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Effectiveness and safety of pirfenidone for radiation-induced lung injury in non-small cell lung cancer: a retrospective pilot study

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Abstract

Background Radiotherapy (RT) remains a cornerstone in the treatment of thoracic malignancies; however, approximately one-third of patients with non-small cell lung cancer (NSCLC) develop Grade ≥ 2 radiation-induced lung injury (RILI). Despite its clinical significance, no pharmacologic standard of care has been established for RILI. Pirfenidone, an antifibrotic agent with anti-inflammatory and antioxidant properties, has demonstrated potential in preclinical models of RILI. This study aimed to evaluate the clinical efficacy and safety of pirfenidone in NSCLC patients with RILI following thoracic RT.

Methods We retrospectively analyzed 33 NSCLC patients diagnosed with Grade ≥ 2 RILI who received pirfenidone (400 mg three times daily) in combination with standard-of-care treatment. The corticosteroid regimen included intravenous methylprednisolone (20-40 mg/day for 5 days), tapered and discontinued by Day 14. Radiologic response was assessed via monthly high-resolution computed tomography (HRCT), and symptoms were graded using common terminology criteria for adverse event(CTCAE) version 5.0. Dose-volume metrics (V5, V20, mean lung dose) were recorded and analyzed for correlation with RILI severity.

Results Radiographic improvement was observed in 78.8% (26/33) of patients, with a trend toward increased response over time. No Grade ≥ 3 pirfenidone-related adverse events (AEs) were observed. One patient experienced transient Grade 3 thrombocytopenia attributed to prior chemotherapy. Univariate analysis showed no significant association between baseline characteristics and treatment response. Four patients with overlapping RILI and immune-related pneumonitis also showed clinical improvement.

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Conclusions Our findings provide preliminary evidence supporting the clinical benefit and tolerability of pirfenidone for RILI in NSCLC patients. These results warrant further investigation in prospective controlled trials to establish its role in routine clinical practice.

Keywords Non-small cell lung cancer, Pirfenidone, Radiation-induced lung injury, Corticosteroids, Radiotherapy, Immune-related pneumonitis

Background

Radiation-induced lung injury (RILI) remains a major dose-limiting complication of thoracic radiotherapy (RT) in patients with non-small cell lung cancer (NSCLC) [1]. Despite advances in RT techniques—including intensity-modulated radiation therapy (IMRT) and stereotactic body radiation therapy (SBRT)—RILI continues to affect approximately 15–30% of patients, particularly those receiving concurrent or sequential systemic therapies [2]. Notably, the integration of immune checkpoint inhibitors (ICIs) with thoracic RT has been associated with an increased incidence of pneumonitis, further complicating the clinical landscape [3, 4].

RILI typically encompasses two phases: an early phase characterized by radiation pneumonitis (RP) and a late phase involving radiation-induced pulmonary fibrosis (RPF). In the acute phase, radiation-mediated injury to alveolar epithelial cells and pulmonary endothelium initiates a cascade of inflammatory responses, leading to alveolar wall thickening, interstitial edema, and impaired gas exchange [5]. If unresolved, chronic inflammation drives fibroblast activation, extracellular matrix deposition, and irreversible pulmonary fibrosis. Currently, corticosteroids remain the mainstay of treatment for symptomatic RP, but they demonstrate limited efficacy against established fibrosis and carry significant adverse effects, including immunosuppression, hyperglycemia, and opportunistic infections with long-term use [6, 7].

Emerging therapies such as stem cell transplantation, targeted biologics, and gene-based interventions are under investigation; however, these approaches are not yet supported by robust clinical evidence [1]. Therefore, there is a critical need for pharmacologic agents that exert both anti-inflammatory and anti-fibrotic effects to effectively manage RILI and prevent disease progression.

Pirfenidone is an oral small-molecule drug approved for the treatment of idiopathic pulmonary fibrosis (IPF). Its mechanisms include inhibition of the TGF-β/Smad signaling pathway, suppression of pro-inflammatory cytokines (e.g., TNF-α, IL-6), and attenuation of oxidative stress [8]. Given the mechanistic overlap between RILI and IPF—particularly in the fibrotic phase—pirfenidone has been proposed as a candidate therapy for RILI. Preclinical studies have demonstrated its ability to reduce radiation-induced pneumonitis and fibrosis in animal models [9, 10]. Limited clinical data also suggest that pirfenidone may improve pulmonary function in patients with radiation-induced lung injury [11]. However, its safety and effectiveness in this context remain inadequately characterized.

In this retrospective pilot study, we aimed to evaluate the clinical efficacy and safety of pirfenidone in NSCLC patients with symptomatic RILI. We systematically assessed radiologic and symptomatic responses, dose-volume correlations, and treatment-related adverse events to determine whether pirfenidone could serve as a viable therapeutic strategy in the post-radiotherapy setting.

Methods

Study design and patient selection

This was a single-center retrospective observational study conducted at the Second Affiliated Hospital of Guizhou Medical University. Patients with histologically or cytologically confirmed NSCLC who developed Grade ≥ 2 RILI following RT between January 2022 and September 2024 were screened for inclusion. The diagnosis of RILI was based on clinical presentation, radiologic findings, and exclusion of infectious etiologies.

Inclusion criteria were as follows: (1) Diagnosis of NSCLC; (2) Radiologic and/or clinical evidence of CTCAE v5.0 Grade ≥ 2 RILI; (3) History of thoracic RT within the preceding 6 months; (4) Availability of at least one post-treatment HRCT scan and complete follow-up records.

Exclusion criteria included: (1) Severe organ dysfunction (e.g., heart, liver, or kidney failure); (2) Known hypersensitivity to pirfenidone; (3) Inability to complete follow-up imaging or clinical assessments.

This study was approved by the institutional ethics committee, and the requirement for written informed consent was waived due to the retrospective nature of the study. A detailed flowchart of the patient screening process is presented in Fig. 1.

Treatment regimen

All patients received oral pirfenidone in addition to standard supportive care, which typically included corticosteroids and/or antibiotics. Pirfenidone was initiated using a stepwise titration protocol: (1)Week 1: 200 mg three times daily (600 mg/day); (2)Week 2: 300 mg three times daily (900 mg/day); (3)Week 3 and beyond: 400 mg three times daily (1200 mg/day).

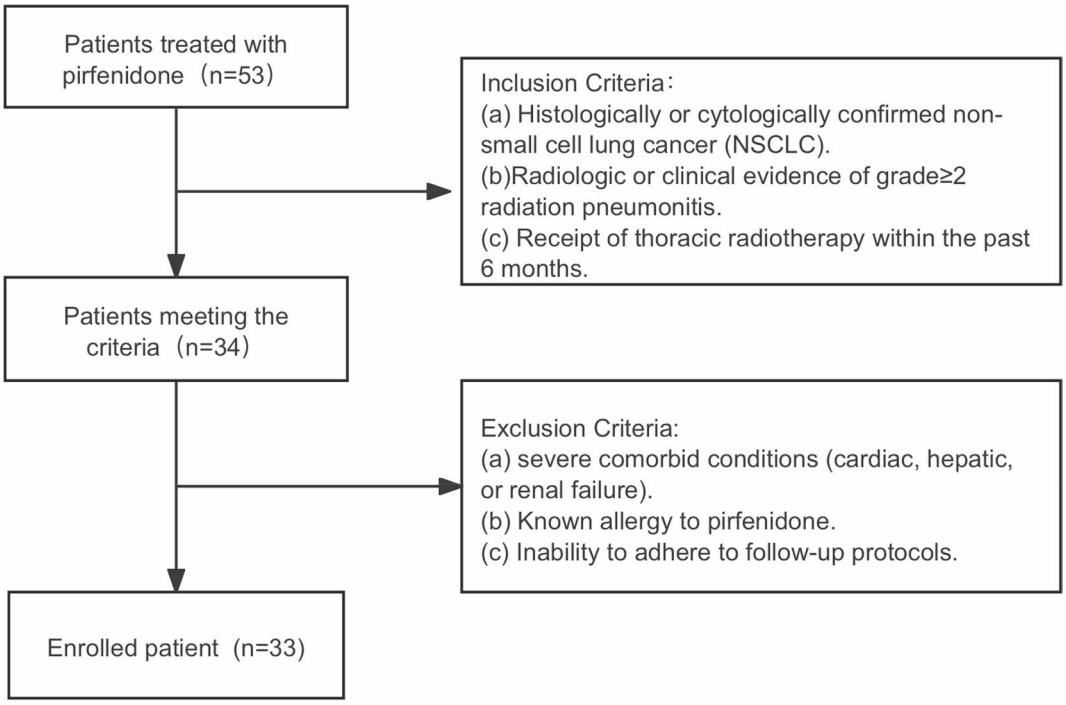

Fig. 1 Patient screening flowchart. A total of 53 patients with non-small cell lung cancer receiving pirfenidone therapy were initially enrolled. Following the application of inclusion and exclusion criteria, 34 patients met the eligibility requirements without any violations. Nineteen patients were excluded due to protocol deviations. During follow-up, one patient withdrew from the study, leaving 33 patients in the final analysis cohort

Intravenous methylprednisolone was initiated at 20–40 mg/day for five days, followed by a taper of 5–10 mg every 2–3 days, with cessation by day 14 according to clinical response. Total treatment duration ranged from 4 to 24 weeks and was tailored to each patient's clinical trajectory. Liver function tests and hematological indices were obtained at baseline and monitored serially to guide dose adjustments.

Radiotherapy and dose-volume parameters

RT plans and dose-volume histograms (DVHs) were retrieved from the treatment planning system for all patients. Lung dosimetric parameters included: V5: percentage of lung volume receiving ≥ 5 Gy; V20: percentage receiving ≥ 20 Gy; Mean lung dose (MLD): average dose delivered to the lung. These parameters were analyzed to explore their association with RILI severity and pirfenidone response.

Assessment of pneumonitis

Diagnosis and grading of RILI were based on common terminology criteria for adverse event(CTCAE) version 5.0. RILI was defined by the presence of ground-glass opacities or consolidations confined to the radiation field, occurring within 6 months post-RT, in the absence of infection. Immune-related pneumonitis was diagnosed in patients with prior PD-1/PD-L1 inhibitor exposure who exhibited infiltrates outside the radiation field and compatible clinical features. A comparison of diagnostic criteria is provided in Supplementary Table 1.

Evaluation of treatment effectiveness

High-resolution computed tomography (HRCT) of the chest was performed at baseline and repeated every 4 weeks for up to 6 months. Radiologic responses were independently assessed by two blinded thoracic radiologists and categorized as: (1)Complete resolution: full disappearance of radiographic lesions; (2)Partial resolution:≥50% reduction in lesion extent; (3)Stable disease: minimal change (<50% reduction, no progression); (4) Progressive disease: lesion enlargement or new opacities (Supplementary Table 2).

Symptomatic evaluation included dyspnea, cough, and chest tightness, assessed at each visit and graded using CTCAE v5.0. The primary endpoint was overall radiographic response rate (ORR) at 1, 2, and 3 months. The secondary endpoints included symptom improvement and treatment-related adverse events.

In cases where symptomatic improvement and radiographic resolution were inconsistent, radiographic assessment served as the primary criterion for determining the overall response category (CR/PR/SD/PD) in this study, as HRCT offers an objective evaluation of lung injury resolution. Nonetheless, substantial symptomatic improvement was still regarded as an important clinical outcome.

Safety assessment

All patients were monitored for adverse events (AEs) throughout treatment. Laboratory evaluations included hematology, liver enzymes, renal function, and electrolytes. AEs were graded using CTCAE v5.0 criteria. Special attention was given to pirfenidone-associated toxicities, such as hepatotoxicity, gastrointestinal reactions, photosensitivity, and hematologic changes. Any Grade ≥ 3 AEs were documented in detail and managed with dose adjustments or supportive interventions.

Table 1 Baseline demographics and disease characteristics

Baseline characteristics	Number of patients (*n* = 33)
Age, years	
Mean (SD)	59.09 (9.402)
Min-Max	37–74
Sex, n(%)	
Males	27 (81.8)
Females	6 (18.2)
ECOG score, n(%)	
1	27 (81.8)
2	6 (18.2)
Pathological type, n(%)	
Adenocarcinoma	13 (39.4)
Squamous cell	18 (54.5)
Others	2 (6.1)
Smoking, n(%)	
Yes	22 (66.7)
No	11 (33.3)
Staging, n(%)	
Stage I	1(3.0)
Stage III	22(66.7)
Stage IV	10(30.3)
T Stage, n(%)	
T1	1(3)
T2	5(15.2)
T3	6(18.2)
T4	21(63.6)
Pirfenidone pre-treatment, n(%)	
Chemoradiotherapy	21(63.6)
Immunotherapy + Chemotherapy	4 (12.1)
Others	8(27.3)
Pirfenidone co-treatment, n(%)	
None	12(36.4)
Radiotherapy	5(15.2)
Immunotherapy + Chemotherapy	16(48.5)
Pneumonitis Type, n(%)	
Radiation pneumonitis	29(87.9)
Radiation pneumonitis with immune-related pneumonitis	4(12.1)
Pirfenidone response rate, n(%)	
Responsive	26(78.8.6)
Non-responsive	7(21.2)
Pulmonary comorbidity, n(%)	
Emphysema	4(12.1)
Non-emphysema	29(87.9)

Table notes:T, tumor; ECOG, eastern cooperative oncology group.

Statistical analysis

All efficacy analyses followed the intention-to-treat principle. Continuous variables were summarized as means (± SD) or medians (interquartile range), and categorical variables as counts and percentages. Fisher's exact test and Chi-square test were used to compare response rates across time points. A linear trend test assessed the association between treatment duration and response. Univariate logistic regression was performed to identify potential predictors of pirfenidone efficacy, including age, sex, eastern cooperative oncology group(ECOG) performance status, histology, disease stage, smoking history, treatment history. A two-tailed p-value<0.05 was considered statistically significant. Analyses were conducted using SPSS (version 30.0) and GraphPad Prism (version 10.4.0).

Results

Patient characteristics

A total of 33 patients with NSCLC and Grade ≥ 2 radiation-induced lung injury (RILI) were included in the final analysis. The median interval from RT completion to symptom onset was 5.2 weeks (range 3–9 weeks). The baseline characteristics are summarized in Table 1. The median age was 59 years (range: 37–74), and 81.8% (27/33) of the cohort were male. The majority of patients had an ECOG performance status of 1 (81.8%), and the most common histological subtype was squamous cell carcinoma (54.5%), followed by adenocarcinoma (39.4%). Advanced disease was predominant, with 66.7% (22/33) having stage IIIB and 30.3% (10/33) stage IV disease.

All patients underwent thoracic radiotherapy (median total dose ≈ 60 Gy). The median lung V5 was 56% (IQR, 52–60%), V20 was 25% (IQR, 23–27%), and the MLD was 20 Gy (IQR, 18–21 Gy). Prior to pirfenidone initiation, 63.6% (21/33) had received chemotherapy, and 12.1% (4/33) received combined chemoradiotherapy and immunotherapy. During pirfenidone treatment, 48.5% (16/33) continued systemic therapy, 15.2% (5/33) received additional palliative RT, and 36.4% (12/33) had no further oncologic interventions. Comorbid pulmonary emphysema was present in 4 patients (12.1%).

Among the 33 patients, 29 (87.9%) had isolated RILI, while 4 (12.1%) had overlapping immune checkpoint inhibitor (ICI)-related pneumonitis. All four cases were confirmed by radiographic criteria and clinical context (Supplementary Table 1).

Radiation parameters in stage IV patients

Detailed radiotherapy parameters for stage IV patients are presented in Supplementary Table 3. Despite oligometastatic disease (1–2 sites), all patients received curative-intent RT to the primary lung lesions (median dose 60 Gy in 28–30 fractions). Common metastatic sites included lung, bone, pleura, liver, brain, and cervical lymph nodes.

Clinical grading of RILI

Based on clinical and radiological evaluation, 29 patients (87.9%) were diagnosed with Grade 2 pneumonitis and 4 (12.1%) with Grade 3 (**Supplementary Table 4**). Grade 2 cases manifested as exertional dyspnea with patchy ground-glass opacities confined to the radiation field. Grade 3 presentations featured resting dyspnea, severe cough, and oxygen dependence, alongside extensive CT abnormalities such as lobar consolidation and air bronchograms.

Efficacy of Pirfenidone

The ORR was 78.8% (26/33), including complete resolution (CR) in 6 patients (18.2%) and partial resolution (PR) in 20 patients (60.6%) at any timepoint during the follow-up period (Fig. 2A). Stable disease (SD) was observed in 5 patients (15.2%), and disease progression (PD) in 2 (6.1%).

Time-based response trends were as follows: (1)1 month: PR in 62.1%, SD in 24.1%, PD in 13.8%, CR = 0; (2)2 months: CR in 4.5%, PR in 50.0%, SD or PD in 45.5%; (3)3 months: CR in 28.0%, PR in 48.0%, SD in 12.0%, PD in 12.0%.

The distribution of response categories differed significantly across timepoints (χ^2 $p<0.001$), with pairwise significance between 1 and 2 months ($p=0.034$), and highly significant differences between 1 vs. 3 months and 2 vs. 3 months (both $p<0.0001$). Linear trend analysis revealed a statistically significant improvement over time ($p=0.022$), indicating a cumulative treatment effect (Fig. 2B-C).

Representative radiologic changes

Representative HRCT images (Fig. 3) demonstrated consistent radiologic regression in responsive patients, with reduction in lesion extent and density. In contrast, non-responders showed persistent or worsening infiltrates. These findings visually underscore the heterogeneity in response patterns.

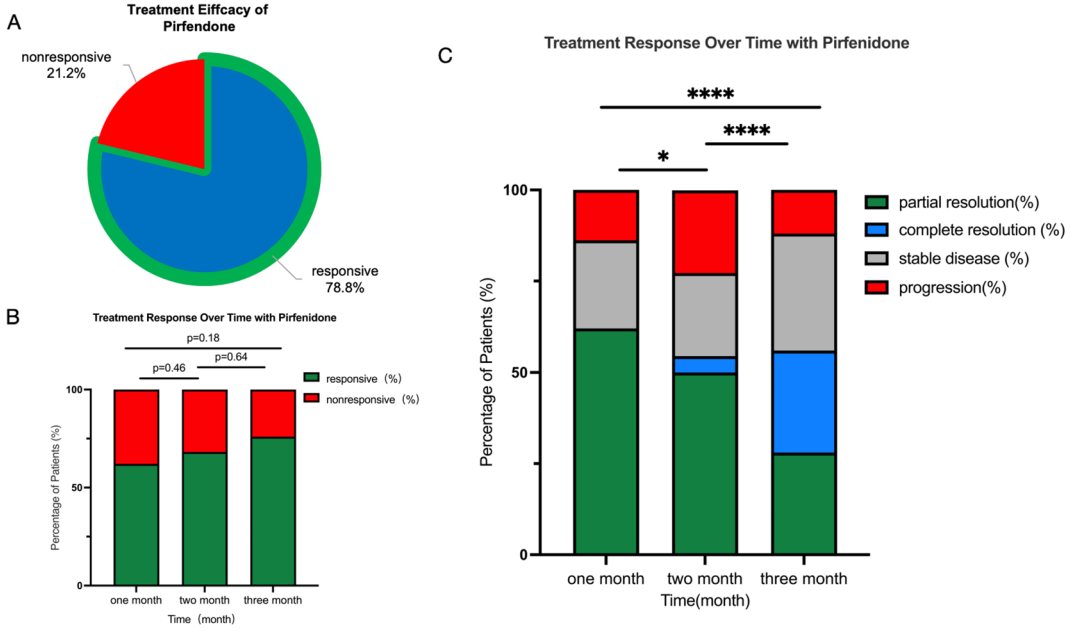

Fig. 2 Primary efficacy outcomes during the study period. (a) Overall response rate among patients treated with pirfenidone. Patients were classified as responsive (showing lesion reduction or absorption; green, 78.8%) or non-responsive (no change or progression; red, 21.2%). Stacked bar charts illustrate the proportions of responsive patients at 1 month (62.1%), 2 months (68.2%), and 3 months (76.0%), and non-responsive patients (37.9%, 31.8%, and 24.0%, respectively). Primary chi-square analysis revealed no statistical significance ($p=0.108$). Pairwise comparisons also showed no significant differences across time points (1 vs. 2 months: $p=0.175$; 1 vs. 3 months: $p=0.643$; 2 vs. 3 months: $p=0.459$). (c) Dynamic response profiles displayed in a stacked column chart, with stratified outcomes: Partial Resolution (dark green), Complete Resolution (blue), stable disease (gray), and Progression (red). The overall distribution of responses differed significantly ($p<0.001$), with significant intergroup differences observed between 1 and 2 months ($p=0.034$), 1 and 3 months, and 2 and 3 months (both $p<0.0001$). *p* values in (b) and (c) were calculated using Fisher's exact test; $p<0.05$ was considered statistically significant

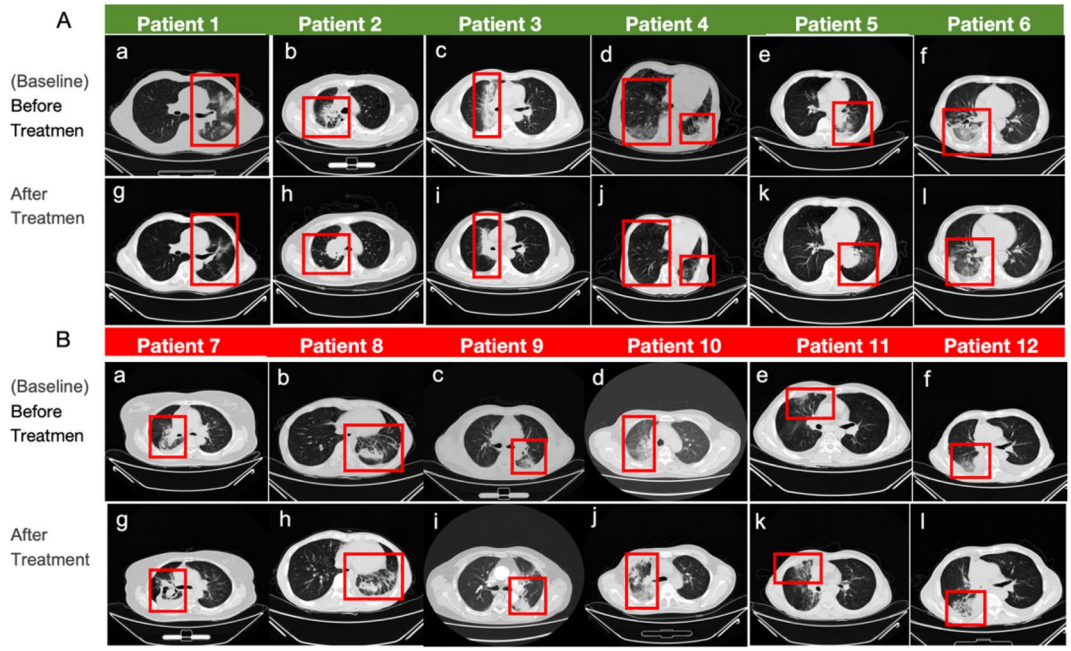

Fig. 3 CT imaging characteristics of pneumonitis following pirfenidone treatment. (a) The treatment-responsive group displays lesion changes in six patients (Patients 1–6) after pirfenidone therapy. All exhibited varying degrees of lesion regression and absorption, as indicated by substantial shrinkage or complete resolution of baseline lesions (labeled a-f) compared with post-treatment scans (labeled g-l). (b) In contrast, the treatment-nonresponsive group includes six patients (Patients 7–12) who showed either disease progression or minimal radiographic changes. Patients 7–10 demonstrated exacerbation of lesions (baseline: a-d; post-treatment: g-j), while Patients 11 and 12 showed minimal or no change (baseline: e-f; post-treatment: k-l). These radiological findings visually underscore the heterogeneous response to pirfenidone, with some patients experiencing marked clinical improvement, whereas others showed limited benefit or disease progression

Predictors of treatment response

Univariate logistic regression identified no significant predictors of pirfenidone efficacy. Factors analyzed included age, sex, ECOG performance status, histological subtype, smoking history, disease stage, T-stage, prior or concurrent treatments, and pulmonary comorbidities. All odds ratios were near unity, and none of the covariates reached the pre-specified significance threshold ($p<0.10$), thus no multivariate modeling was performed (Fig. 4).

Safety and adverse events

Pirfenidone was generally well tolerated. No patients discontinued treatment due to toxicity. Most AEs were mild (Grade 1–2), reversible, and managed with supportive care.

Laboratory abnormalities included: (1)Elevated transaminases (ALT in 12.1%, AST in 15.2%); (2)Creatinine increase (12.1%); (3)Hematologic events: anemia (Grade 1–2, 24.2%), neutropenia (6.1%), thrombocytopenia (Grade 3, 3.0%). Non-laboratory AEs included: (1)Fatigue (30.3%); (2)Nausea or vomiting (21.2%); (3)Heartburn/dyspepsia (12.1%); (4)Rash (3.0%).

No Grade 4 or 5 events were reported. One case of Grade 3 thrombocytopenia occurred in a patient with prior chemotherapy and was managed without permanent drug discontinuation (Tables 2 and 3).

Comparative analysis of current therapeutic approaches for RILI

Current therapeutic strategies for RILI include corticosteroids, pirfenidone, nintedanib, observation only, and experimental therapies. A summary of current pharmacologic strategies for RILI is presented in Supplementary Table 5.

Discussion

In this retrospective pilot study, we provide preliminary clinical evidence supporting the use of pirfenidone for managing RILI in patients with NSCLC. Radiological assessments demonstrated a high overall response rate of 78.8%, including both complete and partial lesion resolution. Notably, no grade ≥ 3 treatment-related adverse events were observed, and the overall safety profile was acceptable. The observed safety outcomes aligned with established tolerability data from prior fibrotic disease trials, with no new adverse signals identified [12, 13]. As a novel pharmacological option for RILI, pirfenidone could potentially mitigate radiation-induced pulmonary damage; however, confirmatory evidence from prospective controlled trials is required.

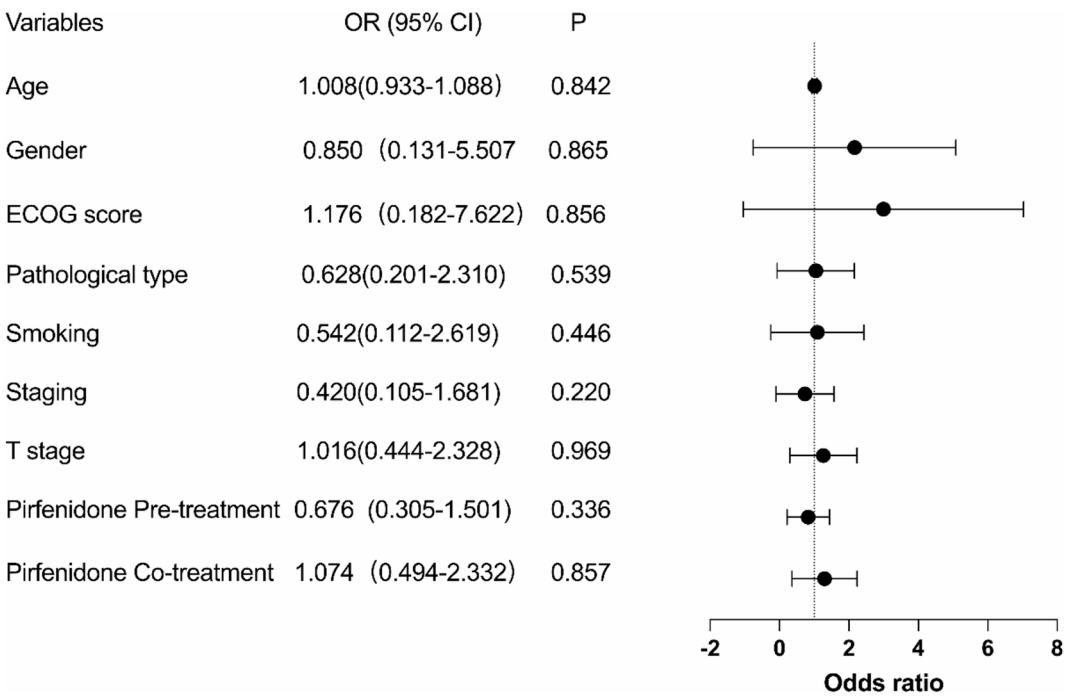

Fig. 4 Univariate analysis of factors influencing pirfenidone response. An unstratified Cox proportional hazards model was employed to estimate hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). Clinical variables-including age, sex, histological subtype, smoking status, smoking history, disease stage, T stage, prior pirfenidone exposure, and concurrent pirfenidone treatment-were assessed for their association with treatment outcomes. Each variable was analyzed using odds ratios (ORs), 95% CIs, and corresponding p-values. The forest plot (right panel) graphically illustrates OR estimates and their precision. Most variables exhibited no statistically significant associations ($p>0.05$); however, disease stage ($p=0.220$) showed a potential trend toward significance. No other factors emerged as strong predictors of treatment response in this analysis

Table 2 Treatment-related adverse events in all patients ($n=33$)

Blood Test Results	Grade 1	Grade 2	Grade 3	Grade 4	Grade≥3
ALT	4(12.1%)	0	0	0	0
AST	5(15.2%)	1(3%)	0	0	0
Total bilirubin	0	0	0	0	0
Direct bilirubin	0	0	0	0	0
Indirect bilirubin	0	0	0	0	0
Urea	0	0	0	0	0
Creatinine	4(12.1%)	0	0	0	0
White blood cells	0	0	0	0	0
Absolute neutrophil count	2(6%)	0	0	0	0
Hemoglobin	6(18.2%)	2(6%)	0	0	0
Platelets	0	0	1(3%)	0	0

Abbreviations: AST, Aspartate aminotransferase; ALT, Alanine aminotransferase

Table 3 Treatment-related adverse events in all patients (n=33)

Side Effects	Grade 1	Grade 2	Grade 3	Grade 4	Grade≥3
Photosensitivity	0	0	0	0	0
Rash	1(3%)	0	0	0	0
Arthralgia	0	0	0	0	0
Dizziness	1(3%)	0	0	0	0
Fatigue	8(24.2%)	2(6%)	0	0	0
Nausea, vomiting	7(21.2)	0	0	0	0
Heartburn	1(3%)	1(3%)	0	0	0
Bloating	0	1(3%)	0	0	0
Constipation	0	0	0	0	0
Diarrhea	0	0	0	0	0
Decreased appetite	2(6%)	0	0	0	0

The observed efficacy of pirfenidone in our study appears superior to previously reported response rates with glucocorticoid monotherapy, which typically range from 42–56% in RILI patients [14, 15]. This therapeutic advantage may reflect pirfenidone's multifaceted mechanism of action. In addition to its well-established anti-fibrotic effects via inhibition of the TGF-β/Smad signaling pathway, pirfenidone also downregulates key pro-inflammatory mediators such as interleukin-6 and tumor necrosis factor-α through suppression of NF-κB activity [16–19]. These dual anti-inflammatory and anti-fibrotic effects enable simultaneous mitigation of acute alveolitis and prevention of fibrotic remodeling. In contrast, corticosteroids primarily target acute-phase inflammation and have limited impact on fibrotic progression [6, 15].

Our analysis revealed a time-dependent cumulative therapeutic effect of pirfenidone in RILI, with response rates increasing from 62% at one month to 76% at three months, and non-response rates declining from 38–24%. Although the Fisher-Freeman-Halton exact test did not demonstrate overall statistical significance ($p=0.108$), the linear trend analysis indicated a significant positive

correlation between treatment duration and clinical efficacy (two-tailed $p = 0.033$). Compared to the delayed therapeutic response in IPF—as reported by King and the ASCEND Study Group [13], where benefits emerged only after ≥6 months—patients with RILI in our study exhibited a more rapid clinical response (22.6% increase in 3 months). This divergence may reflect differences in the temporal dynamics of inflammatory-fibrotic transitions; TGF-β activation in RILI peaks at 6–8 weeks post-radiotherapy [20], while IPF involves persistently active fibrotic signaling cascades [21]. These findings highlight RILI's distinct temporal sensitivity to intervention.

The evolving therapeutic response to pirfenidone demonstrated a temporally distinct pattern. In the first month, lesion shrinkage accounted for the majority of responses (62%), with complete resolution in 5% of cases. By the second month, lesion shrinkage decreased to 49.5% ($p = 0.034$), suggesting the initiation of fibrotic repair following inflammation control. This pattern mirrors phase transitions observed in murine RILI models [22, 23]. At three months, a qualitative shift was observed: complete resolution increased to 28%, while progression decreased to 12%. Chi-square testing confirmed a strong association between time and treatment response grades ($p<0.001$), supported by a significant linear trend ($p = 0.022$). These findings underscore the importance of treatment duration in optimizing therapeutic efficacy and suggest that extending the therapeutic window may help surpass critical pathological thresholds.

In this study, combined treatment with pirfenidone and corticosteroids for radiation pneumonitis achieved a 3-month complete radiographic remission (CR) rate of 28%, exceeding historical data [24]. We speculate that this favorable CR rate may be attributed to the dual anti-inflammatory and anti-fibrotic mechanisms of pirfenidone [25], timely intervention within the early post-radiotherapy therapeutic window, and the potential synergistic effects of the combination regimen (pirfenidone plus corticosteroids) [26]. Furthermore, the predominance of lower-grade (Grade 2) pneumonitis among the study population may have been an additional favorable factor. The generalizability of these results requires validation in larger-scale studies.

We included four patients with overlapping radiation and ICI pneumonitis. All showed radiographic improvement following pirfenidone therapy, including one complete and three partial responses. With the increasing adoption of sequential radiotherapy and immunotherapy, the incidence of RILI has risen [3]. While current guidelines recommend observation for Grade 1–2 RP [27], the growing use of immunotherapy presents new clinical challenges. Mild RP cases may progress to severe mixed-type pneumonitis due to immune hyperactivation post-immunotherapy [4], necessitating proactive management. These findings emphasize the need for early therapeutic intervention in RILI to enhance disease control and facilitate subsequent oncologic treatment.

Additionally, the median onset time of RILI in our cohort was approximately 5.2 weeks after radiotherapy, indicating that most cases were classified as "early-onset RILI." Although previous studies have suggested that early-onset RILI may be associated with poorer outcomes [28], we did not perform formal statistical analysis due to sample size limitations. Nonetheless, patients in our study exhibited favorable radiological improvements, suggesting that pirfenidone may offer therapeutic benefit during the early inflammatory phase, warranting further validation in larger cohorts.

No clinical or demographic variables were found to significantly correlate with pirfenidone response in univariate analyses. Factors such as age, sex, smoking status, tumor stage, and concurrent therapies had no observable impact on treatment outcomes (all $p \geq 0.10$). While advanced age and smoking have previously been associated with diminished pirfenidone efficacy in IPF [13, 29], our findings may reflect the relatively homogeneous cohort, or the more dominant influence of acute radiation injury on treatment responsiveness. Larger studies will be needed to clarify predictive markers of pirfenidone benefit in this population.

Pirfenidone's safety profile in RILI was consistent with IPF data, with a lower incidence of severe hepatic events (12–15% vs. 20–30%) and rare Grade 3 thrombocytopenia [30]. Gastrointestinal and dermatologic adverse events were comparable to prior reports [31–33]. Nonetheless, cumulative toxicity in previously chemoradiated patients necessitates vigilant monitoring of hepatic and hematologic parameters during treatment.

Although our study supports the feasibility and potential benefit of pirfenidone in RILI management, several limitations should be acknowledged. First, the retrospective single-arm design precludes causal inference and is susceptible to selection bias. Second, the sample size was modest, limiting statistical power and subgroup analyses. Third, pulmonary function tests (PFTs) were not routinely available, precluding assessment of functional recovery alongside imaging response. Lastly, while imaging review was blinded, CT-based assessment remains a surrogate endpoint and may not fully capture clinical benefit. Future prospective studies incorporating standardized symptom scales, PFTs, and longer-term follow-up will be essential to validate these findings.

To contextualize our results, Supplementary Table 5 presents an overview of current pharmacologic strategies for RILI management, emphasizing pirfenidone's combined anti-inflammatory and antifibrotic mechanisms in comparison to established therapies and emerging agents.

In conclusion, pirfenidone may represent a promising pharmacologic option for patients with radiation-induced lung injury following thoracic radiotherapy. Its dual anti-inflammatory and anti-fibrotic activity, acceptable safety profile, and observed radiologic benefit support further investigation. Future prospective, controlled trials are warranted to establish its role in routine clinical care and to identify patient subgroups most likely to benefit.

Conclusions

In this retrospective pilot study, pirfenidone was associated with significant radiographic improvement and a favorable safety profile in NSCLC patients with RILI. These preliminary findings suggest that pirfenidone may mitigate fibrotic progression and preserve pulmonary function when integrated into standard RILI management. Confirmation in larger, prospective, controlled trials is essential before routine clinical implementation.

Abbreviations

RILI	Radiation-Induced Lung Injury
RT	Radiotherapy
NSCLC	Non-Small Cell Lung Cancer
IMRT	Intensity-Modulated Radiation Therapy
SBRT	Stereotactic Body Radiation Therapy
ICIs	Immune Checkpoint Inhibitors
RP	Radiation Pneumonitis
RPF	Radiation Pulmonary Fibrosis
IPF	Idiopathic Pulmonary Fibrosis
DVHs	Dose-Volume Histograms
MLD	Mean Lung Dose
CTCAE	Common Terminology Criteria for Adverse Event
HRCT	High-Resolution Computed Tomography
ORR	Overall Response Rate
AEs	Adverse Events
ECOG	Eastern Cooperative Oncology Group
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Death-Ligand 1
PCR	Polymerase Chain Reaction
CR	Complete Resolution
PR	Partial Resolution
SD	Stable Disease
PD	Disease Progression
HRs	Hazard Ratios
CIs	Confidence Intervals
ORs	Odds Ratios
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
CS	Current Study
LFTs	Liver Function Tests
VEGFR	Vascular Endothelial Growth Factor Receptor
FGFR	Fibroblast Growth Factor Receptor
PDGFR	Platelet-derived Growth Factor Receptor
TGF-β	Transforming Growth Factor-beta
PFTs	Pulmonary Function Tests

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-14896-1.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

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Author contributions

Conception and design: XL, BL, and JP. Administrative support: SF S, JP, and FY L. Provision of study materials and enrollment of patients: XL, HL Y, GH L, LL Z, DZ, TC H, and YH, LY W, JX, BL L, ZJ H, MF W. Collection and assembly of data: XL. Data analysis and interpretation: XL, JP. Manuscript writing: all authors. All authors contributed to the article and approved the submitted version.

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Data availability

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki, and approval was obtained from the Ethics Committee of the Second Affiliated Hospital of Guizhou Medical University. The requirement for written informed consent was waived by the Ethics Committee of the Second Affiliated Hospital of Guizhou Medical University due to the retrospective nature of the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

1. Chang S, Lv J, Wang X, Su J, Bian C, Zheng Z, et al. Pathogenic mechanisms and latest therapeutic approaches for radiation-induced lung injury: a narrative review. Crit Rev Oncol Hematol. 2024;202: 104461.

2. Chun SG, Hu C, Choy H, Komaki RU, Timmerman RD, Schild SE, et al. Impact of intensity-modulated radiation therapy technique for locally advanced non–small-cell lung cancer: a secondary analysis of the NRG oncology RTOG 0617 randomized clinical trial. J Clin Oncol. 2017;35:56–62.
3. Weisman M, Durm G, Shields MD, Hanna NH, Althouse S, Lautenschlaeger T. Evaluation of radiation pneumonitis in a phase 2 study of consolidation immunotherapy with nivolumab and ipilimumab or nivolumab alone following concurrent chemoradiation therapy for unresectable stage IIIA/IIIB non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 2025;121:720–7.
4. Pu D, Liu Q, Zhang S, Wang L, Xu F, Hofman P, et al. Real-world incidence and risk factors of pneumonitis in chemoradiation plus immune checkpoint inhibitors compared with chemoradiation alone in lung cancer: a retrospective cohort study. Transl Lung Cancer Res. 2024;13:139–51.
5. Hanania AN, Mainwaring W, Ghebre YT, Hanania NA, Ludwig M. Radiation-induced lung injury: assessment and management. Chest. 2019;156:150–62.
6. Abratt RP, Morgan GW, Silvestri G, Willcox P. Pulmonary complications of radiation therapy. Clin Chest Med. 2004;25:167–77.
7. Chastain DB, Spradlin M, Ahmad H, Henao-Martínez AF. Unintended consequences: risk of opportunistic infections associated with long-term glucocorticoid therapies in adults. Clin Infect Dis. 2024;78:e37-56.
8. Martinez FJ, Collard HR, Pardo A, Raghu G, Richeldi L, Selman M, et al. Idiopathic pulmonary fibrosis. Nat Rev Dis Primers. 2017;3:17074.
9. Sun YW, Zhang YY, Ke XJ, Wu XJ, Chen ZF, Chi P. Pirfenidone prevents radiation-induced intestinal fibrosis in rats by inhibiting fibroblast proliferation and differentiation and suppressing the TGF-β1/Smad/CTGF signaling pathway. Eur J Pharmacol. 2018;822:199–206.
10. Ying H, Fang M, Hang QQ, Chen Y, Qian X, Chen M. Pirfenidone modulates macrophage polarization and ameliorates radiation-induced lung fibrosis by inhibiting the TGF-β1/Smad3 pathway. J Cell Mol Med. 2021;25:8662–75.
11. Chen M, Hou Z, Yao Q, Chen H, Shao Q, Li M, et al. Pirfenidone in the treatment of radiation-induced lung injury: a randomized, controlled, multicenter clinical trial. Int J Radiat Oncol Biol Phys. 2024;120(2): 14.
12. Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet. 2011;377:1760–9.
13. King TE, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, et al. A phase 3 trial of Pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2014;370:2083–92.
14. Rimner A, Moore ZR, Lobaugh S, Geyer A, Gelblum DY, Abdulnour RE, et al. Randomized phase 2 placebo-controlled trial of nintedanib for the treatment of radiation pneumonitis. Int J Radiat Oncol Biol Phys. 2023;116:1091–9.
15. Sekine I, Sumi M, Ito Y, Nokihara H, Yamamoto N, Kunitoh H, et al. Retrospective analysis of steroid therapy for radiation-induced lung injury in lung cancer patients. Radiother Oncol. 2006;80:93–7.
16. Tie Y, Tang F, Peng D, Zhang Y, Shi H. TGF-beta signal transduction: biology, function and therapy for diseases. Mol Biomed. 2022;3:45.
17. Antar SA, Saleh MA, Al-Karmalawy AA. Investigating the possible mechanisms of Pirfenidone to be targeted as a promising anti-inflammatory, anti-fibrotic, anti-oxidant, anti-apoptotic, anti-tumor, and/or anti-SARS-CoV-2. Life Sci. 2022;309:121048.
18. Abdulaal WH, Omar UM, Zeyadi M, El-Agamy DS, Alhakamy NA, Ibrahim SR, et al. Pirfenidone ameliorates ANIT-induced cholestatic liver injury via modulation of FXR, NF-κB/TNF-α, and Wnt/GSK-3β/β-catenin signaling pathways. Toxicol Appl Pharmacol. 2024;490: 117038.
19. Zhang S, Wang Y, Luo D, Cheng Z, Zeng Q, Wang G, et al. Pirfenidone inhibits TGF-β1-induced metabolic reprogramming during epithelial-mesenchymal transition in non-small cell lung cancer. J Cell Mol Med. 2024;28: e18059.
20. Bian C, Qin WJ, Zhang CY, Zou GL, Zhu YZ, Chen J, et al. Thalidomide (THD) alleviates radiation induced lung fibrosis (RILF) via down-regulation of TGF-β/Smad3 signaling pathway in an Nrf2-dependent manner. Free Radic Biol Med. 2018;129:446–53.
21. Chanda D, Otoupalova E, Smith SR, Volckaert T, De Langhe SP, Thannickal VJ. Developmental pathways in the pathogenesis of lung fibrosis. Mol Aspects Med. 2019;65:56–69.
22. Farh ME, Kim HJ, Kim SY, Lee JH, Lee H, Cui R, et al. Transcriptional changes in radiation-induced lung injury: a comparative analysis of two radiation doses for preclinical research. Int J Mol Sci. 2024;25: 3766.
23. Yang M, Fan Q, Hei TK, Chen G, Cao W, Meng G, et al. Single-cell transcriptome analysis of radiation pneumonitis mice. Antioxidants. 2022;11: 1457.
24. Henkenberens C, Janssen S, Lavae-Mokhtari M, et al. Inhalative steroids as an individual treatment in symptomatic lung cancer patients with radiation pneumonitis grade II after radiotherapy - a single-centre experience. Radiat Oncol. 2016;11:12.
25. Torre A, Martínez-Sánchez FD, Narvaez-Chávez SM, Herrera-Islas MA, Aguilar-Salinas CA, Córdova-Gallardo J. Pirfenidone use in fibrotic diseases: what do we know so far? Immun Inflamm Dis. 2024;12(7): e1335.
26. Rasooli R, Pourgholamhosein F, Kamali Y, Nabipour F, Mandegary A. Combination therapy with pirfenidone plus prednisolone ameliorates paraquat-induced pulmonary fibrosis. Inflammation. 2018;41(1):134–42.
27. Voruganti Maddali IS, Cunningham C, McLeod L, Bahig H, Chaudhuri N, Chua LM. Optimal management of radiation pneumonitis: findings of an international Delphi consensus study. Lung Cancer. 2024;192:107822.
28. Arroyo-Hernández M, Maldonado F, Lozano-Ruiz F, Muñoz-Montaño W, Nuñez-Baez M, Arrieta O. Radiation-induced lung injury: current evidence. BMC Pulm Med. 2021;21:9.
29. Kuipers ME, van Doorn-Wink KC, Hiemstra PS, Slats AM. Predicting radiation-induced lung injury in patients with lung cancer: challenges and opportunities. Int J Radiat Oncol Biol Phys. 2024;118:639–49.
30. Lancaster LH, de Andrade JA, Zibrak JD, Padilla ML, Albera C, Nathan SD, et al. Pirfenidone safety and adverse event management in idiopathic pulmonary fibrosis. Eur Respir Rev. 2017;26:170057.
31. Cottin V, Koschel D, Günther A, Albera C, Azuma A, Sköld CM, et al. Long-term safety of pirfenidone: results of the prospective, observational passport study. ERJ Open Res. 2018;4: 00084–2018.
32. Ferrer Guillén B, Giácaman MM, Valenzuela Oñate C, Magdaleno Tapial J, Hernández Bel P, Pérez ferriols A. Pirfenidone-induced photosensitivity confirmed by pathological phototest. Photodiagnosis Photodyn Ther. 2019;25:103–5.
33. Kim HJ, Seo JW, Kim TH, Choi SH, Song KH, Kim KH. Pirfenidone-induced photosensitivity in a patient with idiopathic pulmonary fibrosis. Ann Dermatol. 2018;30:614–6.

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