International Journal of Chronic Obstructive Pulmonary Disease

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Impact of Emphysema on Therapeutic Efficacy and Immune-Related Pneumonitis Risk in NSCLC Patients Receiving ICIs: A Meta-Analysis of Improved Survival but Increased Toxicity

Wenjuan Li, Shilan Liu, Xiaodan Yu, Wenyi Lan, Xiao Liu

Department of Pulmonary and Critical Care Medicine, Chengdu Fifth People's Hospital, Chengdu, 611130, People's Republic of China

Correspondence: Xiao Liu, Department of Pulmonary and Critical Care Medicine, Chengdu Fifth People's Hospital, Chengdu, 611130, People's Republic of China, Email lxz111@126.com

Purpose: To identify the impact of CT-defined emphysema on efficacy and immune checkpoint inhibitor-related pneumonitis (ICIP) risk among non-small cell lung cancer (NSCLC) patients who receive ICIs.

Methods: PubMed, EMBASE, Web of Science and CNKI databases were searched up to January 8, 2025. Primary outcome was the therapeutic efficacy including the progression-free survival (PFS), overall survival (OS), complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), objective response rate (ORR) and disease control rate (DCR). Second outcome was the ICIP. The hazard ratio (HR) or odds ratio (OR) with 95% confidence interval (CI) were combined.

Results: Nine studies with 1076 cases were included. Pooled results demonstrated that the presence of emphysema was significantly associated with improved PFS (HR = 0.43, 95% CI: 0.28–0.67, P < 0.001), OS (HR = 0.43, 95% CI: 0.25–0.75, P = 0.003), PR (OR = 2.10, 95% CI: 1.18–3.75, P = 0.012), PD (OR = 0.60, 95% CI: 0.43–0.83, P = 0.002) and DCR (OR = 1.48, 95% CI: 1.14–1.94, P = 0.004). However, emphysema was associated with increased incidence of ICIP (OR = 1.32, 95% CI: 1.15–1.53, P < 0.001).

Conclusion: Based on available evidence, CT-defined emphysema indicates better therapeutic efficacy with longer PFS and OS, but increased risk of ICIP among NSCLC patients receiving ICIs. These findings suggest emphysema may guide personalized immunotherapy decisions in NSCLC.

Keywords: non-small cell lung cancer, emphysema, therapeutic efficacy, immune-related pneumonitis, immune checkpoint inhibitors

Introduction

Non-small cell lung cancer (NSCLC) is one of the most prevalent and deadly malignancies worldwide.[1] In recent years, immune checkpoint inhibitors (ICIs), such as programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors, have achieved significant progress in the treatment of NSCLC and have become a crucial therapeutic option for patients with advanced NSCLC. Clinical studies have shown that ICIs can significantly prolong progression-free survival (PFS) and overall survival (OS) in some patients, particularly those with high PD-L1 expression or a high tumor mutation burden (TMB).[2,3] However, the response of NSCLC patients to ICIs varies substantially, with reported objective response rates (ORR) ranging from 20% to 50% between responders and non-responders, so that only a subset of patients achieve meaningful clinical benefit. Currently, predicting treatment efficacy remains challenging due to the lack of precise and reliable biomarkers, the complexity of the tumor microenvironment, and the heterogeneity of patients' immune status. Although PD-L1 expression levels and TMB are widely studied as predictive markers for ICI efficacy, their sensitivity and specificity are still limited.[4,5] Additionally, multifactorial interactions involving the tumor immune microenvironment (TME), gut microbiota, and genetic mutations further complicate efficacy prediction.[5] Despite the clinical benefits of ICIs, their use is frequently accompanied by immune-related adverse events, among

https://doi.org/10.2147/COPD.S569504
Received: 25 September 2025
Accepted: 22 December 2025
Published: 9 January 2026

which immune checkpoint inhibitor–related pneumonitis (ICIP) is one of the most serious and potentially life-threatening toxicities. ICIP often leads to treatment interruption or discontinuation and can markedly affect patients' prognosis. However, its incidence varies widely across studies, and the clinical course remains unpredictable, underscoring the importance of identifying patients at increased risk. To date, the risk factors associated with ICIP have not been clearly established, and current evidence remains insufficient to guide individualized risk assessment.

Computed tomography (CT)-defined emphysema is a common but often underrecognized comorbidity in patients with NSCLC. Epidemiological studies have shown that the prevalence of emphysema in NSCLC patients is relatively high with the incidence over 30%, largely due to shared risk factors such as smoking and chronic lung inflammation.[6,7] However, emphysema is frequently overlooked in clinical practice, which may lead to inadequate risk assessment and management. Recent studies have indicated that emphysema is associated with poor prognosis in NSCLC patients, particularly in those undergoing surgical treatment.[8,9] Patients with emphysema are more prone to postoperative pulmonary complications, including pneumonia, prolonged air leakage, and respiratory failure, which can adversely affect recovery and overall survival.[10,11] While previous studies have focused on emphysema's impact on surgical outcomes and prognosis in NSCLC, few have systematically evaluated its effect on immunotherapy efficacy and toxicity. Understanding this relationship could guide patient selection and risk stratification in clinical practice. Notably, a meta-analysis reported that emphysema was associated with favorable clinical outcomes, including improved survival and response rates, but also with a higher risk of immune-related adverse events, particularly immune checkpoint inhibitor–related pneumonitis (ICIP).[12] Although this evidence suggests a potential predictive role of emphysema in patients undergoing ICI therapy, the available data remain limited. The prior meta-analysis included a relatively small number of studies, and several newly published cohorts were not incorporated. Moreover, important efficacy endpoints—such as complete response, partial response, stable disease, progressive disease, and disease control rate—were only partially evaluated. Therefore, up to now, the impact of emphysema on the efficacy and safety of ICIs in NSCLC patients remains unclear. Specifically, it is not well understood whether emphysema influences treatment outcomes or increases the risk of immune-related adverse events, such as immune-related pneumonitis. This may be partly explained by emphysema-induced alterations in the pulmonary immune microenvironment and chronic baseline inflammation, which could modulate both the antitumor response and susceptibility to pneumonitis.[12]

Previous observational studies assessing emphysema in NSCLC patients were limited by potential confounding factors such as smoking history, tumor stage, and treatment heterogeneity, highlighting the need for a pooled analysis to obtain more robust and generalizable conclusions. Therefore, this study aimed to further identify the impact of CT-defined emphysema on the therapeutic efficacy and risk of immune checkpoint inhibitor-related pneumonitis (ICIP) among NSCLC patients receiving ICIs.

Materials and Methods

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020.[13]

Literature Search

The PubMed, EMBASE, Web of Science and CNKI databases were searched from database inception to January 8, 2025 with following terms: emphysema, PD-1, PD-L1, CTLA-4, immune checkpoint inhibitor, immunotherapy and ICI. Detailed search strategy in the PubMed was as follows: (emphysema) AND (PD-1 OR PD-L1 OR CTLA-4 OR immune checkpoint inhibitor OR immunotherapy OR ICI). Besides, the MeSH terms and free texts were applied and references in included studies were reviewed.

Inclusion Criteria

Studies met following criteria were included: 1) patients were pathologically diagnosed with primary NSCLC and received the ICIs; 2) the presence or absence of emphysema was evaluated according to the CT images before ICIs use; 3) patients were divided in to emphysema or non-emphysema groups; 4) the relationship between emphysema and at least one of the endpoints including the PFS, OS, complete response (CR), partial response (PR), stable disease (SD),

progressive disease (PD), objective response rate (ORR), disease control rate (DCR) and immune checkpoint inhibitor-related pneumonitis (ICIP) was explored; 5) articles published in English or Chinese and full texts were available.

Exclusion Criteria

Studies met following criteria were excluded: 1) case reports, reviews, animal trials, letters, meeting abstracts or editorials; 2) duplicated or overlapped data; 3) low quality studies with the Newcastle-Ottawa Scale (NOS) score <6;[14] 4) studies lacking hazard ratio (HR)/odds ratio (OR) values were excluded.

Data Extraction

Following information was collected from each included studies: the first author, publication year, country, sample size, number of patients with emphysema, age, ICI drug, combination of other therapies, definition of CT-defined emphysema, primary outcomes including the PFS, OS, CR, PR, SD, PD, ORR and DCR, secondary outcomes including the ICIP, HR, OR and corresponding 95% confidence interval (CI).

In several of the included studies, detailed patient characteristics—such as age, smoking history, pulmonary comorbidities (eg, COPD), PD-L1 expression levels, and prior treatments—were not consistently reported or fully accessible. As a result, these variables could not be incorporated into subgroup analyses, adjusted analyses, or sensitivity assessments. Therefore, the present meta-analysis was primarily based on the available outcome data rather than comprehensive patient-level covariates. This limitation was taken into account when interpreting the pooled estimates.

Methodological Quality Assessment

In our meta-analysis, the quality of included studies was evaluated by the NOS score tool and studies with a NOS score >5 were defined as high-quality studies and included.[14]

Two authors performed the literature search, selection, data extraction, and methodological quality assessment independently, and all disagreements were resolved by team discussion.

Statistical Analysis

All statistical analyses were conducted using STATA (version 15.0) software. Heterogeneity between included studies was assessed by I^2 statistics. If significant heterogeneity was detected ($I^2 > 50\%$), the random-effects model was applied; otherwise, the fixed-effects model was applied. HRs and ORs with 95% CIs were combined to identify the impact of emphysema on the therapeutic efficacy and incidence of ICIP among ICIs treated NSCLC patients. Sensitivity analysis was conducted to detect the sources of heterogeneity and assess the stability of the overall results. Begg's funnel plot and Egger's test were conducted to detect publication bias.

Results

Literature Search

A total of 529 records were searched from the four databases and 79 duplicated records were removed. After reviewing the titles and abstracts, 409 and 26 publications were excluded. Eventually, nine studies were included in this meta-analysis after reviewing the full texts.[15–23] (Figure 1)

Basic Characteristics of Included Studies

All nine studies were from China or Japan and published between 2018 and 2024. A total of 1076 patients were enrolled with the sample size ranged from 56 to 188 and 39.2% (422/1076) of them were divided into the emphysema group. Other detailed data were presented in Table 1.

Impact of Emphysema on the Primary Outcomes Among ICIs Treated NSCLC Patients

Pooled results demonstrated that presence of emphysema was significantly related to better PFS (HR = 0.43, 95% CI: 0.28–0.67, P < 0.001; I^2= 0.0%, P = 0.492) (Supplementary Figure 1A), OS HR = 0.433, 95% CI: 0.25–0.75,P = 0.0033;

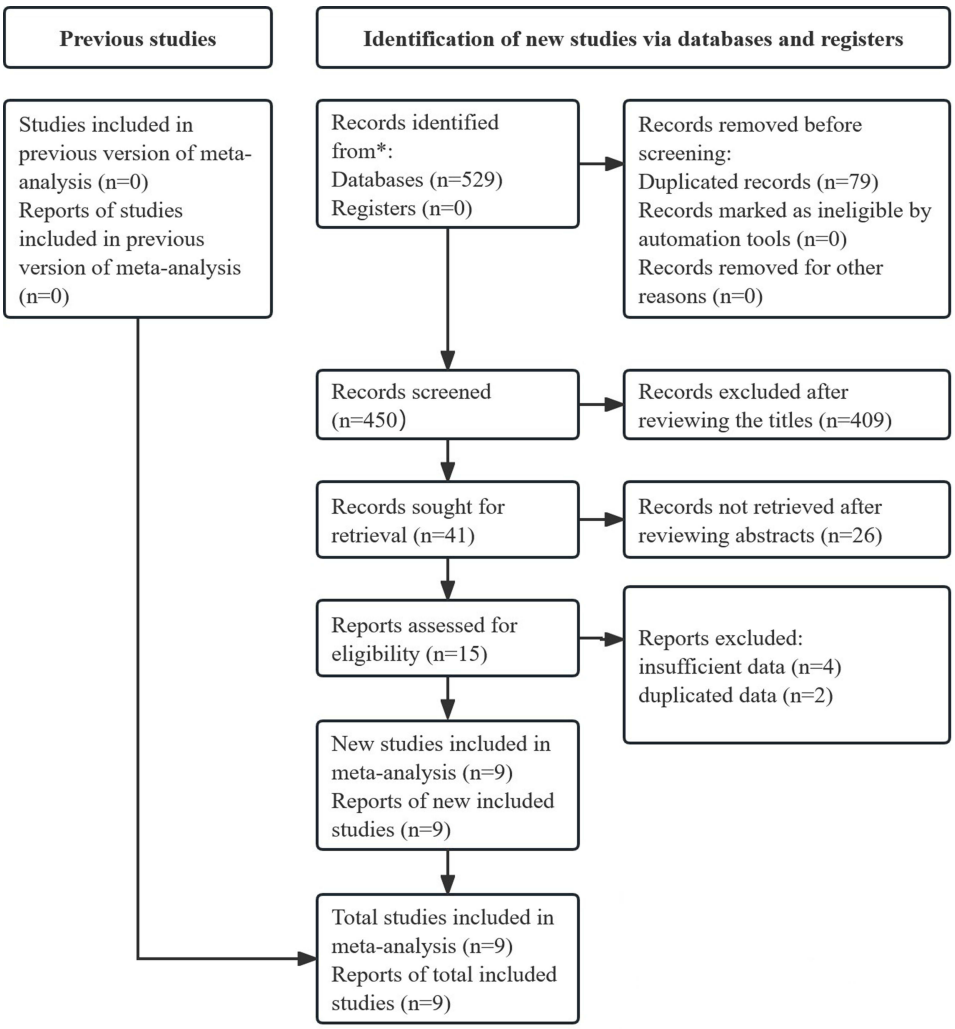

Figure 1 PRISMA flow diagram of this meta-analysis. *PubMed (n = 180), CNKI (n = 107), EMBASE (n = 62) and Web of Science (n = 180).

I^2= 20.1%,P = 0.2633) (Supplementary Figure 1B), PR OR = 2.100, 95% CI: 1.18–3.75,P = 0.0122; I^2= 0.0%,P = 0.4388) (Supplementary Figure 1C), DCR OR = 1.488, 95% CI: 1.14–1.94,P = 0.0044; I^2= 0.0%,P = 0.7322) (Supplementary Figure 1E) and decreased PD rate OR = 0.600, 95% CI: 0.43–0.83,P = 0.0022; I^2= 0.0%,P = 0.9188) (Supplementary Figure 1D). However, no significant association between the emphysema and CR OR = 1.588, 95% CI: 0.31–7.90,P = 0.5800) (Supplementary Figure 1F), SD OR = 1.099, 95% CI: 0.72–1.65,P = 0.6788) (Supplementary Figure 1G) or ORR OR = 1.555, 95% CI: 0.58–4.15,P = 0.3800) (Supplementary Figure 1H) was observed (Table 2).

Impact of Emphysema on the Secondary Outcome Among ICIs Treated NSCLC Patients

Seven studies explored the relationship between the presence of emphysema and risk of ICIP.[15,16,18–22] Pooled results manifested that emphysema was significantly associated with increased incidence of ICIP (OR = 1.32, 95% CI: 1.15–1.53, P < 0.001; I^2= 46.3%, P = 0.083; Figure 2).

Sensitivity Analysis and Publication Bias

Sensitivity analysis for the ICIP was performed (Figure 3), which manifested that our results were stable and none of included studies had an obvious impact on the overall findings. Furthermore, according to the Begg's funnel plot (Figure 4) and Egger's test (P = 0.111), no significant publication bias was observed.

Table 1 Basic Characteristics of Included Studies

Author	Year	Country	Sample Size	Patients with Emphysema	Age	ICIs	Combination of Other Therapies	Definition of Emphysema	ENDPOINT	NOS
Yamaguchi[15]	2018	Japan	123	48	68 (37–87)	Nivolumab; pembrolizumab	No	Emphysema score ≥1	ICIP	7
Takayama[16]	2021	Japan	153	71	68.0 ± 9.5; 68.0 ± 10.3	Nivolumab; Pembrolizumab; Atezolizumab	No	Goddard score >8	PFS, OS, CR, PR, SD, PD, ORR, DCR, ICIP	7
Noda[17]	2022	Japan	56	41	72 (64–75); 70 (66–74)	Nivolumab; Pembrolizumab; Atezolizumab	No	Goddard score >0	PFS, OS, CR, PR, SD, PD, ORR, DCR	6
Gao[18]	2023	China	155	65	65 (36–84)	PD-1 inhibitors; PD-L1 inhibitors	Mixed	NR	ICIP	6
Zhao[19]	2023	China	69	21	64 (36–88)	PD-1 inhibitors	Mixed	NR	ICIP	6
Du[20]	2024	China	186	65	NR	NR	Mixed	NR	ICIP	7
Qiu[21]	2024	China	188	47	NR	NR	Mixed	Continuous LAA%	ICIP	6
Sumi[22]	2024	Japan	76	38	NR	Nivolumab plus ipilimumab	Mixed	Emphysema score ≥1	ICIP	6
Zhang[23]	2024	China	70	26	NR	Nivolumab; Pembrolizumab; Atezolizumab	No	Continuous LAA%	ORR	6

Abbreviations: ICIs, immune checkpoint inhibitors; ICIP, immune checkpoint inhibitor-related pneumonitis; NOS, Newcastle-Ottawa Scale; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

https://doi.org/10.2147/COPD.S569504

Table 2 Results of Meta-Analysis

Items	Number of Studies	HR/OR	95% CI	P Value	I^2	P Value
Progression-free survival	2	0.43	0.28–0.67	<0.001	0.0%	0.492
Overall survival	2	0.43	0.25–0.75	0.003	20.1%	0.263
Complete response	2	1.58	0.31–7.90	0.580	0.0%	0.671
Partial response	2	2.10	1.18–3.75	0.012	0.0%	0.438
Stable disease	2	1.09	0.72–1.65	0.678	0.0%	0.552
Progressive disease	2	0.60	0.43–0.83	0.002	0.0%	0.918
Objective response rate	3	1.55	0.58–4.15	0.380	69.0%	0.040
Disease control rate	2	1.48	1.14–1.94	0.004	0.0%	0.732
Immune checkpoint inhibitor-related pneumonitis	7	1.32	1.15–1.53	<0.001	46.3%	0.083

Abbreviations: HR, hazard ratio; OR, odds ratio; CI, confidence interval.

Discussion

This meta-analysis demonstrated that the presence of emphysema was associated with improved therapeutic efficacy among NSCLC patients who received ICIs but was related to increased risk for ICIP. Therefore, CT-defined emphysema might serve as a prognostic indicator for the prediction of efficacy and ICIP among this group of patients.

The improved efficacy of ICIs in NSCLC patients with emphysema may be related to several mechanisms. Emphysema is typically caused by long-term smoking and chronic inflammation. This chronic inflammatory state leads to the persistent activation and accumulation of immune cells, such as macrophages, T cells, and dendritic cells, within lung tissue. These changes may promote specific alterations in the tumor immune microenvironment, including increased PD-L1 expression and higher $CD8^+$ T-cell infiltration, which can enhance anti-tumor immune responses and sensitivity to ICI therapy.[24] Smoking is a common risk factor for both emphysema and NSCLC. Prolonged smoking can cause the accumulation of genetic mutations, resulting in an increased TMB. A high TMB generates more neoantigens, making tumor cells more easily recognized and attacked by the immune system, thereby enhancing the therapeutic

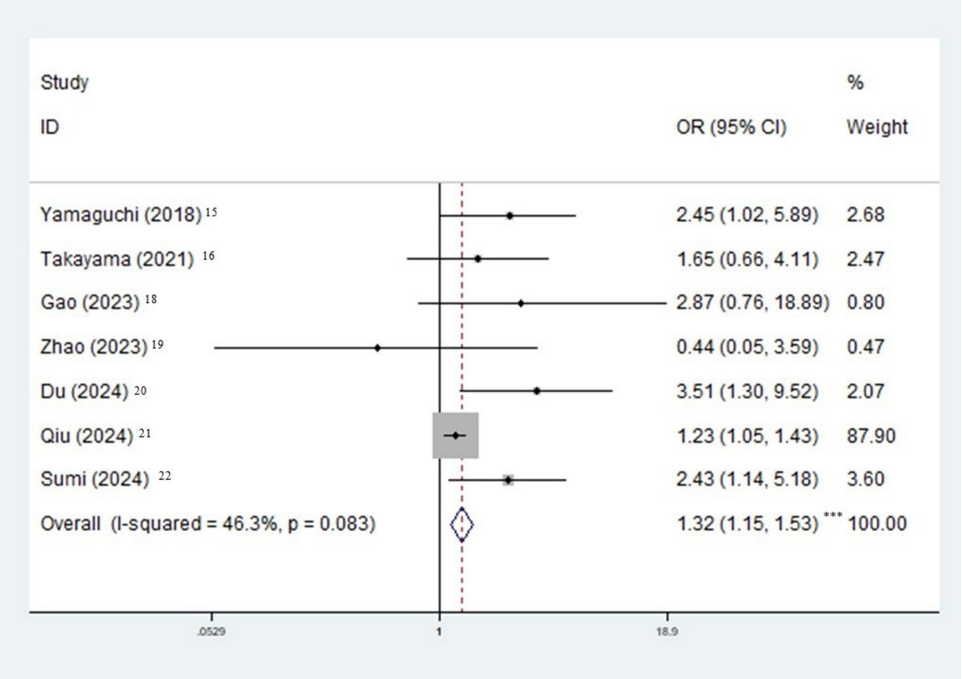

Figure 2 Association of emphysema with the incidence of immune checkpoint inhibitor-related pneumonitis among non-small cell lung cancer patients receiving immune checkpoint inhibitors. ***: P < 0.001.

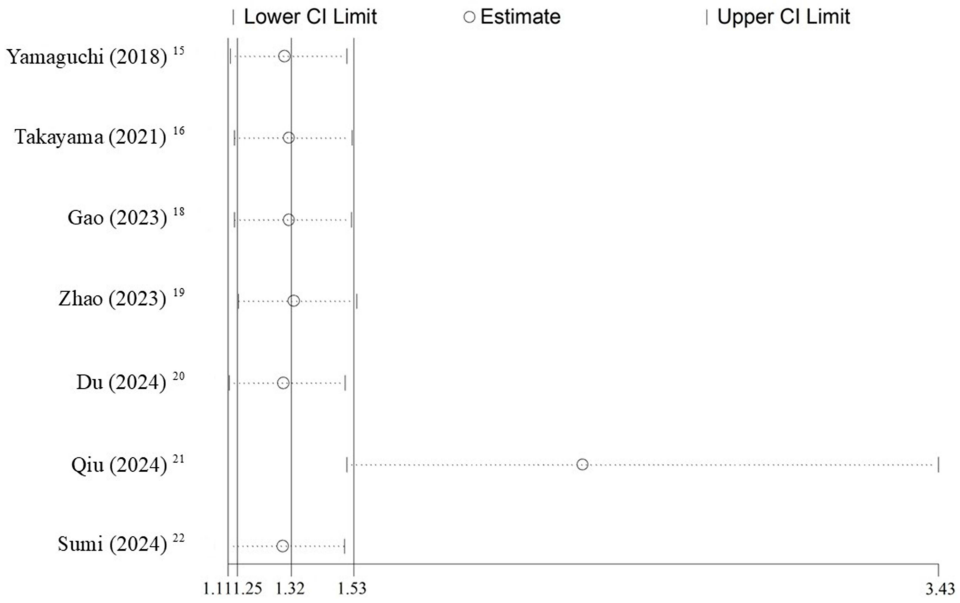

Figure 3 Sensitivity analysis for the association of emphysema with the incidence of immune checkpoint inhibitor-related pneumonitis among non-small cell lung cancer patients receiving immune checkpoint inhibitors.

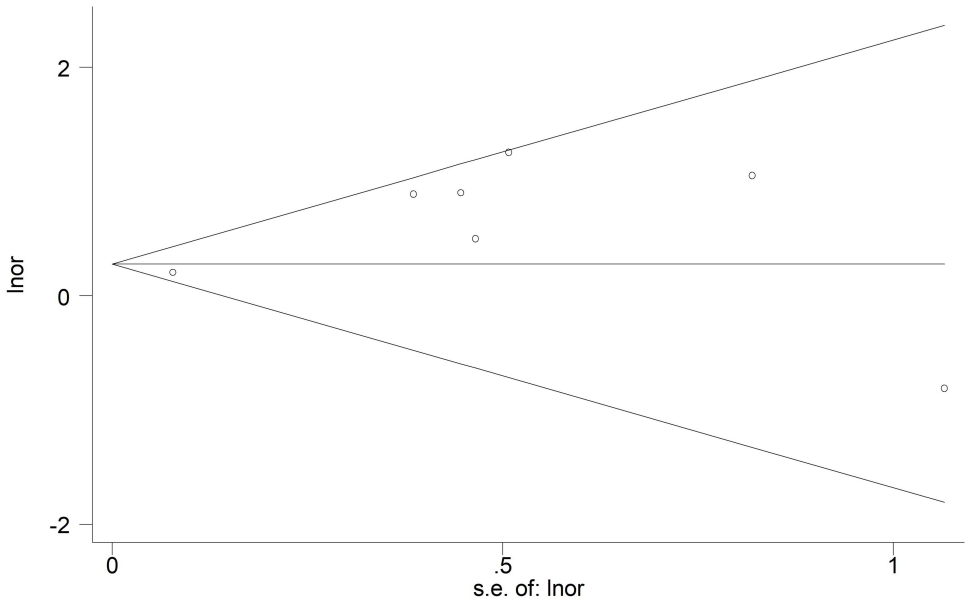

Figure 4 Begg's funnel plot for the association of emphysema with the incidence of immune checkpoint inhibitor-related pneumonitis among non-small cell lung cancer patients receiving immune checkpoint inhibitors.

efficacy of ICIs.[25] Some studies have suggested that chronic inflammation may lead to the upregulation of PD-L1 expression in tumor tissues. High PD-L1 expression is associated with better responses to ICIs, which may allow NSCLC patients with emphysema to benefit more from PD-1/PD-L1 inhibitors.[25] Additionally, emphysema patients may exhibit higher infiltration of immune cells, such as CD8+ T cells and macrophages, in lung tissue. This immune-activated state can further enhance the anti-tumor effects of ICIs.[16] Emphysema may also lead to structural damage and vascular remodeling in localized lung tissue, potentially affecting the hypoxic state of the tumor microenvironment. Hypoxia can suppress immune cell activity, but the microenvironmental changes induced by emphysema may alleviate hypoxia, thereby improving the efficacy of ICIs.[24]

https://doi.org/10.2147/COPD.S569504

On the other hand, NSCLC patients with emphysema are more prone to developing ICIP after receiving ICI therapy. Emphysema causes alveolar wall destruction and reduced lung elasticity, making the lung tissue more fragile. This structural damage lowers the lung's ability to tolerate immune-mediated inflammation, increasing the risk of irP.[26] Chronic inflammation in emphysema leads to the persistent activation of immune cells. ICIs further enhance immune responses by lifting immune suppression, which can result in excessive immune activation and lung tissue damage.[27] Emphysema changes the lung's immune microenvironment, increasing pro-inflammatory cytokines and chemokines. This inflammatory setting may amplify immune responses after ICIs treatment, leading to pneumonitis.[28] Damaged lung tissue in emphysema has a reduced capacity for repair. When immune cells become overactive due to ICIs, the lungs cannot effectively recover, making inflammation more severe. Emphysema-induced hypoxia can activate pathways like HIF-1α, which may intensify immune responses. ICIs may worsen this effect, promoting lung inflammation.[24]

Actually, there are many fields worth further exploration regarding the impact of emphysema on the efficacy and adverse effects of ICIs in NSCLC patients. For example, the relationship between the severity of emphysema (mild, moderate, severe) and ICI efficacy, as well as the risk of ICIP could be investigated. Quantitative CT imaging techniques can be utilized to assess the extent and severity of emphysema, providing insights into its predictive value for treatment response and adverse reactions. It is also necessary to analyze the impact of different types of emphysema (such as centrilobular, paraseptal, or mixed types) on ICI efficacy and ICIP incidence to determine whether different emphysema subtypes exhibit distinct clinical outcomes and risks. By analyzing the characteristics of immune cell infiltration, PD-L1 expression, TMB, and cytokine levels in the TME of emphysema patients, the potential mechanisms influencing ICI efficacy and ICIP risk can be elucidated. Additionally, exploring emphysema-related genetic mutations (such as *TP53* and *KRAS* mutations) and inflammatory markers (such as IL-6 and TNF-α) for their predictive roles in ICI efficacy and ICIP risk may help identify molecular targets for precision therapy.

CT-defined emphysema may serve as a stratification biomarker in precision oncology. Identifying patients with emphysema could help tailor ICI therapy, guide proactive monitoring for pneumonitis, and improve trial design by accounting for differential efficacy and toxicity profiles. Moreover, the consistency between our findings and those of previous analyses further strengthens the evidence that CT-defined emphysema may serve as a clinically meaningful prognostic marker for predicting ICI efficacy and identifying patients at elevated risk of pneumonitis or other irAEs. These converging results highlight the importance of conducting prospective studies to validate emphysema-based risk stratification and to determine whether early monitoring or prophylactic strategies are warranted in this high-risk population.

However, there are several limitations in this meta-analysis. First, since all included studies were conducted in East Asian populations, caution is needed when generalizing the findings to other ethnic or geographic populations. Second, due to the lack of original data, we are unable to perform more detailed analysis to further identify the impact of emphysema among patients with different clinical characteristics such as age, smoking history and pulmonary comorbidities. Third, only two or three studies investigating the impact of emphysema on primary outcomes. Thus, more studies are still needed to verify our findings. Four, the definition methods for emphysema differed in included studies, which may cause some bias. Five, in addition to the limitations previously noted, all included studies were retrospective in nature, with variability in treatment lines and follow-up durations across studies. These factors may contribute to heterogeneity and should be considered when interpreting the results.

Conclusion

CT-defined emphysema is associated with better therapeutic efficacy with longer PFS and OS, but increased risk of ICIP among NSCLC patients receiving ICIs based on current available evidence. These findings highlight the potential utility of incorporating emphysema assessment into clinical decision-making and risk stratification, which may help guide personalized immunotherapy strategies. However, as most included studies were conducted in East Asian populations and were retrospective in nature, the generalizability of these results is limited, and further prospective studies in diverse cohorts are needed to confirm these findings.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Ethical Statement

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. All procedures performed in studies that involved human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by Health Commission of Chengdu - Joint Innovation Fund of Chengdu University of Traditional Chinese Medicine (WXLH202406001) and Sichuan Provincial Administration of Traditional Chinese Medicine Scientific Research Project (222).

Disclosure

The authors declare that they have no conflict of interest.

References

1. Kratzer TB, Bandi P, Freedman ND, et al. Lung cancer statistics, 2023. *Cancer*. 2024;130(8):1330–1348. doi:10.1002/cncr.35128
2. Zhang Q, Tang L, Zhou Y, He W, Li W. Immune checkpoint inhibitor-associated pneumonitis in non-small cell lung cancer: current understanding in characteristics, diagnosis, and management. *Front Immunol*. 2021;12:663986. doi:10.3389/fimmu.2021.663986
3. Zeng Y, Hu CH, Li YZ, et al. Association between pretreatment emotional distress and immune checkpoint inhibitor response in non-small-cell lung cancer. *Nat Med*. 2024;30(6):1680–1688. doi:10.1038/s41591-024-02929-4
4. Bodor JN, Boumber Y, Borghaei H. Biomarkers for immune checkpoint inhibition in non-small cell lung cancer (NSCLC). *Cancer*. 2020;126 (2):260–270. doi:10.1002/cncr.32468
5. Hu Y, Wang Y, Wang T, Che G, Li L. Addition of metformin for non-small cell lung cancer patients receiving antineoplastic agents. *Front Pharmacol*. 2023;14:1123834. doi:10.3389/fphar.2023.1123834
6. Tubío-Pérez RA, Torres-Durán M, Pérez-Ríos M, Fernández-Villar A, Ruano-Raviña A. Lung emphysema and lung cancer: what do we know about it? *Ann Transl Med*. 2020;8(21):1471. doi:10.21037/atm-20-1180
7. Durawa A, Dziadziuszko K, Jelitto M, et al. Emphysema and lung cancer risk. *Transl Lung Cancer Res*. 2024;13(8):1918–1928. doi:10.21037/tlcr-24-197
8. Koo HJ, Do KH, Lee JB, Alblushi S, Lee SM. Lung cancer in combined pulmonary fibrosis and emphysema: a systematic review and meta-analysis. *PLoS One*. 2016;11(9):e0161437. doi:10.1371/journal.pone.0161437
9. Oh JY, Lee YS, Min KH, et al. Impact and prognosis of lung cancer in patients with combined pulmonary fibrosis and emphysema. *Sarcoidosis Vasc Diffuse Lung Dis*. 2020;37(4):e2020020. doi:10.36141/svdld.v37i4.7316
10. Ishida M, Mimae T, Kamigaichi A, et al. The role of emphysema on postoperative prognosis in early-stage nonsmall cell lung cancer. *Ann Surg Oncol*. 2024;31(8):5055–5063. doi:10.1245/s10434-024-15126-x
11. Fukui M, Suzuki K, Matsunaga T, Oh S, Takamochi K. Outcomes of lung cancer resection for patients with combined pulmonary fibrosis and emphysema. *Surg Today*. 2016;46(3):341–347. doi:10.1007/s00595-015-1234-z
12. Zhang Y, Zhao J, Ma Z, et al. Immune checkpoint inhibitors for advanced non-small cell lung cancer with preexisting COPD and CT-defined emphysema: a systematic review and meta-analysis. *Lung Cancer*. 2025;207:108700. doi:10.1016/j.lungcan.2025.108700
13. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372: n71. doi:10.1136/bmj.n71
14. Wang Y, Li J, Chang S, Dong Y, Che G. Risk and influencing factors for subsequent primary lung cancer after treatment of breast cancer: a systematic review and two meta-analyses based on four million cases. *J Thorac Oncol*. 2021;16(11):1893–1908. doi:10.1016/j.jtho.2021.07.001
15. Yamaguchi T, Shimizu J, Hasegawa T, et al. Pre-existing pulmonary fibrosis is a risk factor for anti-PD-1-related pneumonitis in patients with non-small cell lung cancer: a retrospective analysis. *Lung Cancer*. 2018;125212–125217. doi:10.1016/j.lungcan.2018.10.001
16. Takayama Y, Nakamura T, Fukushiro Y, Mishima S, Masuda K, Shoda H. Coexistence of emphysema with non-small-cell lung cancer predicts the therapeutic efficacy of immune checkpoint inhibitors. *In vivo*. 2021;35(1):467–474.

17. Noda Y, Shiroyama T, Masuhiro K, et al. Quantitative evaluation of emphysema for predicting immunotherapy response in patients with advanced non-small-cell lung cancer. *Sci Rep*. 2022;12(1):8881.
18. Gao P. Analysis of risk factors for immune checkpoint inhibitor-associated pneumonia in advanced non-small cell lung cancer [Master]2023.
19. Zhao D, Ding Y, Wen Y, et al. Incidence rate and risk factors of immune checkpoint inhibitor-related pneumonitis in patients with advanced lung cancer treated with programmed death-1 inhibitors. *J Harbin Med Univ*. 2023;57(05):562–566. doi:10.20010/j.issn.1000-1905.2023.05.0562
20. Du Y, Zhang S, Jia X, et al. Radiomics biomarkers to predict checkpoint inhibitor pneumonitis in non-small cell lung cancer. *Acad Radiol*. 2024. doi:10.1016/j.acra.2024.09.053
21. Qiu L, Cheng J, Wang H. Analysis of clinical characteristics and risk factors for immune checkpoint inhibitor-related pneumonitis in NSCLC patients. *Med J Chin PLA*. 2024;49(08):861–867.
22. Sumi T, Sekikawa M, Koshino Y, et al. Risk factors for severe immune-related pneumonitis after nivolumab plus ipilimumab therapy for non-small cell lung cancer. *Thoracic Cancer*. 2024;15(20):1572–1581. doi:10.1111/1759-7714.15385
23. Zhang Y, Zhang Z, Wang J, Zhou Y, Liang F. A study on the relationship serum TRAIL level and immunotherapy response in patients with advanced non-small cell lung cancer. *Chin J New Clin Med*. 2024;17(06):645–650.
24. Tian H, Chao YC, Hu J, Song YL. Immunotherapy advances for lung cancer combined with chronic obstructive pulmonary disease. *Zhonghua Jie He He Hu Xi Za Zhi*. 2024;47(1):70–74. doi:10.3760/cma.j.cn112147-20230905-00142
25. Pan Y, Fu Y, Zeng Y, et al. The key to immunotherapy: how to choose better therapeutic biomarkers for patients with non-small cell lung cancer. *Biomark Res*. 2022;10(1):9. doi:10.1186/s40364-022-00355-7
26. Zeng Z, Qu J, Yao Y, et al. Clinical outcomes and risk factor of immune checkpoint inhibitors-related pneumonitis in non-small cell lung cancer patients with chronic obstructive pulmonary disease. *BMC Pulm Med*. 2022;22(1):458. doi:10.1186/s12890-022-02190-w
27. Suresh K, Psoter KJ, Voong KR, et al. Impact of checkpoint inhibitor pneumonitis on survival in NSCLC patients receiving immune checkpoint immunotherapy. *J Thorac Oncol*. 2019;14(3):494–502. doi:10.1016/j.jtho.2018.11.016
28. Guo X, Chen S, Wang X, Liu X. Immune-related pulmonary toxicities of checkpoint inhibitors in non-small cell lung cancer: diagnosis, mechanism, and treatment strategies. *Front Immunol*. 2023;14:1138483. doi:10.3389/fimmu.2023.1138483