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Clinical evaluation of acute lung injury in patients with severe pneumonia after radiotherapy: A respiratory system perspective

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► ***Original article***

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ABSTRACT

Background: Acute lung injury (ALI) in patients with severe pneumonia after thoracic radiotherapy is a clinical problem, because infectious infiltrates may overlap radiation-induced lung changes. The present study aimed to investigate the clinical characteristics, radiological findings, inflammatory markers and outcomes in this population. ***Materials and Methods:*** A prospective observational study of 68 adults with severe pneumonia, prior thoracic radiotherapy, and concurrent ALI at a tertiary teaching hospital from January to December 2024. ALI severity was classified using PaO_2/FiO_2 ratios according to the Berlin definition. Clinical variables, inflammatory markers, chest imaging findings, respiratory-support requirements, intensive care unit (ICU) admission and in-hospital mortality were evaluated. ***Results:*** Mild, moderate and severe ALI was seen in 45.6%, 47.0% and 7.3% of patients respectively. Radiation and organizing pneumonia patterns of fibrosis were observed in 32.4% and 20.6% of patients, respectively. Mean C-reactive protein concentrations were higher in patients with consolidation (129.2 mg/L), patchy opacities (124.4 mg/L) and lower in patients with radiation fibrosis (78.3 mg/L). ICU admission was required in 50% of patients and invasive mechanical ventilation in 45.6%. In-hospital mortality was 25.0% overall. None of the predictors evaluated were statistically significant in the multivariate mortality model. ***Conclusion:*** Severe pneumonia with ALI after thoracic radiotherapy is associated with overlapping infectious and radiation-related radiological findings, substantial critical-care requirements, and substantial in-hospital mortality. Early recognition and integrated assessment of oxygenation, inflammatory markers and imaging findings may support clinical risk stratification.

INTRODUCTION

Acute lung injury (ALI) is a critical and potentially fatal spectrum of pulmonary insufficiency secondary to a variety of insults to the lung parenchyma [1]. The clinical picture is particularly complex when ALI occurs in patients who had thoracic radiotherapy as radiation induced lung damage and infectious pneumonia generate synergic pathological processes. Severe pneumonia continues to be a major public health problem worldwide, especially in older patients and those with underlying comorbidities, among which cancer survivors are a particularly vulnerable population [2]. Radiation-induced pulmonary fibrosis, decreased mucociliary clearance and altered immune surveillance make these patients prone to severe respiratory infections and subsequent ALI.

Radiotherapy is an important modality in the treatment of thoracic malignancies but can also cause significant lung injury by direct cellular damage and indirect inflammatory cascades. Radiation pneumonitis is an acute inflammatory reaction observed in 5-20% of patients receiving thoracic irradiation and is characterized by alveolar epithelial damage, capillary leak and cytokine mediated inflammation [3]. Once these patients develop severe pneumonia, the pre-existing pulmonary compromise greatly increases the risk of ALI. The pathogenesis of pneumonia-induced ALI in this population is multifactorial, including overlapping mechanisms such as direct infectious injury, radiation-induced fibrosis, surfactant production disruption, and exaggerated systemic inflammatory responses [4].

The clinical picture of ALI in patients after radiotherapy often does not correspond to classical descriptions. Radiographic interpretation can be particularly challenging because prior radiation

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induced architectural changes may complicate acute rapidly progressive dyspnea with refractory hypoxemia and bilateral infiltrates on imaging [5]. Differentiation of infectious infiltrates, radiation pneumonitis and organizing pneumonia often requires correlation with clinical history, inflammatory markers and temporal relationship to radiotherapy. Early recognition and adequate grading of ALI severity is essential to guide targeted respiratory care in these complex cases [6]. Recent progress in diagnostic techniques have underlined the importance of combining radiological findings, biochemical markers and clinical parameters in the evaluation of ALI [7]. The PaO_2/FiO_2 ratio, the basis of the Berlin criteria to quantify hypoxemia, has been validated in heterogenous patient populations but should be interpreted with caution in patients with pre-existing radiation-induced pulmonary dysfunction [8]. Inflammatory markers such as C-reactive protein (CRP), procalcitonin and neutrophil-to-lymphocyte ratio (NLR) may be useful markers of the degree of systemic and pulmonary inflammation [9]. High-resolution computed tomography (HRCT) shows characteristic patterns, but in patients' post-radiotherapy these may also include patterns of radiation fibrosis, traction bronchiectasis and organizing pneumonia that overlap with infectious findings [10, 11].

There are unique challenges in the management of ALI in patients who have had previous thoracic radiotherapy. Decreased pulmonary reserve, pre-existing fibrosis, delayed onset of respiratory symptoms, and concomitant cancer-related immunosuppression increase the risk of ICU admission, prolonged mechanical ventilation, and poor outcome [12]. Although severe ALI usually comes with high mortality, there is increasing recognition that moderate hypoxemia and radiographic infiltrates can lead to significant morbidity in this vulnerable population [13, 14]. Previous studies have reported conflicting results on the predictive value of early markers, and few studies have focused on the intersection of radiation-induced lung injury and pneumonia-associated ALI [15].

In this clinical context, the present study was aimed to perform a full clinical analysis of ALI in patients with severe pneumonia and previous thoracic radiotherapy. Main purposes were: (1) to describe demographic and clinical characteristics of this peculiar patient population; (2) to stratify ALI severity in terms of PaO_2 /FiO_2; (3) to correlate inflammatory markers with radiological patterns, with particular attention to the distinction between radiation-related changes and infectious findings; (4) to evaluate risk factors related to ICU admission and in-hospital mortality. The prospective observational study design aimed to improve understanding of ALI in post-radiotherapy pneumonia patients and to provide evidence-based guidance for early diagnosis, risk stratification and therapeutic decisions.

The present study was aimed to provide a complete clinical evaluation of acute lung injury in patients with severe pneumonia who had previously been subjected to thoracic radiotherapy in this clinical setting. The novelty of this work is the simultaneous assessment of severity of hypoxemia, systemic inflammatory markers, radiological patterns, respiratory-support needs and in-hospital outcomes in this clinically complex population. In contrast to studies of radiation induced lung injury or pneumonia-associated acute respiratory failure alone, this study is interested in the diagnostic overlap of infectious pulmonary infiltrates and radiation-associated changes such as fibrosis and organizing pneumonia. This study seeks to improve clinical characterization and early risk stratification of severe pneumonia and acute lung injury patients' post-radiotherapy by integrating severity classification based on PaO_2/FiO_2 with inflammatory and imaging features. The objectives were to describe demographic and clinical characteristics of these patients, to classify severity of lung injury, to examine associations between inflammatory markers and radiological patterns, and to evaluate factors associated with ICU admission and in-hospital mortality.

MATERIALS AND METHODS

Study design and setting

This prospective observational study was conducted in the Department of Emergency Medicine and Department of Thoracic Oncology of a tertiary care teaching hospital from January 2024 to December 2024. The study was conducted following the Declaration of Helsinki and approved by the institutional ethics committee (Approval No. X-221-9943). All participants or their legally authorized representatives provided written informed consent.

Study population

Participants were recruited over the 12-month study period by a systematic screening process. All adult patients with a clinical diagnosis of severe pneumonia and a history of thoracic radiotherapy were eligible for inclusion. Severe pneumonia was diagnosed in accordance with the criteria of the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS), which included major clinical signs (respiratory distress, hypoxemia, bilateral infiltrates on chest imaging) and systemic manifestations (altered mental status or hypotension requiring vasopressors) [17, 18].

Patients were identified by preliminary case

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finding by attending physicians and research staff. Inclusion criteria were: (1) age ≥18 years; (2) diagnosis of severe pneumonia according to IDSA/ATS criteria; (3) documented history of thoracic radiotherapy (within the preceding 12 months); (4) evidence of acute respiratory failure; and (5) provision of written informed consent. Exclusion criteria were strictly applied to avoid confounding factors that may affect the assessment of ALI. Patients with pre-existing chronic interstitial lung disease not related to radiotherapy, active pulmonary tuberculosis or significant immunocompromise (chemotherapy-induced neutropenia, HIV/AIDS) were excluded. Pregnant women were also excluded, due to potential physiological and ethical concerns. Additionally, patients who left against medical advice or had incomplete medical records were excluded from the final analysis. After the selection criteria were applied, 76 patients were identified as potentially eligible. After removing patients who withdrew consent, who were discharged early or had incomplete records, the final cohort of 68 patients was evaluated in detail and underwent statistical analysis.

Data collection

Data were prospectively collected using a structured case record form designed for this study. Each patient was assigned a unique study identification number to maintain anonymity and traceability throughout the analysis. The SOFA score was recorded at admission and daily during the course of the hospital stay until discharge or death. Demographic characteristics (age, sex, height, weight, and body mass index (BMI)) were recorded at admission as a baseline [22]. Clinical histories were obtained directly from patients whenever possible or from accompanying family members, and supplemented by review of electronic medical records. Special attention was given to document radiotherapy characteristics: radiation field, total dose, fractionation schedule, and time since end of radiotherapy. Pre-existing comorbidities such as hypertension, diabetes mellitus, COPD and/or asthma, chronic kidney disease, and congestive heart failure were meticulously documented.

Radiotherapy was delivered either by external-beam photon therapy (three-dimensional conformal radiotherapy, intensity-modulated radiotherapy, or volumetric-modulated arc therapy) according to primary malignancy, disease stage, treatment intent, and anatomical target. The treatment was delivered using 6-MV photons from a medical linear accelerator. The total prescribed dose was 30 to 66 Gy. Palliative thoracic radiotherapy was typically given as 30 Gy in 10 once-daily fractions of 3 Gy, while definitive treatment was given as 60–66 Gy in 30–33 once-daily fractions of 2 Gy. Selected postoperative or adjuvant courses were given as about 50 Gy in 25 once-daily 2 Gy fractions. Treatment was generally given 5 days per week, leading to a total treatment duration of about 2-6.5 weeks. The prescribed regimen was tailored according to tumor type, treatment intent, performance status, target volume and normal-tissue constraints. Systemic anticancer treatment was noted as concurrent or sequential due to its possible effect on pulmonary toxicity.

At presentation and at regular intervals thereafter, vital signs including respiratory rate, heart rate, systolic and diastolic blood pressure, body temperature, and peripheral oxygen saturation (SpO 2) were measured and recorded. Arterial blood gas (ABG) analysis (Edan Instruments, Inc., Shenzhen, China) was performed on admission and within 6 hours of initial presentation to assess the degree of hypoxemia and the severity of ALI. The arterial partial pressure of oxygen (PaO2) and fraction of inspired oxygen (FiO_2) were measured and the PaO_2/FiO_2 ratio was calculated for each patient. The cut-off value for diagnosis of ALI was set at a PaO_2/FiO_2 ratio ≤300 mmHg according to the Berlin criteria [24]. Inflammatory markers such as C-reactive protein (CRP), procalcitonin, total leukocyte count (TLC) and neutrophil-to-lymphocyte ratio (NLR) were measured according to the hospital protocols. These markers were used to evaluate systemic inflammatory responses and their correlation with clinical outcome [25]. Other laboratory investigations like renal function panel, hepatic function panel, serum electrolytes and coagulation profile were done as a part of total diagnostic work-up.

All patients underwent radiological investigations which included chest X-ray (Orich Medical Equipment, Tianjin, China) and/or high-resolution computed tomography (HRCT) (Shanghai United Imaging Healthcare Co., Ltd., Shanghai, China) of the chest. Two radiologists, who were blinded to clinical outcomes, independently interpreted the imaging studies. Radiographic findings were graded as ground-glass opacities, diffuse alveolar damage, patchy opacities, consolidation, bilateral infiltrates or radiation fibrosis. The degree of lung involvement was evaluated in a semi-quantitative manner. Particular attention was given to distinguishing radiation-induced changes (fibrosis, traction bronchiectasis, organizing pneumonia) from infectious infiltrates. Data regarding respiratory support were meticulously collected, noting whether the patient required supplemental oxygen, non-invasive ventilation (NIV), high-flow nasal cannula (HFNC), or invasive mechanical ventilation (IMV). Type, duration and settings of respiratory support were recorded. We also recorded the use of vasopressor or renal replacement therapy, admission to the ICU and length of stay in the ICU.

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Study outcomes

The primary outcome was in-hospital mortality from any cause. Secondary outcomes included ICU admission rate, duration of mechanical ventilation, length of hospital stay, and respiratory support requirements. All outcomes were measured at the time of discharge or death.

All datasets were cross-verified by two independent reviewers to ensure accuracy and completeness. Discrepancies were resolved through consensus. Data were then coded and entered into a secure computer database for statistical analysis.

Definition of Acute Lung Injury (ALI)

ALI was diagnosed using the Berlin Definition for Acute Respiratory Distress Syndrome (ARDS), providing a standardized approach to diagnose and grade lung injury severity in acute hypoxemic respiratory failure [27, 28]. The key diagnostic criteria included:

1. **Timing:** Acute onset within 1 week of clinical insult or new/worsening respiratory symptoms
2. **Imaging:** Bilateral opacities on chest imaging (chest radiograph or HRCT) not fully explained by effusions, lobar collapse, or nodules [27]
3. **Origin:** Respiratory failure not fully explained by cardiac failure or fluid overload (echocardiography and/or B-type natriuretic peptide [BNP] levels assessed when available) [29]
4. **Hypoxemia:** PaO_2/FiO_2 ratio ≤300 mmHg with at least 5 cm H_2O positive end-expiratory pressure (PEEP)

Severity stratification based on PaO_2/FiO_2 ratio:

- **Mild ALI:** PaO_2/FiO_2 201–300 mmHg
- **Moderate ALI:** PaO_2/FiO_2 101–200 mmHg
- **Severe ALI (ARDS):** PaO_2/FiO_2 ≤100 mmHg

Hypoxemia was measured within 6 hours of hospital admission via arterial blood gas analysis. For mechanically ventilated patients, FiO_2 was determined directly from ventilator settings.

Statistical analysis

Data were summarized using descriptive statistics. Continuous variables were expressed as mean ± standard deviation (SD) or median and interquartile range (IQR) for data not normally distributed. Categorical variables were expressed as frequencies and percentages. Between group comparisons were performed using: • Student's t-test or Mann-Whitney U test for continuous data Chi-square or Fisher exact test for categorical variables. Univariable and multivariable logistic regression models were used to identify independent predictors for ICU admission and mortality. Statistical significance was determined by $p < 0.05$. All statistical analysis was performed using SPSS software (IBM Corp., Release 26.0).

RESULTS

Baseline demographics and clinical characteristics

The study cohort included 68 patients with severe pneumonia and concomitant ALI who had received previous thoracic radiotherapy. The mean age of the patients was 53.9 ± 22.5 years with a broad age spectrum representative of the broad variety of the cancer population. Males predominated accounting for 61.8% (42 males and 26 females). The most common comorbidities were hypertension (32.4%), diabetes mellitus (23.5%) and COPD (20.6%). Sixteen point two percent of patients had no documented comorbidities. Chemotherapy was administered concurrently or sequentially in 68% of patients. The mean admission oxygen saturation (SpO2) was 85.5 ± 5.7% suggesting significant respiratory dysfunction in majority of the patients. Baseline characteristics are summarized in table 1.

The total prescribed radiation dose ranged from 30 to 66 Gy. Patients treated with palliative intent generally received 30 Gy in 10 fractions, whereas those undergoing definitive thoracic radiotherapy generally received 60–66 Gy in 30–33 fractions. Selected patients receiving postoperative or adjuvant radiotherapy were treated with approximately 50 Gy in 25 fractions. Radiotherapy was administered once daily, five days per week. The mean interval between completion of radiotherapy and admission for severe pneumonia was 4.2 ± 2.8 months, and 68% of patients had received concurrent or sequential chemotherapy.

Respiratory function and ALI classification

Table 1. Baseline characteristics of the study population.

Variable	Value (n=68)
Mean Age (± SD)	53.9 ± 22.5 years
Sex (M/F)	42 / 26
Common Comorbidities	
Hypertension	32.4%
Diabetes Mellitus	23.5%
Chronic Obstructive Pulmonary Disease	20.6%
Congestive Heart Failure	7.3%
None	16.2%
Mean SpO_2 (%) (± SD)	85.5 ± 5.7
Mean BMI (± SD)	25.5 ± 3.6
Smokers (Yes/No)	22 / 46
Mean Symptom Duration (± SD)	6.8 ± 4.0 days
Time Since Radiotherapy (months ± SD)	4.2 ± 2.8
Radiation Dose Range (Gy)	30-66

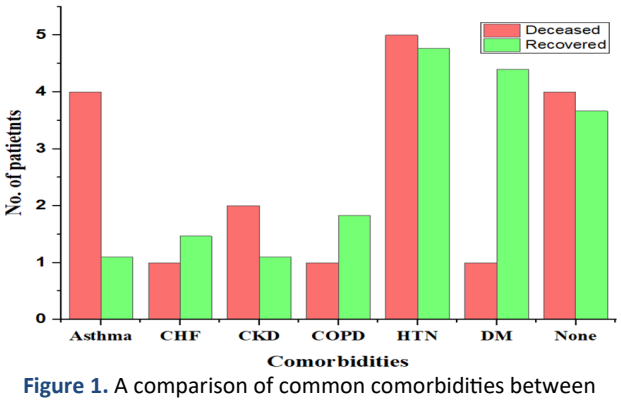


Figure 1. A comparison of common comorbidities between deceased and recovered patients.

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Patients were classified as mild (PaO2/FiO2: 201-300), moderate (101-200) or severe (≤100) ALI according to Berlin criteria. The distribution was mild ALI (45.6%), moderate ALI (47.0%) and severe ALI (7.3%). Table 2 shows the relationship of severity of ALI with patient outcomes. The distribution of severity categories is shown in the stacked bar graph (figure 2), and the box plot of PaO_2/FiO_2 ratios by outcome illustrates the degree of hypoxemia among those who died.

Inflammatory markers and radiological patterns

Table 2. Severity of ALI and patient outcomes.

ALI Severity	Deceased (n)	Recovered (n)	Total (n)
Mild	8	23	31
Moderate	7	25	32
Severe	2	3	5
Total	**17**	**51**	**68**

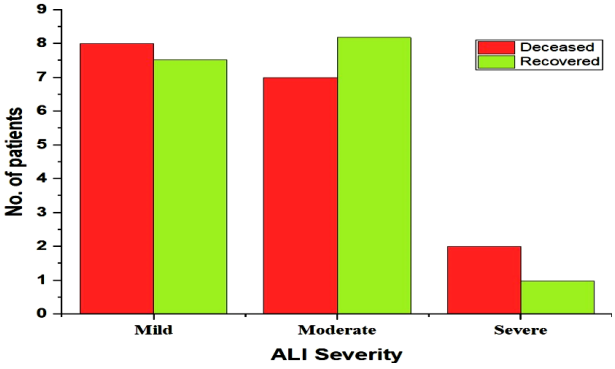


Figure 2. The distribution of patient's outcomes by the ALI severity.

To evaluate the relationship between inflammatory markers and radiological patterns, analysis of chest CT findings and CRP levels was performed. The most common radiological finding was ground glass opacities (27.9%), followed by diffuse alveolar damage (23.5%), patchy opacities (19.1%), consolidation (16.2%) and bilateral infiltrates (13.2%). Radiation-induced lung changes included radiation fibrosis in 22 (32.4%) and organizing pneumonia patterns in 14 patients (20.6%).

Higher mean CRP values were observed in patients with consolidation (129.2 mg/L) and patchy opacities (124.4 mg/L), suggesting these findings are associated with more intense systemic inflammation [10]. The mean CRP level was lower in patients with radiation fibrosis (78.3 ± 42.6 mg/L), consistent with the chronic, less inflammatory nature of established radiation damage.

Table 3. Radiological patterns and associated CRP levels.

CT Finding	Mean CRP (mg/L)	SD CRP	Number of Patients
Ground-glass opacities	119.2	65.8	19
Diffuse alveolar damage	107.1	63.4	16
Patchy opacities	124.4	65.9	13
Consolidation	129.2	31.3	11
Bilateral infiltrates	95.2	66.0	9
Radiation fibrosis	78.3	42.6	22

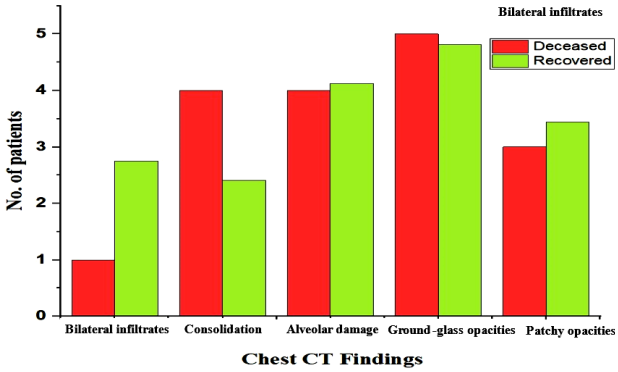


Figure 3. The distribution of chest CT findings among patients, grouped by clinical outcomes.

ICU Admission, mechanical ventilation, and hospital stay

Of the 68 patients evaluated, 50% required ICU admission, demonstrating the severity of respiratory compromise in this population. Invasive mechanical ventilation was required in 45.6% of patients, while non-invasive ventilation was utilized in 29.4%. The mean hospital stay was approximately 15 days, reflecting substantial healthcare resource utilization.

Table 4. ICU and respiratory support summary.

Variable	No. of Patients (%)
ICU Admissions	34 (50.0%)
Mechanical Ventilation	31 (45.6%)
Non-Invasive Ventilation	20 (29.4%)
Mean Hospital Stay (± SD)	15.1 ± 5.2 days
ICU: Intensive Care unit	

Clinical outcomes

In-hospital mortality was 25.0% (n = 135) and survival to discharge from the hospital was 75.0% (n = 405). Patients needing mechanical ventilation had higher mortality rates (35.5% versus 16.2% in non-ventilated patients) and severe ALI had a mortality of 60%. Patients with multiple comorbidities, especially COPD and chronic kidney disease, had higher mortality. Importantly, mortality was not limited to patients with severe ALI; 25.8% of mild ALI and 21.9% of moderate ALI patients died, highlighting the importance of early intervention in all severity categories.

Table 5. Outcome distribution in the study population.

Outcome	No. of Patients (%)
Recovered	51 (75.0%)
Deceased	17 (25.0%)

Predictors of ICU admission and mortality

Multivariate logistic regression analysis evaluated potential predictors of mortality, including CRP, age, PaO_2/FiO_2 ratio, and mechanical ventilation requirement [32]. Though no predictor reached statistical significance, trends were observed toward increased mortality with lower PaO_2/FiO_2 ratios and higher CRP levels. Mechanical ventilation demonstrated an odds ratio of 1.229 for mortality, consistent with its role as both a marker of severe illness and a potential contributor to complications such as ventilator-associated pneumonia.

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Table 6. Logistic regression for predictors of mortality.

Predictor	Odds Ratio	95% CI Lower	95% CI Upper	P-value
Intercept	0.168	0.008	3.459	0.248
C-reactive protein	0.998	0.989	1.008	0.730
PaO_2/FiO_2	1.002	0.994	1.011	0.594
Age	1.010	0.981	1.041	0.492
Mechanical Ventilation	1.229	0.348	4.344	0.748

DISCUSSION

ALI is a life-threatening complication of patients admitted to hospital with severe pneumonia and when superimposed on radiation-induced lung damage presents unique diagnostic and therapeutic challenges [33]. This study offers a comprehensive evaluation of the clinical features, pulmonary function, inflammatory response, and prognosis of adult patients with severe pneumonia and ALI who had previously undergone thoracic radiotherapy. Using a case definition based on Berlin criteria we have characterized the clinical spectrum of ALI in this vulnerable population and identified key associations with radiological patterns, inflammatory biomarkers and clinical outcomes [34, 35]. The mean age of patients was about 54 years old, which is in line with the usual patient population with thoracic malignancies that develop radiation pneumonitis with subsequent pneumonia. The male preponderance (61.8%) is consistent with the higher incidence of lung cancer and head and neck cancers in males, which are common indications for thoracic radiotherapy. The prevalence of comorbidities such as hypertension (32.4%), diabetes mellitus (23.5%) and COPD (20.6%) was high and in agreement with literature describing the burden of chronic diseases among patients at risk for respiratory infections and lung injury [36, 37]. In particular, comorbidities such as COPD and chronic kidney disease were more frequent in non-survivors, highlighting their well-known negative effect on the prognosis of respiratory failure [38]. The mean duration from the completion of radiotherapy (4.2 months) falls within the usual latency period for radiation pneumonitis (1-6 months after radiotherapy), indicating a possible synergistic effect between radiation-induced inflammation and infectious pneumonia. The classification of ALI severity by the PaO 2 /FiO 2 ratio revealed mild ALI in 45.6%, moderate ALI in 47.0%, and severe ALI in 7.3%. The lower proportion of severe ALI compared with some ARDS cohorts may be due to inclusion of patients with less severe illness, as well as the potential protective effect of prior radiation-induced fibrosis in limiting edema formation. The distribution pattern is generally consistent with previous cohorts, including the LUNG SAFE study [39], but the moderate ALI predominance in our population may reflect the unique pathophysiology of post-radiation pneumonia. Significantly, even patients with "mild ALI" had significant morbidity, emphasizing the point that early hypoxemia in patients with limited pulmonary reserve should never be taken lightly. A clear association was observed between severity of ALI and mortality with survival in only 60% of patients with severe ALI emphasizing the prognostic significance of early PaO_2/FiO_2 assessment. PaO_2 / FiO_2 plays a crucial role in guiding management decisions including initiation of mechanical ventilation and early referral to ICU as demonstrated in previous studies [41]. This relationship may be even more important in the post-radiotherapy population because of reduced pulmonary reserve and impaired compensatory mechanisms. Of particular interest was the association between radiological pattern and systemic inflammation. The most common CT finding was ground-glass opacities (27.9%) that are reported in viral and bacterial pneumonia as well [42]. However, radiation fibrosis (32.4%) and organizing pneumonia patterns (20.6%) were also common, reflecting the underlying radiation-induced lung changes. Patients with consolidation (129.2 mg/L) and patchy opacities (124.4 mg/L) had the highest mean CRP levels, which may indicate more severe systemic inflammation [43]. In contrast, radiation fibrosis had lower CRP levels (78.3 mg/L), reflecting its chronic, less inflammatory nature. These results have important clinical implications. First, CRP seems to be not only a marker of systemic inflammation but also associated with lung parenchymal injury and may assist in differentiation of active infection and stable radiation fibrosis. Second, radiographic interpretation in this population needs to be carefully correlated with clinical history as radiation-induced changes may mimic or mask infectious infiltrates. Third, serial CRP measurements can be a surrogate for radiologic progression, especially in resource-limited settings where repeat CT scans may not be feasible [44]. Half of the patients required ICU admission and almost 46% of the patients required invasive mechanical ventilation. These rates are comparable to ICU admission rates for ALI/ARDS patients worldwide and confirm the severity of illness in this population [45]. However, the need for mechanical ventilation in post-radiotherapy patients may be particularly important as the presence of pre-existing fibrosis and reduced lung compliance can make ventilator management challenging. The median hospital stay of approximately 15 days underscores the high clinical and logistic burden of these cases, comparable to the hospitalization duration in severe pneumonia and radiation pneumonitis. Patients requiring mechanical ventilation tended to have worse outcomes (OR 1.229), but this was not statistically significant, likely because of a limited sample size. This finding is consistent with previous studies that have shown that mechanical ventilation is not only a marker of severe illness but also an exposure that may promote

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complications such as ventilator-associated pneumonia and barotrauma [47, 48]. Mechanical ventilation can be particularly challenging in patients who have undergone radiotherapy due to decreased lung compliance and an increased risk of pneumothorax resulting from radiation-induced architectural changes. The overall mortality rate of 25% is similar to classical figures for ALI/ARDS due to pneumonia [49], although a little lower than some contemporary ARDS mortality estimates. This may be due to inclusion of less severely ill patients and improvements in supportive care. Lower PaO_2/FiO_2 ratios and higher CRP levels were associated with mortality, indicating hypoxemia and systemic inflammation are important outcome predictors. Importantly, mortality was not limited to severe ALI, with a substantial number of deaths occurring in patients with moderate injury (21.9%) and even mild ALI (25.8%), challenging traditional paradigms of risk stratification and highlighting the importance of early identification and intervention across all levels of ALI severity. Multivariate logistic regression did not identify significant independent predictors, probably because of limited statistical power, but trends suggested associations between CRP, PaO_2/FiO_2, mechanical ventilation and mortality risk. These findings are consistent with previous work but also highlight the heterogeneity of host response that could limit the predictive precision in smaller cohorts [50]. The broad confidence limits highlight again the need for larger multicenter trials to confirm these trends.

Some important observations in this study have particular relevance for clinical practice. First, the conjunction of severe pneumonia with previous radiotherapy constitutes a singular clinical entity with atypical radiographic manifestations, exaggerated inflammatory responses, and intricate management issues. Second, CRP levels correlate with the degree of systemic inflammation and with specific radiographic patterns, indicating the possible use of serial CRP monitoring in the evaluation of disease progression. Third, the risk of death in this population is not restricted to those with the most severe ALI, highlighting the need for early and aggressive intervention even in patients with apparently moderate disease.

There are a few limitations of this study that should be mentioned. First, the single-center design and a relatively small sample size (n=68) limit the generalization of findings, and may have limited statistical power for detecting significant predictors. Second, the lack of long-term follow-up does not allow for evaluation of post-discharge outcomes, including chronic respiratory dysfunction and progression of pulmonary fibrosis. Third, heterogeneity in radiation parameters (dose, field, fractionation) and cancer types may have introduced variability that could not be fully accounted for in our analyses. Fourth, we did not systematically screen for radiation-induced organizing pneumonia using specific diagnostic criteria, which may have provided additional insights. Fifth, the absence of a control group of pneumonia patients without previous radiotherapy limits our capacity to compare outcomes directly and to identify radiation specific effects. Future work should concentrate on a few key areas. Larger, multi-center studies with longer term follow-up are needed to validate our findings and to identify robust predictors of outcome in this population. The integration of molecular and genetic biomarkers with clinical and radiological factors could further enhance prognostic accuracy and guide personalized therapeutic strategies. Further prospective studies are urgently needed to assess optimal ventilator strategies in post-radiotherapy patients with ALI. Also, studies on the role of anti-inflammatory therapies including corticosteroids in managing ALI in this population may provide useful guidance for clinical practice. Finally, the development of predictive models incorporating radiation parameters, inflammatory markers and clinical variables may facilitate early identification of high-risk patients.

CONCLUSION

In patients with severe pneumonia after thoracic radiotherapy, acute lung injury was characterized by overlapping infectious and radiation-related radiological findings, frequent need for intensive care and mechanical ventilation, and a considerable in-hospital mortality. Increased CRP levels were associated with consolidation and patchy opacities, and radiation fibrosis showed reduced inflammation. Although no independent predictors of mortality were found, a combined assessment of oxygenation, inflammatory markers, imaging findings and prior radiotherapy may help to early clinical evaluation and risk stratification in this vulnerable group.

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***Ethical considerations*:** The study protocol was reviewed and approved by the Institutional Ethics Committee of The First People's Hospital of Jiashan (Approval No. X-221-9943). The study was conducted in accordance with the principles of the Declaration

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of Helsinki and applicable institutional and national ethical standards. Written informed consent was obtained from all participants or, when patients were unable to provide consent, from their legally authorized representatives before enrollment. Patient data were anonymized and handled confidentially throughout data collection and analysis.

***Consent for publication*:** The manuscript does not contain identifiable personal information, images, or clinical details requiring separate consent for publication. Therefore, consent for publication was not applicable.

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