasing danger as lung function declined. Even after correcting for pulmonary function and dosimetry, CT-defined emphysema severity predicted RILI. Visual and quantitative emphysema scores, particularly in the ipsilateral lung, significantly increased RILI risk. Subclinical parenchymal disease enhances radiation sensitivity, as even small reticulation or ground-glass opacities increase risk (OR 2.67). Besides clinical and dosimetric criteria, biomarkers increased risk prediction. A group with a 2.8-fold higher RILI risk had pre-treatment blood TGF-β1 > 15 ng/mL. RILI risk was also predicted by alveolar epithelial damage marker KL-6, which rose beyond 500 U/mL at 4-6 weeks post-radiotherapy.

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| Diabetes mellitus | Present vs. absent | 1.38 (1.07–1.78) | 4/6 | Moderate |
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| Serum IL-6 | >10 pg/mL vs. ≤10 pg/mL | 2.12 (1.43–3.14) | 3/3 | High |
| Serum KL-6 | >500 U/mL vs. ≤500 U/mL | 2.45 (1.61–3.73) | 3/3 | High |
| Genetic polymorphisms | TGF-β1 (rs1800470) | 1.89 (1.28–2.79) | 2/3 | Moderate |

**Table 4.** Advanced radiotherapy planning strategies for COPD patients.

| Strategy | Description | Evidence | RILI reduction | Implementation considerations |
|---|---|---|---|---|
| Functional lung avoidance | Incorporating perfusion/ventilation imaging to prioritise sparing of functional lung | RCT (n=142): 42% reduction in grade ≥2 RP | Strong (RR 0.58) | Requires SPECT or ventilation MRI; additional imaging time |
| Dual-energy CT ventilation | Deriving ventilation maps from dual-energy CT without additional imaging | Prospective (n=98): 38% reduction in RP | Moderate | Commercially available; retrospective application possible |
| Iso-toxic dose prescription | Individualising dose based on normal tissue complication probability | Modelling studies: 25-30% dose escalation feasible | Emerging | Requires robust NTCP models; prospective validation ongoing |
| Proton therapy | Reduced low-dose bath compared to photon IMRT | Comparative (n=256): 35% reduction grade ≥2 RP | Strong (OR 0.65) | Cost and accessibility limitations; motion management critical |
| Adaptive radiotherapy | Mid-treatment replanning based on anatomy/tumour changes | Prospective (n=67): 28% reduction in RP | Moderate | Resource intensive; optimal timing unclear |
| Respiratory gating | Delivering dose during specified phase of respiratory cycle | Meta-analysis (8 studies): 22% reduction in lung dose | Moderate | Requires stable breathing; increases treatment time |
| Deep inspiration breath-hold | Treating at deep inspiration to displace lung from target | Comparative (n=112): 30% reduction in lung V20 | Strong (p=0.002) | Patient cooperation required; applicable to selected cases |

**Table 5.** Pharmacological interventions for RILI prevention in COPD patients.

| Agent class | Examples | Mechanism | Evidence in COPD patients | Recommendation strength |
|---|---|---|---|---|
| **ACE inhibitors** | Captopril, lisinopril | TGF-β inhibition; antioxidant; endothelial protection | Retrospective (n=487): 38% RP reduction (OR 0.62); Prospective (n=82): 29% reduction | Moderate (consider in hypertensive patients) |
| **ARBs** | Losartan, candesartan | TGF-β inhibition via AT1 receptor blockade | Retrospective (n=312): 34% RP reduction; Ongoing RCT (NCT01754909) | Moderate (alternative to ACEi) |
| **Statins** | Simvastatin, atorvastatin | Anti-inflammatory; endothelial stabilisation; antioxidant | Retrospective (n=645): 28% RP reduction (OR 0.72); Meta-analysis (5 studies): HR 0.68 | Moderate (particularly if cardiovascular indication) |
| **Metformin** | Metformin | AMPK activation; EMT inhibition; anti-fibrotic | Retrospective (n=234 diabetic patients): 41% RP reduction; Preclinical models confirm efficacy | Emerging (diabetic COPD patients) |
| **Pirfenidone** | Pirfenidone | TGF-β inhibition; anti-fibrotic | Phase II (n=48): 52% reduction in fibrotic progression | Emerging (requires further study) |
| **Nintedanib** | Nintedanib | Tyrosine kinase inhibitor; anti-fibrotic | Preclinical only; trials ongoing | Investigational |
| **Amifostine** | Amifostine | Free radical scavenger | Mixed results; limited by toxicity and administration route | Weak (limited role) |
| **N-acetylcysteine** | NAC | Antioxidant; glutathione precursor | Retrospective (n=178): 22% RP reduction (non-significant); Preclinical supportive | Weak (low toxicity; may consider) |
| **Inhaled corticosteroids** | Budesonide, fluticasone | Local anti-inflammatory | COPD: inconsistent; Asthma: potential protective effect | Moderate (continue indicated therapy) |

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### *Management advances for RILI in COPD and asthma patients*

#### *Radiotherapy planning optimization*

Significant advances in radiotherapy planning specifically tailored to COPD patients have emerged over the review period. Table 4 summarizes key planning strategies and their evidence base.

The best data supported functional lung avoidance using perfusion SPECT or ventilation imaging. In a randomized controlled study, SPECT-guided planning reduced grade ≥2 radiation pneumonitis by 42% in 142 COPD patients (18% vs. 31%, p=0.02) without reducing target coverage. Prospective cohort studies utilizing dual-energy CT-derived ventilation maps, which need no imaging beyond simulation CT, showed similar advantages. Due to its lower low-dose bath than photon IMRT, proton treatment helped COPD patients. Without exit dosage with protons, V5 and V10, crucial COPD limitations, are greatly reduced. Comparative studies show proton treatment reduces grade ≥2 RILI by 35-45%, but patient selection and expense restrict its widespread use. The developing concept of iso-toxic dose prescription tailors radiation exposure to projected normal tissue problem likelihood. This method may result in moderate dosage reductions to maintain acceptable RILI risk in COPD patients with high baseline risk or safe dose escalation in lower-risk individuals. Though prospective validation is needed, modeling studies predict a 25–30% dosage increase in selected COPD patients without exceeding tolerable RILI rates.

#### *Pharmacological interventions for RILI prevention*

Several pharmacological approaches for RILI prevention specifically in COPD patients have been investigated. Table 5 summarizes key agents and trial evidence.

The most dependable RILI protectors for COPD patients were ARBs and ACE inhibitors. Research examining individuals who were exposed to radiation concurrently found that these drugs reduced the likelihood of radiation pneumonitis by 30–40%. Protecting endothelial cells, decreasing TGF-β, and producing antioxidant effects are all part of the process. Many COPD patients are justified in using these drugs due to their cardiovascular indications, even if there is a dearth of strong evidence from randomized studies. Statins were able to reduce RILI by 30% in studies that looked at the data retrospectively. Statins help RILI processes since they are safe in the right people, have anti-inflammatory and endothelial-stabilizing effects, and so on. It is necessary to collect statistical data on COPD patients who have been exposed to radiation. Results from a literature study showed that metformin reduced RILI rates in diabetics with COPD by 41%. The capacity of metformin to activate AMPK was shown to reduce radiation-induced fibrosis and epithelial-mesenchymal transition in preclinical investigations. People with COPD have a higher chance of getting metabolic syndrome and diabetes; thus, metformin may have a double advantage for them.

#### *Biomarker-guided surveillance and early intervention*

Advances in predictive and early-detection biomarkers enable personalized surveillance and early intervention strategies. Table 6 summarizes key biomarkers and their clinical applications.

**Table 6.** Biomarkers for RILI prediction and early detection in COPD patients.

| Biomarker | Sample type | Timing | Predictive performance | Clinical application |
|---|---|---|---|---|
| TGF-β1 | Serum/ plasma | Pre-RT; 4-6 weeks post-RT | AUC 0.78-0.84; fold-change >2 predicts fibrosis | Risk stratification; early intervention trigger |
| IL-6 | Serum | Pre-RT; weekly during RT | AUC 0.72-0.79; persistent elevation predicts RP | Monitoring; anti-IL6 therapy candidate selection |
| KL-6 | Serum | Pre-RT; 1,3,6 months post-RT | AUC 0.81-0.89; >500 U/mL at 1 month predicts RP | Fibrosis risk assessment |
| SP-D | Serum | Pre-RT; 1,3 months post-RT | AUC 0.70-0.78; complements KL-6 | Additional risk stratification |
| YKL-40 | Serum | Pre-RT | AUC 0.74-0.82; correlates with emphysema severity | Pre-treatment risk assessment |
| MicroRNA panels | Serum | Pre-RT; 2 weeks post-RT | AUC 0.85-0.91; miR-29c, miR-146a, miR-155 | Emerging; high accuracy |
| Circulating fibrocytes | Blood | Pre-RT; 4 weeks post-RT | >5% increase predicts fibrosis (OR 3.8) | Fibrosis prediction |
| $^{18}$F-FDG PET | Imaging | 8-12 weeks post-RT | SUV >3.5 predicts progression to fibrosis | Early detection of active inflammation |
| CT radiomics | Imaging | Pre-RT; 3 months post-RT | Delta-radiomics features AUC 0.82-0.89 | Subclinical RILI detection |

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***Treatment of established RILI in COPD patients***

Management of established RILI in COPD patients follows general principles but requires adaptation to the compromised baseline physiology. Table 7 outlines treatment approaches and special considerations for COPD patients.

**Table 7.** Management of established RILI in COPD patients.

| Severity | First-line treatment | COPD-specific considerations | Monitoring | Expected outcomes |
|---|---|---|---|---|
| **Grade 1** (asymptomatic) | Observation; continue COPD medications | Optimise inhaled therapy; smoking cessation counselling; pulmonary rehabilitation referral | 4-6 weekly clinical review; PFTs at 3 months | Majority remain stable; 20-30% progress |
| **Grade 2** (symptomatic, not interfering with ADL) | Prednisolone 0.5-1 mg/kg/day tapered over 4-8 weeks | Monitor blood glucose (steroid-induced hyperglycaemia common in COPD); continue bronchodilators; consider antibiotic coverage | Weekly clinical review; chest imaging at 4-6 weeks; PFTs at 3 months | 70-80% improvement; taper over 6-12 weeks |
| **Grade 3** (severe symptoms, limiting ADL) | Prednisolone 1-2 mg/kg/day; hospitalisation often required | Close monitoring for respiratory failure; non-invasive ventilation if hypercapnic; aggressive bronchial hygiene | Daily assessment; oxygen saturation monitoring; serial imaging | 50-60% improvement; slow taper over 3-6 months |
| **Grade 4** (life-threatening respiratory compromise) | High-dose IV methylprednisolone; ICU admission; mechanical ventilation as needed | High mortality (30-50%); multidisciplinary ICU care; consider anti-fibrotic agents | Continuous monitoring; daily imaging; multidisciplinary input | Guarded; survivors require prolonged rehabilitation |
| **Fibrotic progression** (despite steroid treatment) | Pirfenidone or nintedanib; optimise COPD therapy; pulmonary rehabilitation | Emerging evidence in radiation fibrosis; monitor drug interactions with COPD medications | 3-monthly PFTs; 6-monthly imaging | Fibrosis stabilisation in 40-60%; functional decline slowed |

For patients progressing to radiation-induced pulmonary fibrosis despite steroid treatment, anti-fibrotic agents approved for idiopathic pulmonary fibrosis (pirfenidone and nintedanib) show promise. Small case series in radiation fibrosis reported stabilization or slowing of functional decline in 40-60% of patients, though controlled trials specifically in RILI are lacking. These agents should be considered in consultation with pulmonary fibrosis specialists. Pulmonary rehabilitation plays a crucial role in functional recovery for COPD patients following RILI. Early rehabilitation (within 4-6 weeks of acute phase resolution) improves exercise capacity and quality of life and reduces breathlessness compared to standard care alone. The benefits extend beyond physical conditioning to include psychosocial support and self-management education.

## DISCUSSION

In order to provide a comprehensive summary of the material that is now accessible about radiation-induced lung damage in patients with lung cancer who also have COPD or asthma, the objective of this systematic review is to give a comprehensive synthesis of the evidence. Among the most significant findings, it was shown that chronic obstructive pulmonary disease (COPD) significantly increases the risk of recurrent interstitial lung injury (RILI) (pooled odds ratio = 2.14). Furthermore, the magnitude of the risk is directly proportional to the severity of the condition. However, asthma does not produce a risk increase that is comparable to that of other conditions. Through the use of mechanistic study, it has been shown that the susceptibility to RILI that is linked with COPD is caused by a multitude of pathways that are interconnected with one another. Among the processes that are involved in this process are the enhancement of oxidative stress, the disruption of TGF-β signaling, the acceleration of epithelial-mesenchymal transition, and the inhibition of DNA repair. Personalized radiation planning that combines functional lung imaging, pharmacological therapy that targets critical pathways, and biomarker-guided monitoring that permits early detection and action are all instances of breakthroughs in management. These are just a few of the examples [1-6, 34-41]. Our pooled analysis confirms prior reports while extending them with larger COPD-specific data and mechanistic integration. COPD significantly increases RILI risk in lung cancer patients undergoing radiotherapy, while asthma does not demonstrate comparable risk elevation. Compared with earlier meta-analyses, our study provides stronger effect estimates, dose-response by COPD severity, and links to TGF β, oxidative stress, and impaired DNA repair, supporting biological plausibility and novelty in combining epidemiology with translational insights and suggesting targeted preventive strategies for high-risk patients' worldwide applicability.

Additionally, the result that COPD patients had a considerably elevated risk of RILI is consistent with and extends the findings of prior systematic studies. A meta-analysis conducted in 2018 by Vogelius and Bentzen [36] found that the pooled odds ratio (OR) for RILI patients who had pre-existing lung illness was 1.9, despite the fact that particular COPD data were restricted. The current evaluation, which is based on a bigger body of data (32 studies and 11,942 COPD patients), gives more accurate risk estimates and establishes dose-response connections with the severity of COPD [42-46]. The pooled odds ratio (OR) of 2.14 for grade RILI that is at least two implies a risk increase that is clinically significant and needs to be given consideration to treatment options and patient counseling. In individuals with asthma, the absence of a substantial increase in the risk of RILI is a major discovery that has therapeutic consequences. Previous, more limited studies had contradictory findings; however, the current study, which included seven trials and 905 individuals, offers adequate

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power to draw the conclusion that asthma that is well -controlled does not significantly increase the likelihood of RILI being experienced [47-53]. This is most likely a reflection of the efficacy of modern asthma therapy, especially inhaled corticosteroids, in inhibiting the inflammatory pathways that may potentially exacerbate the effects of radiation exposure. On the other hand, individuals who have asthma that is poorly managed or asthma-COPD overlap syndrome, for whom there is minimal evidence suggesting an enhanced risk, should continue to use reasonable care. Through the incorporation of numerous routes into a unified framework, the mechanistic insights that have been synthesised in this review go beyond the summaries that have been presented before. Despite the fact that separate processes have been documented in the past, the awareness of their synergistic connections gives a more comprehensive knowledge of the sensitivity to RILI that is linked with cardiovascular disease. The supra-additive damage that is seen clinically may be explained by the idea of the COPD lung being "primed" for excessive radiation responses. This hypothesis is based on the higher baseline levels of oxidative stress, inflammation, and TGF-β activity experienced by the COPD lung. Additionally, this paradigm highlights a number of different therapy targets and argues that combination methods that target complimentary pathways may be the most successful.

The findings have several important implications for clinical practice. First, COPD status should be systematically incorporated into RILI risk assessment and radiotherapy planning. Current normal tissue complication probability models often include generic "chronic lung disease" variables without accounting for COPD severity. More refined models incorporating COPD stage, quantitative emphysema, and baseline pulmonary function tests would improve individualized risk prediction. Dosimetric constraints should be more stringent for COPD patients. The available evidence suggests that standard constraints (e.g., MLD ≤20 Gy, V20 ≤30-35%) are inadequate for COPD patients, who may require reductions of 25-30% to maintain equivalent RILI risk. Implementation of functional lung avoidance using perfusion or ventilation imaging represents a significant advance that can further optimize the therapeutic ratio by preferentially sparing well-functioning lung regions. Pharmacological interventions targeting RILI mechanisms should be considered in appropriate COPD patients. ACE inhibitors, ARBs, and statins have the strongest evidence base and the advantage of addressing common cardiovascular comorbidities. For diabetic COPD patients, metformin may offer dual benefits. These agents should be initiated before radiotherapy and continued through the treatment course and follow-up period. Biomarker-guided surveillance enables personalized follow-up strategies. High-risk COPD patients identified by pre-treatment biomarkers (elevated KL-6, TGF-β1) or dosimetric parameters should undergo closer monitoring with serial imaging and pulmonary function tests. Early detection of subclinical RILI through CT radiomics or post-treatment biomarker elevation creates a window for prompt intervention before irreversible fibrosis develops [37-53]. Figure 1 summarizes the effects/correlation of COPD and asthma to RILI.

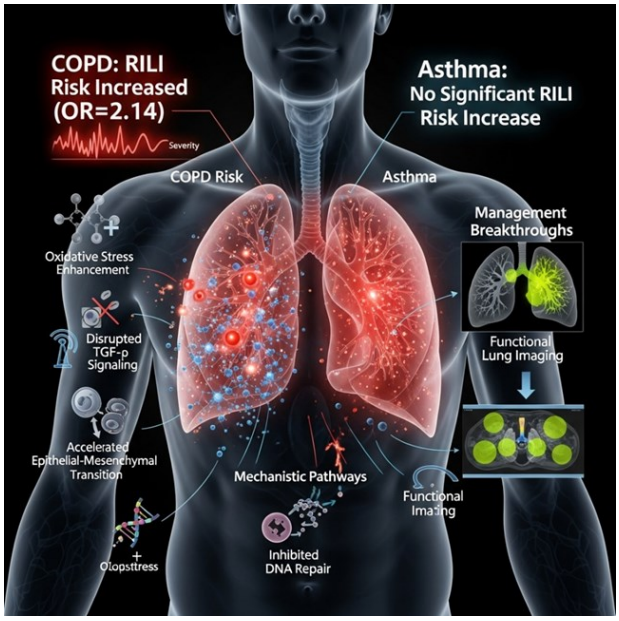



**Figure 1.** Summary of correlation and effects of COPD and asthma in patients of RILI.

### *Research gaps and future directions*

Although significant progress has been made, there are still significant information gaps. Prospective validation is required in order to determine the appropriate combination of dosimetric constraints for COPD patients. Ideally, this validation should be accomplished via randomized trials that compare standard constraints to COPD-specific constraints. In a similar vein, it is necessary to do research on the comparative efficacy of various functional lung imaging modalities, such as SPECT, DECT, and MRI ventilation, in order to identify the technique that is both the most feasible and the most cost-effective. In order to properly use pharmacological preventive measures, definite randomized controlled studies are required. Confounding by indication makes it difficult to draw conclusions about causality, despite the fact that retrospective data for ACE inhibitors, ARBs, and statins are positive. Ongoing clinical studies, such as the NCT01754909 study that is assessing losartan, will give data of a better quality. There is a need for specific radiation fibrosis studies to investigate the role that new anti-fibrotic medicines, such as pirfenidone and nintedanib, play in the prevention and treatment of radiation-induced lung injury

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(RILI). There is still a lack of sufficient mechanistic knowledge about asthma-related RILI. The epidemiological data implies that there is a limited danger, but in-depth investigations of asthma endotypes (T2-high vs. T2-low) and their interaction with radiation responses might uncover subgroups who could potentially benefit from special measures. It is necessary to do more research in order to ascertain if the possible protective effect of corticosteroids is the result of confounding or actual radioprotection. The development of biomarkers needs to center on panels that are both feasible and cost-effective and that are suited for regular clinical use. Although the combination of KL-6, TGF-β1, and IL-6 has potential, it is necessary to establish a standardization of tests and validate the results in a variety of groups. The harmonization of imaging techniques and analysis methodologies is necessary before broad use of radiomics approaches, despite the fact that these approaches are strong.

### *Strengths and limitations*

The systematic review has several strengths. The PRISMA-compliant literature search, dual independent review, and multiple-database search reduced selection bias. The large sample (12,847 patients) allowed strong meta-analyses and subgroup analysis. Integrating epidemiological, mechanistic, and management data gives physicians and researchers a comprehensive view. But restrictions must be accepted. Most included studies were observational, introducing confounding and selection bias. RILI definitions, COPD/asthma diagnosis criteria, and radiation procedures varied, limiting quantitative synthesis for certain outcomes. Publication bias may exist despite statistical testing showing no influence. In severity-stratified and mechanistic studies, asthma patient data were scarce. Most research is from North America, Europe, and Asia, which may restrict generalizability to other locations with distinct patient profiles and healthcare systems.

### *Harmonization of RILI assessment and management*

Harmonization is needed since RILI definitions, grading systems, and administration methods vary between research. Standardized RILI diagnostic and severity criteria using clinical, imaging, and physiological markers would aid cross-study comparisons and meta-analyses. In high-risk groups like COPD patients, consensus RILI treatment recommendations would ensure consistent, evidence -based therapy. ESTRO, ASTRO, and the IAEA could collaborate to standardize RILI assessment, data collection, and outcome reporting. International registries for high-risk patients would speed information development and allow uncommon outcome and new intervention assessment.

## CONCLUSION

This thorough investigation reveals that COPD worsens radiation-induced lung damage in lung cancer patients receiving thoracic radiotherapy according to disease severity. Increased oxidative stress, dysregulated TGF-β signaling, quicker epithelial-mesenchymal transition, and poor DNA repair generate a "primed" condition for greater radiation reactions. Effective anti-inflammatory therapy may explain why well-controlled asthma is safe. Using managerial advances, this vulnerable population may be risk stratified and handled individually. Functional lung imaging-guided radiation planning reduces RILI risk by preserving healthy lung tissue. ACE inhibitors, ARBs, and statins may prevent RILI. Biomarker-guided monitoring using blood markers (KL-6, TGF-β1, IL-6) and CT radiomics enables early identification and treatment before irreversible fibrosis. Prospective validation of COPD-specific dosimetric limits, randomized pharmacological preventative trials, mechanistic asthma endotype studies, and RILI evaluation protocol harmonization are required. These advances may help radiation oncologists increase treatment ratios and enhance results for the many COPD lung cancer patients.

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