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REVIEW

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Interactions between interstitial lung abnormalities and immune checkpoint inhibitor therapy in non-small cell lung cancer: A review of current understanding and future directions

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ABSTRACT

Immunotherapy has revolutionized the treatment landscape of non-small cell lung cancer (NSCLC), significantly improving survival outcomes and offering renewed hope to patients. However, the presence of interstitial lung abnormalities (ILAs) in patients with NSCLC presents unique challenges, especially due to the elevated risk of immune checkpoint inhibitor (ICI)-related pneumonitis, which can result in treatment interruptions and adversely affect prognosis. ILAs, often detected incidentally on computed tomography imaging, are associated with an increased risk of progression to interstitial lung disease and have been identified as a potential predictor of poor clinical outcomes in patients with NSCLC receiving immunotherapy. This review offers an overview of the current understanding of the interaction between ILAs and ICI therapy, discussing prevalence, radiological features, risk stratification, and management strategies. Additionally, it highlights the need for prospective, multicenter studies to establish optimal treatment modalities for patients with NSCLC having ILAs, to ensure safer and more effective immunotherapy.

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Introduction

Clinical impact of ICIs in NSCLC

Lung cancer, a prevalent malignancy, characterized by high incidence and mortality rates,[1] is histologically classified into two main subtypes: non-small cell lung cancer (NSCLC, 85% of cases), and small cell lung cancer (15%).[2] Recent treatment advances, particularly immune checkpoint inhibitors (ICIs) have reduced NSCLC mortality rates.[3,4] ICIs target immune checkpoint molecules such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death 1 (PD-1), blocking inhibitory signals and reactivating T cells, to bolster the anti-tumor immune response.[5,6] A Phase III clinical trial demonstrated that pembrolizumab monotherapy significantly improved overall survival (OS) in patients with stage IV NSCLC exhibiting a tumor proportion score of ≥ 50% compared to platinum-based chemotherapy.[7] Moreover, combinations of PD-1/programmed cell death ligand 1 (PD-L1) inhibitors or CTLA-4 inhibitors with platinum-based chemotherapy have shown substantial OS improvement regardless of PD-L1 expression.[8,9] Consequently, ICIs have emerged as key agents in NSCLC management.

Immune-related adverse events: focus on pneumonitis

Despite their therapeutic efficacy, ICIs are associated with immune-related adverse events that can resemble autoimmune disorders and affect multiple organs.[10] Pneumonitis represents one of the most severe adverse events, accounting for approximately 35% of ICI-related fatalities.[11] Clinical trials have reported an incidence of ICI-related pneumonitis (ICI-P) ranging from 3–5%, whereas real-world data suggest an incidence of 14.5–19%.[12,13] Furthermore, mortality rates among patients treated for ICI-P fluctuate between 12–33%.[14,15] These findings underscore the gravity of ICI-P and accentuate the need to identify its risk factors. Risk factors for ICI-P encompass ICI type, combination immunotherapy, primary tumor site, prior radiotherapy, and preexisting lung disease.[16,17] Notably, interstitial lung disease (ILD) and interstitial lung abnormalities (ILAs) detected on pre-treatment computed tomography (CT) scans have been acknowledged as significant risk factors for ICI-P.[16]

Emerging importance of ILAs in ICI therapy

ILAs refer to interstitial alterations detected incidentally on CT scans in asymptomatic patients. ILAs are associated with an elevated risk of progression to ILD and are considered potential early indicators for ILD development.[18–20] Recent studies have illustrated that preexisting lung diseases, particularly ILAs, heighten the risk of pneumonitis linked with ICIs therapy. Understanding this interaction is imperative for devising effective treatment strategies.This review consolidates the latest findings on the interaction between ICIs and ILAs in

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NSCLC, accentuating their clinical significance and future directions. By integrating advancements in oncology with the management of pulmonary diseases, this review aims to provide clinicians and researchers with a comprehensive resource to enhance the safety and efficacy of ICI therapy.

Literature selection

This narrative review is based on a non-systematic search of the literature conducted using PubMed and Google Scholar. We focused on English-language articles published between January 2015 and March 2025 that addressed the relationship between ILAs and ICIs in NSCLC. The year 2015 was selected as the starting point because ICIs were first approved for NSCLC around that time – for example, the Food and Drug Administration approved nivolumab in 2015 following clinical trials that demonstrated improved survival outcomes. Thus, studies published from 2015 onward are more likely to reflect the current treatment landscape and real-world clinical experience with ICIs. Search terms included combinations of "interstitial lung abnormalities," "immune checkpoint inhibitors," "non-small cell lung cancer," and "pneumonitis." Articles were selected based on their relevance, novelty, clinical significance, and contribution to the understanding of ILAs and ICIs. Reference lists of key publications were also reviewed to identify additional pertinent studies.

Prevalence and characteristics of ILAs in NSCLC

Epidemiology of ILAs in the general and NSCLC populations

Population-based cohort studies have reported ILAs prevalence of 4–9% and 2–7% among smoker and nonsmokers, respectively.[18] Conversely, the prevalence of ILAs in patients with NSCLC ranges from 6.0%–37.8%, which is higher than that seen in the general population[21–32] (Table 1). This increased prevalence is believed to be influenced by common risk factors such as smoking history, male sex, and advanced age.

Radiologic features and classification of ILAs

Radiologically, ILAs are characterized by the following findings: ground-glass opacities (GGO), reticular abnormalities, architectural distortion, traction bronchiectasis, honeycombing, and non-emphysematous cysts.[18] The Fleischner Society classifies ILAs into three subtypes[18:]

- Non-subpleural ILAs (NS-ILAs): Findings that do not primarily involve the subpleural regions.
- Subpleural, non-fibrotic ILAs (SNF-ILAs): Changes predominantly located in the subpleural areas without signs of fibrosis.
- Subpleural, fibrotic ILAs (SF-ILAs): Findings predominantly in the subpleural regions accompanied by radiological features indicative of pulmonary fibrosis.

Note: Pulmonary fibrosis is defined by architectural distortion, including features such as traction bronchiectasis and/or honeycombing.

These subtypes can be broadly categorized into non-SF-ILAs and SF-ILAs groups, each with distinct clinical implications[33,34] (Figure 1). SF-ILAs are associated with higher risks of disease progression and mortality than non-SF-ILAs.

Subtype-specific prevalence in NSCLC patients

Regarding the prevalence of ILAs in patients with NSCLC, Petranovic et al. reported that 16.4% of 475 patients had

Table 1. A comprehensive review of interstitial lung abnormalities as a risk factor for immune-checkpoint inhibitors-related pneumonitis and outcomes in non-small cell lung cancer.

Number	Number of Patiets with NSCLC	Frequency of ILAs (%)	Frequency of ICI-P (%)	Risk Factors for ICI-P	Outcomes	Reference Number
1	112	18.7	44.6	Smoking history	ICI-P and OS: No correlation (HR: 0.91)	21
2	83	15.6	16.9	GGO	Not specified	22
3	264	21.6	12.1	None	Not specified	23
4	402	14.4	8.5	ILAs, chest radiation	Severe vs. Mild ICI-P: Worse OS (not reached vs. 9.5 months, respectively; $p = .001$)	24
5	175	36.5	41.0	ILAs, SF-ILAs, radiotherapy method, V20	SF-ILAs: Associated with worse OS ($p = .02$)	25
6	475	16.4	9.1	ILAs, chest radiation	Not specified	26
7	207	6.0	4.2	ILAs, reduced total lung capacity	ICI-P and non-ICI-P group: No significant difference in OS (18.7 vs. 11.8 months, respectively; $p = .332$)	27
8	71	35.0	Not specified	Not specified	Pretreatment ILAs: Correlated with partial radiological resolution (OR: 4.8, $p = .05$)	28
9	148	37.8	33.8	ILAs, V20 ≥ 22.4, GGO	Not specified	29
10	94	25.0	17.9	Extent of GGO	ILA and non-ILA groups: No significant difference in PFS ($p = .054$)	30
11	481	16.4	31.6	SF-ILAs	SF-ILAs and non-SF-ILAs group: No significant difference in OS (24.0 vs. 15.7 months, respectively; $p = .193$)	31
12	113	15.0	17.7	Not specified	ILA Score (0 vs. 1): The latter score was correlated with worse OS (HR: 5.649, $p < .001$)	32

NSCLC, non-small cell lung cancer; ILAs, interstitial lung abnormalities; ICI-P, immune checkpoint inhibitor related pneumonitis; OS, overall survival; GGO, Ground-glass opacity; SF-ILAs, subpleural fibrotic interstitial lung abnormalities; OR, odds ratio; HR, hazard ratio; V20, the percentage of total lung volume irradiated with ≥20 Gy; PFS, progression free survival.

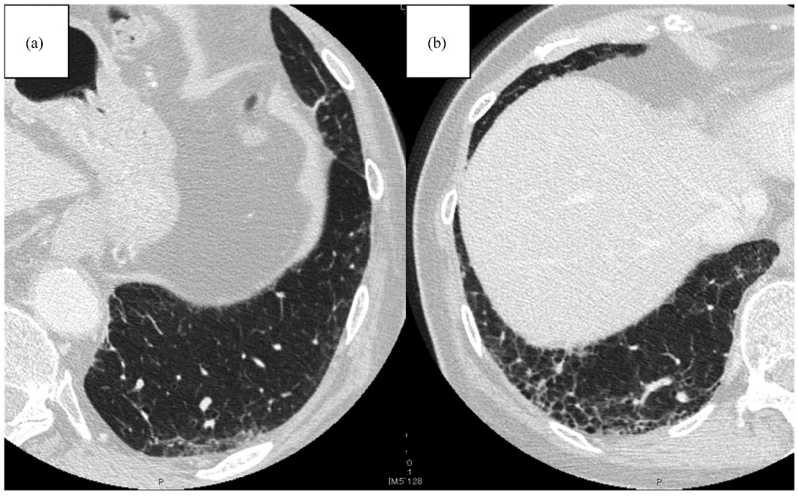

Figure 1. Axial CT scans showing subtypes of interstitial lung abnormalities based on the presence or absence of fibrosis. (a) Non-subpleural fibrotic interstitial lung abnormalities (non-SF-ILAs). (b) Subpleural fibrotic interstitial lung abnormalities (SF-ILAs).

ILAs.[26] The distribution of ILA subtypes was as follows: 10.3% NS-ILAs, 60.3% SNF-ILAs, and 29.5% SF-ILAs. In another study, ILAs were identified in 36.5% of 105 patients, with 7.8% having NS-ILAs, 43.7% SNF-ILAs, and 48.4% SF-ILAs.[25] These findings suggest variability in the prevalence of ILA subtypes among NSCLC patients. Similar heterogeneity has also been reported in population-based cohort studies using health screening data.[35–37] This may be attributed to the reliance on visual assessment for ILA classification, as well as differences in inter-observer interpretation and population characteristics, such as smoking history, age distribution, and comorbidities. The establishment of objective and reproducible diagnostic criteria is warranted for a more precise evaluation of subtype-specific prevalence and clinical significance in patients with lung cancer.

ICI-P in patients with NSCLC and ILAs

Risk of developing ICI-P

ICI-P poses a critical concern for patients with NSCLC and ILAs. Several studies have indicated that such patients possess a significantly higher risk of developing ICI-P compared to their counterparts without ILAs[20,22,24–27,29] (Table 1). A study encompassing 83 patients with advanced NSCLC reported an ICI-P incidence of 16.9% (14/83), with a significantly higher rate observed in the ILAs-positive cohort compared to the ILAs-negative cohort ($p = .007$); univariate logistic regression analysis identified ILAs as an independent risk factor for ICI-P (odds ratio [OR]: 6.643, 95% confidence interval [CI]: 1.782–24.761, $p = .005$).[22] Similar trends have been observed in patients with locally advanced NSCLC. A study involving 148 patients with NSCLC treated with durvalumab revealed that the prevalence of pre-treatment ILAs was 37.8%, with 63.5% of these patients developing ILD, including radiation pneumonitis or ICI-P. Multivariate logistic regression analysis identified ILAs as an independent risk factor for grade ≥ 2 ILD (OR: 3.70, 95% CI: 1.69–7.72, $p = .001$).[29] A larger study involving 471 patients (including 402 NSCLC cases) demonstrated that even after accounting for prior chest radiotherapy, preexisting ILAs remained an independent risk factor for ICI-P (hazard ratio [HR]: 9.77, 95% CI: 5.17–18.46, $p < .001$).[24]

Limitations of current evidence

However, a study has reported no significant difference in the incidence of ICI-P between patients with and without ILAs. Horiuchi et al. analyzed 209 patients, including 112 with NSCLC; no statistically significant association was found between preexisting ILAs and ICI-P.[21] Seok et al.[20] integrated data from four studies in their meta-analysis; they reported that cancer patients with ILAs had a substantially higher risk of ICI-P compared to those without ILAs (relative risk [RR]: 3.05, 95% CI: 1.37–6.77). Nonetheless, high heterogeneity among the included studies ($I^2 = 83\%$) was noted as a limitation.[20] The discrepancies among these studies could be ascribed to variations in study design, sample sizes, inconsistencies in definitions and classifications of ILAs, and the influence of confounding factors such as smoking history, prior radiotherapy, and baseline pulmonary function. Additionally, variations in patient characteristics, including cancer type, stage, and concomitant therapies, may also contribute to these differences. To establish a clearer understanding of the association between ILAs and ICI-P risk, future research should prioritize standardizing ILAs definitions and conducting well-designed prospective studies with comprehensive adjustments for potential confounders.

GGO as radiological predictors of ICI-P

ILAs serve as critical radiological markers for assessing the risk and severity of ICI-P in patients with NSCLC. GGO is the most frequently observed radiological feature of ILAs in patients who develop ICI-P,[29] and multiple studies have identified it as an independent predictor of ICI-P[22,29,30] (Table 1). Daido et al.[29] demonstrated that the presence of GGO in ILAs constituted an independent risk factor for the development of grade ≥ 2 ILD, including radiation pneumonitis or ICI-P, with an OR of 6.71

(95% CI: 2.80–16.08, $p < .001$). Furthermore, Wang et al. reported that the proportion of GGO identified using artificial intelligence (AI) served as an independent predictor of ICI-P ($p = .002$).[30] Conversely, Horiuchi et al. found no significant association between GGO and the occurrence of ICI-P.[21]

SF-ILAs and ICI-P risk

Recent studies have suggested that SF-ILAs may also represent a risk factor for ICI-P (Table 1). Based on the Fleischner Society classification, ILAs were categorized into SF-ILAs and non-SF-ILAs to explore their relationship with ICI-P risk.[31] Our findings indicated that the cumulative incidence of ICI-P was significantly higher in the SF-ILAs group compared to the non-SF-ILAs group (HR: 4.57, 95% CI: 1.90–10.98, $p = .001$). The incidence of ICI-P was also significantly greater in patients with SF-ILAs for all-grade (52.9% vs. 15.6%, respectively; $p < .001$) as well as grade ≥ 3 pneumonitis (29.4% vs. 2.2%, respectively; $p = .001$). Multivariate analysis affirmed SF-ILAs as an independent predictor of ICI-P (OR: 5.35, 95% CI: 1.62–17.61, $p = .006$). Similarly, a study involving 175 patients with NSCLC undergoing radiotherapy (including 26 receiving durvalumab) demonstrated that SF-ILAs patients exhibited the highest cumulative incidence of grade ≥ 2 pneumonitis compared to other ILAs subtypes ($p < .001$).[25] However, Petranovic et al. found no significant differences in ICI-P risk among varying ILAs subtypes ($p = .244$).[26] ILAs encompasses a diverse array of radiological findings, from non-fibrotic features such as GGO or reticular abnormalities to fibrotic changes such as honeycombing or architectural distortion. While GGO is typically classified as non-fibrotic ILAs, it may co-occur with fibrotic patterns or signify early stages of fibrosis.[33,38] These findings suggest that both GGO and SF-ILAs serve as important risk factors for ICI-P, reflective of the intricate mechanisms of lung injury associated with ICI-P. Nevertheless, further research is warranted to validate these observations and enhance risk stratification.

Pathological and immunological insights into ILAs

ILAs are increasingly recognized as radiologic indicators of early ILDs, often sharing pathogenic pathways with fibrotic ILDs.[18–20] Notably, ILAs occur more frequently in older patients and smokers and have been linked to the mucin5B promoter polymorphism,[39] a genetic risk factor implicated in idiopathic pulmonary fibrosis (IPF). In the nascent stages of ILD, excessive immune responses – including abnormal proliferation and activation of macrophages and lymphocytes within the alveolar interstitium – are involved.[40,41] IPF, a prototypical disease manifesting with a usual interstitial pneumonia (UIP) pattern, is a chronic progressive fibrotic disorder of unknown etiology, characterized by repeated alveolar epithelial injury and fibroblast overactivation. Historically, the role of inflammation in the pathogenesis of IPF was regarded as limited. However, recent investigations indicate that both the innate and adaptive immune systems may contribute to the progression of IPF.[41,42] Specifically, CD4 + T-cell subsets, such as Th2 and Th17 cells, may facilitate fibrosis, whereas regulatory T cells (Tregs) and Th1 cells may exert antifibrotic effects. A study involving 47 patients with ILAs demonstrated that GGO are pathologically associated with thickening of the lung interstitium. Additionally, many patients exhibiting fibrotic ILAs presented with either a "UIP pattern" or a "probable UIP pattern" upon surgical lung biopsy.[34] These findings suggest that many ILAs represent an incipient fibrotic process with an underlying pro-fibrotic and inflammatory milieu. In an ILA patient, even if clinically silent, the lungs may already exhibit a delicate balance of immune activity and injury/repair responses, potentially vulnerable to perturbation by external stimuli such as ICIs.

Pathophysiological insights into ICI-P in ILAs

The mechanism underlying the development of ICI-P is posited to involve autoimmune toxicity of T cells targeting shared epitopes between tumors and lung tissue.[43] Bronchoalveolar lavage fluid from patients with ICI-P has revealed an increased population of CD8+ and CD4+ T cells, which produce pro-inflammatory cytokines such as tumor necrosis factor-alpha and interferon-gamma. Conversely, the proportion of anti-inflammatory Tregs tends to diminish.[44–46] ICIs therapy may activate immune pathways analogous to those observed in ILAs/ILD, potentially exacerbating existing immune abnormalities and amplifying inflammation. The increased risk of ICI-P among patients with ILAs is likely influenced by the interplay of lung tissue fragility, preexisting inflammation, and dysregulated immune responses induced by ICIs. These findings suggest that patients with ILAs/ILD may experience additional immune dysfunction due to ICIs therapy, resulting in a heightened risk of pneumonitis. Considering these factors, careful assessment of patient risk profiles is essential, and appropriate treatment strategies should be devised to minimize potential complications associated with ICIs therapy.

Clinical outcomes and prognosis

Impact of ILAs on recovery from ICI-P

ILAs not only augment the risk of ICI-P but may also adversely impact long-term clinical outcomes. A study involving 71 patients with NSCLC who developed ICI-P indicated that those with ILAs frequently exhibited incomplete radiological resolution following ICI-P, demonstrating partial improvement rather than returning to baseline.[28] This partial improvement, characterized by residual fibrosis, may contribute to persistent hypoxemia, exacerbating dyspnea and chronic cough.

Prognostic implications of ILAs in NSCLC before the ICI era

Furthermore, the presence of ILAs has been correlated with diminished OS in patients with NSCLC. Several studies have identified ILAs as an independent predictor of poor prognosis. For example, an analysis of 484 patients with stage IV NSCLC revealed that those with ILAs at diagnosis exhibited significantly shorter OS (HR = 2.09, $p = .004$).[47] Similar trends have been observed in other studies.[48,49] However, these studies predated the widespread clinical use of ICIs and may not fully encapsulate the current treatment landscape.

Prognosis of NSCLC with ILAs in the era of immunotherapy

Recent investigations suggest that ILAs continue to influence prognosis even in the context of ICIs therapy (Table 1). Kashihara et al. reported that in patients with locally advanced NSCLC, treated with durvalumab following chemoradiotherapy, baseline ILA scores were significantly associated with shorter OS and cancer-specific survival.[32] This correlation may stem from higher rates of pneumonitis (including radiation pneumonitis or ICI-P) and increased treatment discontinuation in patients exhibiting ILAs. Studies involving patients with NSCLC receiving nivolumab, pembrolizumab, or atezolizumab indicate that, compared to those without SF-ILAs, those with SF-ILAs tend to experience shorter progression-free survival (PFS) and OS (PFS: 5.17 vs. 3.60 months, respectively; HR 1.49, 95% CI: 0.91–2.45, $p = .111$; OS: 24.0 vs. 15.7 months, respectively; HR 1.38, 95% CI: 0.84–2.27, $p = .193$).[31] Additionally, compared to patients without SF-ILAs, patients with SF-ILAs demonstrated a higher incidence of respiratory failure-related mortality due to ICI-P (0.0% vs. 13.6%, respectively; $p = .183$) and a greater tendency for ILAs progression (30.0% vs. 71.4%, respectively; $p = .193$). Similarly, a study involving 175 patients with NSCLC who received radiotherapy, including 26 who underwent durvalumab treatment, demonstrated that SF-ILAs served as an independent predictor of poor OS in multivariate analysis (HR: 3.07, 95% CI: 1.17–8.10, $p = .02$).[25] Furthermore, Wang et al. found that the presence of AI-detected ILA showed a trend toward poorer PFS ($p = .054$).[30] These findings underscore the necessity for larger-scale studies to elucidate the impact of ILAs on prognosis and clinical outcomes in patients with NSCLC receiving ICIs therapy. Future research should prioritize ILAs-specific cohorts and immune therapy-focused investigations to refine treatment strategies and optimize patient outcomes.

Management strategies

Importance of ILAs diagnosis in patients with NSCLC prior to immunotherapy

Accurate diagnosis of ILAs is paramount when considering immunotherapy for NSCLC. Previous studies misclassified smoking-related centrilobular nodules and pleuroparenchymal fibroelastosis as ILAs. Additionally, mild focal or unilateral abnormalities were also incorrectly identified as ILAs. However, these conditions have been excluded from the most recent ILAs definitions.[18,19] Understanding the precise definition of ILAs is critical for developing appropriate diagnostic and treatment strategies. Prior to initiating immunotherapy, a thorough evaluation of suspected ILAs is recommended. Thin-section CT with moderate edge-enhancing reconstruction (<1.5 mm) has proven useful in detecting ILAs.[18] In certain cases, prone CT scans may be performed to differentiate true interstitial abnormalities from gravity-dependent atelectasis and inadequate inspiration (Figure 2). A study on lung cancer screening demonstrated that 46% of ILAs initially observed on supine CT disappeared on prone high-resolution CT (HRCT), suggesting that many such findings were positional artifacts rather than true ILAs.[50] A recent comprehensive review also supports the use of HRCT – particularly with positional techniques – for confirming or excluding ILAs when standard CT findings are equivocal.[39] Based on this evidence, we recommend HRCT in cases where standard CT raises suspicion of ILAs, as it can help ensure accurate diagnosis and avoid misclassification – an important consideration when evaluating risk factors for ICI-P.

Risk-based treatment approaches based on ILAs subtypes

Mitigating the risk of ICI-P is essential for enhancing patient outcomes. To achieve this, the use of HRCT to classify ILAs into subtypes – SF-ILAs and non-SF-ILAs – and to identify specific risk factors is recommended. In patients with SF-ILAs, it is crucial to provide comprehensive information regarding the associated risks before commencing ICIs therapy and to carefully determine the treatment strategy. In some instances, avoidance of ICIs therapy may need to be contemplated. Conversely, patients with non-SF-ILAs potentially possess a comparable risk of developing ICI-P to those without ILAs,[25,31] making aggressive treatment a feasible option. Therefore, subclassification of ILAs can play a pivotal role in shaping treatment strategies for patients with NSCLC undergoing ICIs therapy.

Significance of GGO and treatment approaches

GGO represent a prevalent radiological feature in patients with ILAs, with prevalence rates reported to be 53.8%–

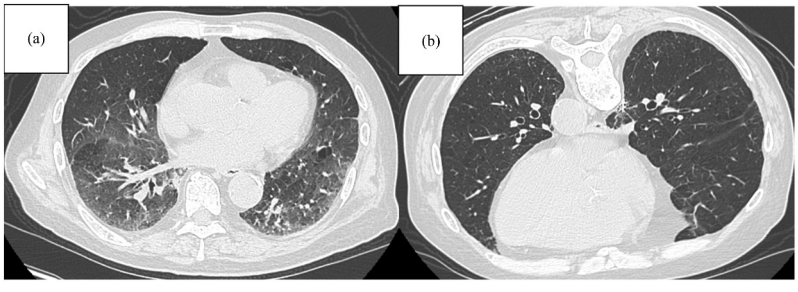

Figure 2. Axial CT scans showing the disappearance of ground-glass opacities due to gravity-dependent atelectasis and insufficient inspiration. (a) A chest CT scan performed with the patient in the supine position showed ground-glass opacities in the lower lobes, which disappeared (b) when the patient was placed in the prone position, proving that the ground-glass opacities were caused by gravity effects and insufficient inspiration.

100%.[22,29,33,51] While Nakanishi et al.[22] documented a prevalence of 53.8%, rates of 73.2% and 70.8% were observed by Daido et al.[29] and Jin et al.[51] respectively. In a study by Putman et al.[33] all patients with ILAs (100%) exhibited GGO. As previously noted, GGO has been recognized as a risk factor for ICI-P. Nevertheless, the exclusion of all patients with ILA exhibiting GGO from ICIs therapy may preclude many patients from potential therapeutic benefits. Therefore, meticulous consideration of the impact of GGO is essential when formulating treatment strategies for patients with NSCLC exhibiting ILAs, and further investigation is warranted.

Early detection and multidisciplinary collaboration in ICI-P management

Early detection and timely intervention are crucial for the successful management of ICI-P. Regular patient monitoring through clinical assessments, pulmonary function tests, imaging studies, and symptom questionnaires is vital during treatment. Establishing a multidisciplinary team comprising oncologists, pulmonologists, and radiologists can enhance diagnostic accuracy and optimize treatment outcomes. Furthermore, patient education is of utmost importance. Emphasis should be placed on the need for patients to recognize early symptoms of pneumonitis – such as dyspnea, cough, and fever – and to report these symptoms promptly to healthcare providers. Smoking cessation should be vigorously encouraged, as smoking exacerbates the risk of ICI-P.[21,52] Respiratory infections pose a significant risk of interrupting ICIs treatment and may complicate the differential diagnosis of ICI-P.[53] Therefore, immunization against respiratory pathogens, including influenza, COVID-19, respiratory syncytial virus, and pneumococcus, is advocated to mitigate infection-related complications and facilitate uninterrupted cancer therapy.

Future perspectives and conclusions

Differentiating ILAs from ILD in lung cancer patients

ILAs have traditionally been regarded as incidental findings devoid of substantial respiratory symptoms, functional impairment, or diagnosed ILD.[19] However, in lung cancer patients with coexisting ILAs, respiratory symptoms and pulmonary function impairment may manifest due to lung cancer itself. Thus, future efforts should focus on establishing precise methodologies to differentiate between ILAs and ILD to guarantee accurate diagnosis and management.

Need for prospective trials in ILAs and NSCLC

Currently, most studies exploring ILAs and NSCLC are based on retrospective, single-center analyses, highlighting a significant deficit in prospective research. Particularly, to ascertain whether ILAs functions as an independent risk factor for ICI-P or as a predictor of poor prognosis in patients with NSCLC undergoing ICIs therapy, multicenter prospective clinical trials are imperative. Moreover, it is essential to investigate the impact of ICIs on the natural course of ILAs and to establish optimal treatment strategies for patients with lung cancer and preexisting ILAs.

Patient selection and safety in future ICI trials

Most existing ICI studies have excluded patients with a history of or risk factors for ILD, including ILAs, due to concerns about treatment-related pneumonitis. However, in clinical practice, these patients are frequently encountered, and the absence of prospective evidence limits clinicians' ability to make informed treatment decisions. Rather than advocating for the broad inclusion of all high-risk individuals, we propose that future trials cautiously consider enrolling carefully selected patients – particularly those with non-SF-ILAs – under strict safety protocols. These may include comprehensive baseline evaluations, radiologic and functional risk stratification, close monitoring, and predefined stopping criteria. Such an approach could help define the true risk – benefit profile of ICIs in this population, ultimately supporting more personalized and evidence-based treatment strategies while maintaining a strong focus on patient safety.

Role of artificial intelligence and machine learning in managing ILAs during immunotherapy

In the context of NSCLC, AI-driven radiomics models derived from chest CT scans have been developed to non-invasively predict molecular markers such as PD-L1 expression and tumor mutation burden, both of which are important for guiding ICI treatment.[54] More importantly for patients with ILAs, recent studies have shown that radiomics signatures can help differentiate between immune ICI-P and radiation pneumonitis – a clinically challenging scenario in those with underlying lung abnormalities.[55] Recent advances in AI and machine learning are revolutionizing precision oncology and have significant potential in the assessment and management of ILAs.[19,56] Furthermore, AI tools that can detect subtle radiographic features associated with early interstitial changes or predict the likelihood of pneumonitis subtype may aid in more personalized treatment planning and monitoring. For example, AI-enhanced imaging analysis could help distinguish SF-ILAs, which carry a higher risk of adverse outcomes, from non-SF-ILAs, or flag early signs of progression to ILD following immunotherapy. Going forward, integrating AI-driven image analytics with clinical and genomic data may enable early identification of high-risk ILA phenotypes, prediction of ICI tolerability, and improved decision-making regarding treatment continuation or immunosuppressive intervention. Such advances would directly support more individualized management strategies for NSCLC patients with ILAs.

Toward personalized and safe ICI use in patients with ILAs

Previous reports indicate that a significant proportion of studies addressing ICIs treatment in patients NSCLC exhibiting concurrent ILAs have originated from Japan. This

trend may stem from the comprehensive role of Japanese pulmonologists in diagnosing and managing NSCLC, ILAs, and ICI-P. Historically, Japanese patients with cancer were noted to exhibit a higher susceptibility to drug-induced pneumonitis.[57] However, recent studies have indicated that the incidence of ICI-P is comparable between Japan and the United States.[12,13,58] In recent years, ILAs have gained global recognition as a risk factor for ICI-P.[39,59] Moving forward, the accumulation of data on optimal treatment strategies for patients with NSCLC and concurrent ILAs will be crucial. This review has the potential to deepen the understanding of the interaction between ICIs and ILAs and provide valuable insights for clinicians and researchers in ensuring safer and more effective immunotherapy for patients with lung cancer.

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Author contributions

R.K. conceptualized the study and drafted the manuscript. S. A. contributed to literature review and critical revisions. All authors reviewed and approved the final manuscript. All authors agree to be accountable for all aspects of the study.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics statement

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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