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Clinical characteristics, risk factors, and risk stratification of interstitial lung disease during systemic treatment for lung cancer: a multicenter retrospective development and external validation study

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Abstract

Background

Interstitial lung disease (ILD) is a major pulmonary complication of lung cancer treatment. We characterized treatment-associated ILD, identified risk factors, and developed and externally validated a simple risk score using routine clinical variables.

Methods

This multicenter retrospective cohort included 871 patients (75 ILD events) at the development center, 308 (32) at external validation center, 99 (8) at center 3, and 104 (3) in a 2026 temporal cohort. Logistic regression was performed in the development cohort. A four-factor score assigned one point each for smoking history, any comorbidity, immunotherapy exposure, and inflammatory abnormality.

Results

Among 1382 patients, 118 developed ILD (8.54%). In development, smoking was 64.0% vs 30.8% (ILD vs non-ILD; OR 3.99, 95% CI 2.41–6.59; P < 0.001); in external validation, 71.9% and 47.1% (OR 2.87, 95% CI 1.28–6.43; P = 0.009). In the four-factor model, smoking (aOR 3.37, 95% CI 1.99–5.69), immunotherapy (aOR 3.77, 95% CI 2.23–6.39), and inflammatory abnormality (aOR 2.25, 95% CI 1.31–3.86) remained independently associated with ILD; comorbidity showed a borderline association (aOR 1.66, 95% CI 0.97–2.84). The score achieved AUCs of 0.771 in development and 0.756 in external validation. ILD incidence reached 29.38% and 25.84% in the high-risk groups.

Conclusions

Treatment-associated ILD reflects host susceptibility, treatment exposure, and inflammatory activation. Smoking, immunotherapy exposure, and inflammatory abnormality were independently associated with ILD, comorbidity added host-related information. A four-factor routine-variable score showed moderate, stable discrimination in external validation and identified a distinct high-risk group. It supports pretreatment and early-treatment monitoring stratification, not ILD diagnosis.

Background

Lung cancer is routinely treated with chemotherapy, molecularly targeted therapy, immune checkpoint inhibitors, radiotherapy, and increasingly complex combinations or sequences of these modalities[1]. As treatment options have expanded and patients remain on anticancer therapy for longer periods, pulmonary toxicities have become an important determinant of treatment continuity, quality of life, and prognosis[2]. Interstitial lung disease (ILD) is particularly challenging because its clinical severity ranges

from mild radiographic abnormalities to rapidly progressive respiratory failure, and recognition may require interruption of effective anticancer therapy, glucocorticoid treatment, or additional supportive care[3,4].

Treatment-associated ILD is clinically heterogeneous and is not confined to a single drug class[5]. Cytotoxic chemotherapy, targeted agents, immune checkpoint inhibitors, and thoracic radiotherapy can each contribute to pulmonary injury, while infection, tumor progression, cardiogenic pulmonary edema, and pre-existing lung abnormalities may produce overlapping symptoms and imaging findings[6,7]. Previous studies have therefore reported a broad range of potential risk factors, including older age, male sex, smoking history, chronic pulmonary disease or interstitial lung abnormalities, squamous histology, prior thoracic radiotherapy, immunotherapy exposure, and abnormalities in systemic inflammatory markers[8,9]. However, the importance of individual factors has varied across cohorts and treatment settings.

This inconsistency is especially relevant in real-world lung cancer care. Patients commonly have multiple comorbidities and may receive several treatment modalities over the course of their disease[10]. A pulmonary event that emerges during systemic therapy may therefore reflect the interaction of baseline host vulnerability, cumulative or concurrent treatment exposures, and the inflammatory response occurring during treatment rather than the effect of one isolated drug[11,12]. Smoking history, for example, is one component of host susceptibility, whereas immunotherapy represents a treatment-related exposure and abnormalities in C-reactive protein or neutrophil measures provide information about inflammatory activation[13,14]. Considering these domains together may better reflect the clinical pathway through which treatment-associated ILD develops.

Most published prediction studies have focused on a specific treatment, particularly checkpoint inhibitor pneumonitis or ILD associated with individual targeted agents[15]. Such models can be useful within narrowly defined populations but may be less transferable to patients receiving multimodal or sequential therapy[16]. From a clinical perspective, a simple risk-stratification approach based on variables routinely available before or early during treatment may be more practical for identifying patients who require closer respiratory surveillance[17]. The purpose of such a tool is not to diagnose ILD or assign causality to a specific drug, but to enrich a higher-risk population in whom symptoms, oxygenation, inflammatory markers, and chest imaging can be monitored more intensively.

A multicenter design is important for evaluating whether this type of risk framework remains useful beyond the institution in which it is developed. Differences in patient characteristics, treatment patterns, documentation, and diagnostic practice can substantially influence the apparent performance of a clinical model. Independent external validation therefore provides a more meaningful test of generalizability than repeated fitting within a single cohort, while additional centers can provide supportive evidence regarding transportability and center-specific heterogeneity.

Accordingly, we conducted a multicenter retrospective study of patients with lung cancer receiving systemic treatment at three independent tertiary hospitals. The study was designed to characterize the

incidence and clinical profile of treatment-associated ILD, identify routinely available clinical factors associated with ILD, develop a simple and interpretable risk-stratification score in a prespecified development cohort, and evaluate its performance in an independent external validation cohort. A third independent center was used to explore transportability, and a subsequent cohort from the development center was retained for temporal assessment.

Methods

Study design and participants

This was a multicenter retrospective real-world cohort study of patients with lung cancer treated at three independent tertiary hospitals. The development cohort included 871 patients treated in 2022–2025, including 75 who developed ILD and 796 who did not. The formal external validation cohort comprised 308 patients, including 32 ILD events. The third independent center included 99 unique patients after patient-level deduplication, including 8 ILD events. A subsequent 2026 cohort from the development center comprised 104 patients, including 3 ILD events, and was retained for temporal description.

Patients were eligible when a definite pulmonary malignancy diagnosis was documented and the available medical record was sufficient to determine both treatment exposure and ILD outcome. Records were excluded when the principal outcome could not be determined, when treatment information was insufficient for patient-level classification, or when an entry represented a duplicate hospitalization rather than a unique patient. For patients with repeated admissions, the analysis unit was the patient rather than the admission, because the aim was to describe an individual's risk of developing ILD during the systemic-treatment course rather than the frequency of ILD-coded hospitalizations.

The development-center source files contained annual non-ILD records as well as a separate ILD dataset. Eight hundred annual non-ILD records were first reconciled by hospitalization identifier and patient name, yielding 799 unique records; three patients who subsequently appeared in the ILD dataset were then removed from the non-ILD pool, leaving 796 non-ILD patients. Candidate ILD records were also reviewed, and one patient with insufficient key treatment-exposure information was excluded, leaving 75 ILD cases. At the external validation center, 519 negative records were deduplicated to 281 patients, five patients overlapping with the ILD dataset were removed, and 276 non-ILD patients remained alongside 32 ILD patients. At the third center, two duplicated patients were resolved by retaining the most complete record consistent with the final outcome, leaving 99 unique patients.

Smoking-history harmonization

Smoking history was treated as a lifetime exposure. For patients with multiple records, any explicit documentation of current or previous smoking classified the patient as having a smoking history. A patient was classified as a non-smoker only when at least one explicit negative record was available and

no positive smoking record was identified. When smoking status could not be determined from the available records, the value was retained as missing rather than being coded as no smoking.

Smoking history was available for 675 of 871 patients (77.5%) in the development cohort, for all 308 patients in the external validation cohort, and for 98 of 99 patients at the third independent center. In the 2026 temporal cohort, smoking history was available for only 33 of 104 patients; this cohort was therefore used for temporal description but not for formal evaluation of the four-factor score.

For repeated records, a documented history of smoking was retained even when a later record indicated that the patient was not currently smoking, because the variable represented lifetime exposure rather than current smoking status. Blank fields or records without smoking documentation were not interpreted as a negative history. This approach reduced the risk of classifying former smokers as never-smokers and avoided treating missing information as absence of exposure.

Outcome and candidate variables

The primary outcome was ILD diagnosed during systemic treatment for lung cancer. The study was designed to identify patients more likely to develop ILD in a real-world treatment pathway rather than to attribute every event to a single drug. The retrospective outcome classification relied on the final clinical diagnosis recorded in the medical record. Central blinded HRCT re-review was not available across all centers.

At the development and formal external validation centers, the final clinical diagnoses and reconciled outcome classifications present in the source datasets were retained. At the third independent center, the structured ILD-classification field was reviewed together with the clinical treatment record. Among the eight ILD cases in that center, five were classified as NSIP, one as UIP, and two were recorded as ILD without further subtype specification. The study did not attempt to retrospectively relabel all cases as checkpoint-inhibitor pneumonitis, chemotherapy-induced pneumonitis, targeted-therapy-associated ILD, or radiation pneumonitis, because the treatment pathways frequently overlapped and uniform central adjudication was not available.

In clinical practice, infection, tumor progression, cardiogenic pulmonary edema, radiation-related change, and treatment-associated ILD may produce overlapping respiratory symptoms and imaging findings. The retrospective classification therefore relied on the final diagnosis recorded by the treating team after routine clinical evaluation. This approach reflects real-world practice but also means that the study evaluates documented treatment-associated ILD rather than a centrally adjudicated imaging endpoint. Lack of blinded central HRCT review and uniform severity grading was consequently recognized in advance as an important limitation.

Candidate variables included age, sex, smoking history, histologic type, clinical stage, driver-gene or other gene alterations, any comorbidity, underlying pulmonary disease, prior lung surgery, prior thoracic or pulmonary radiotherapy, chemotherapy exposure, immunotherapy exposure, targeted therapy

exposure, and inflammatory indicators. Treatment categories were allowed to overlap because combination and sequential regimens were common. Inflammatory abnormality for the bedside score was defined as abnormal CRP and/or abnormal neutrophil percentage documented in the clinical record.

Any comorbidity was defined as at least one chronic underlying disease documented in the medical record. Underlying pulmonary disease was analyzed separately and included diagnoses such as chronic obstructive pulmonary disease, emphysema, bronchiectasis, asthma, pulmonary tuberculosis, pulmonary fungal infection, pulmonary fibrosis, previous ILD, or other chronic conditions considered likely to affect pulmonary reserve. The composite inflammatory abnormality used in the bedside score was defined as abnormal CRP and/or abnormal neutrophil percentage. This variable was intended to capture a clinically recognizable state of inflammatory activation and was not treated as a diagnostic criterion for ILD.

Treatment exposure was classified by treatment class rather than by a single named regimen in order to maintain comparability across centers. Platinum compounds, pemetrexed, taxanes, etoposide, gemcitabine, and similar cytotoxic drugs were classified as chemotherapy; PD-1/PD-L1-directed antibodies and records explicitly documenting immune therapy were classified as immunotherapy; and EGFR/ALK inhibitors or other molecularly targeted agents were classified as targeted therapy. Categories were allowed to overlap because combination and sequential treatment were common. Thoracic or pulmonary radiotherapy was distinguished from radiation delivered to other anatomic sites.

Model development and integer score

Univariable logistic regression was performed in the development cohort. Because smoking history was missing in 22.5% of development patients, the four-factor multivariable analysis used the 675 patients with known smoking status. The model included smoking history, any comorbidity, immunotherapy exposure, and inflammatory abnormality, representing four clinically accessible domains relevant to pulmonary vulnerability and treatment-associated ILD.

Complete-case analysis was used for the four-factor model because smoking status could not be reliably inferred when it was not documented. Coding missing smoking status as no smoking would have introduced systematic exposure misclassification, whereas model-based imputation would have required assumptions that could not be applied consistently across centers. Descriptive analyses for other variables used the largest available denominator, and the denominator for each analysis was reported when data were incomplete. One point was assigned for each of the four factors, producing an integer score from 0 to 4. Risk strata were defined as low risk (0–1 point), intermediate risk (2 points), and high risk (3–4 points). The score was developed in the smoking-complete development subset and then applied without re-estimating weights to the formal external validation cohort. The third independent center was evaluated exploratorily because it contained only eight events.

Statistical analysis

Continuous variables were summarized as mean±standard deviation and compared using Welch's t test. Categorical variables were summarized as counts and percentages and compared using the χ^2 test or Fisher's exact test as appropriate. Logistic regression results are presented as ORs or adjusted ORs with 95% CIs. Discrimination of the integer score was assessed using the AUC, with 95% CIs estimated by 5000 bootstrap resamples. The Brier score was used as a supplementary measure of prediction error. External calibration was summarized using a calibration intercept and slope. A score ≥ 2 was evaluated as a sensitive threshold for intensified monitoring. All tests were two-sided and $P < 0.05$ was considered statistically significant.

For multicategory variables such as histologic type, the reported P value represented the overall distributional comparison rather than a separate hypothesis test for each subtype. Thus, a significant global P value indicated that the histologic composition differed between the ILD and non-ILD groups, while the individual subtype proportions were used descriptively to identify which categories contributed most visibly to that difference. This approach avoided presenting a series of uncorrected post hoc comparisons in the principal baseline table.

Results

Cohort composition and ILD incidence

Across all observation periods, 1382 patients were included, of whom 118 developed ILD, corresponding to an overall incidence of 8.54% (95% CI 7.18–10.13%). The prespecified primary analysis included the 871-patient development cohort, 308-patient external validation cohort, and 99-patient third-center cohort, totaling 1278 patients with 115 ILD events (9.00%). ILD incidence in the three primary-analysis centers was 8.61%, 10.39%, and 8.08%, respectively, with no significant between-center difference ($\chi^2=0.990$, $P = 0.610$) (Table 1; Figs. 1 and 2).

Within the development center, the annual distribution also showed that ILD was not confined to a single calendar period. The 2022, 2023, 2024, and 2025 cohorts included 109, 116, 323, and 323 patients, with 10, 16, 26, and 23 ILD events, respectively; the corresponding annual incidences were 9.17%, 13.79%, 8.05%, and 7.12%. The subsequent 2026 cohort had 3 events among 104 patients (2.88%). Although the later cohort had a numerically lower event rate, the small number of events and its later treatment period precluded interpreting this as a definite temporal decline.

The 2026 temporal cohort included 3 ILD events among 104 patients (2.88%). It was not combined with the development cohort. Because smoking history was available for only 33 patients, this cohort was retained for descriptive temporal comparison rather than formal four-factor score validation.

Table 1
Study cohorts and ILD occurrence

Center/cohort	Role	Total	ILD	Non-ILD	ILD incidence	95% CI
Development center	Development cohort (2022–2025)	871	75	796	8.61%	6.92–10.66%
Development center	Temporal cohort (2026)	104	3	101	2.88%	0.99–8.14%
External validation center	Independent external validation	308	32	276	10.39%	7.46–14.30%
Third independent validation center	Transportability assessment	99	8	91	8.08%	4.15–15.14%
All observed patients	—	1382	118	1264	8.54%	7.18–10.13%
Primary analysis cohort	Development + external + third center	1278	115	1163	9.00%	7.55–10.69%

Between-center comparison for the primary-analysis cohorts: χ^2=0.990, P = 0.610.

Smoking history and ILD risk

In the development cohort, smoking history was available for 675 patients, including all 75 ILD cases and 600 non-ILD patients. Smoking was documented in 48 of 75 ILD patients (64.0%) compared with 185 of 600 non-ILD patients (30.8%), corresponding to a crude OR of 3.99 (95% CI 2.41–6.59; P < 0.001).

The association was reproduced in the formal external validation center, where smoking history was complete: 23 of 32 ILD patients (71.9%) had a smoking history compared with 130 of 276 non-ILD patients (47.1%), yielding a crude OR of 2.87 (95% CI 1.28–6.43; P = 0.009). In contrast, none of the eight ILD patients at the third independent center had a recorded smoking history, compared with 15 of 90 non-ILD patients with available data (P = 0.352). This discordance highlights center-level heterogeneity and the uncertainty created by only eight events at the third center (Table 2).

Table 2
Completeness and association of smoking history across centers

Cohort	Smoking available	Smokers/available	Smokers in ILD	Smokers in non-ILD	Crude OR (95% CI)	P value
Development center	675/871 (77.5%)	233/675 (34.5%)	48/75 (64.0%)	185/600 (30.8%)	3.99 (2.41–6.59)	< 0.001
External validation center	308/308 (100%)	153/308 (49.7%)	23/32 (71.9%)	130/276 (47.1%)	2.87 (1.28–6.43)	0.009
Third independent validation center	98/99 (99.0%)	15/98 (15.3%)	0/8 (0.0%)	15/90 (16.7%)	Not stable with zero cell	0.352*

*Fisher's exact test at the third independent center. Smoking was treated as a lifetime exposure; any positive smoking record overrode a negative record in repeated admissions.

Development-cohort characteristics and inflammatory status

Patients who developed ILD were older and more frequently male. Advanced-stage or extensive-stage disease and gene alterations were also more common among ILD patients in unadjusted comparisons. Smoking history showed one of the largest baseline differences between groups, occurring in 64.0% of ILD patients and 30.8% of non-ILD patients with available smoking data (Table 3).

The distribution of histologic subtypes differed significantly between patients with and without ILD (global P = 0.009). Adenocarcinoma accounted for 58.7% of the ILD group and 71.2% of the non-ILD group, whereas squamous cell carcinoma accounted for 33.3% and 18.1%, respectively. Small-cell lung cancer accounted for 5.3% and 9.2%, and other or unspecified histologies for 2.7% and 1.5%. The global test therefore supports a difference in histologic composition, with the higher proportion of squamous cell carcinoma in the ILD group being the most conspicuous descriptive shift. These subtype comparisons were not interpreted as independent causal effects without multivariable confirmation.

Any comorbidity was more common among ILD patients, whereas the prevalence of underlying pulmonary disease did not differ significantly. Immunotherapy and chemotherapy exposures were more frequent in the ILD group. Prior lung surgery was less frequent among ILD patients, a pattern that is more plausibly interpreted as confounding by resectability, stage, and treatment pathway than as a direct protective effect (Table 4).

Abnormal neutrophil percentage, abnormal CRP, and the composite inflammatory abnormality were more common in the ILD group. These measures should be interpreted as risk signals rather than diagnostic

markers because infection, tumor-related inflammation, and other causes can generate similar abnormalities.

The composite inflammatory abnormality was present in 68.0% of patients with ILD and 42.5% of those without ILD. Abnormal CRP and abnormal neutrophil percentage each showed the same direction of difference. These data support the use of inflammation as a warning domain in the score, but they also underscore why inflammatory laboratory tests cannot be treated as disease-specific biomarkers: infection, tumor progression, tissue injury, and other systemic processes may produce similar abnormalities (Table 5).

Table 3
Demographic and tumor characteristics in the development cohort

Variable	Overall (n = 871)	ILD (n = 75)	Non-ILD (n = 796)	P value
Age, years	67.8 ± 9.3	70.3 ± 7.8	67.6 ± 9.4	0.007
Male sex	565 (64.9%)	61 (81.3%)	504 (63.3%)	0.002
Smoking history (n = 675 available)	233/675 (34.5%)	48/75 (64.0%)	185/600 (30.8%)	< 0.001
Histology: adenocarcinoma	611 (70.1%)	44 (58.7%)	567 (71.2%)	0.009
Squamous cell carcinoma	169 (19.4%)	25 (33.3%)	144 (18.1%)	
Small-cell lung cancer	77 (8.8%)	4 (5.3%)	73 (9.2%)	
Other/unknown	14 (1.6%)	2 (2.7%)	12 (1.5%)	
Stage III–IV/extensive stage	629 (75.5%)	60 (93.8%)	569 (74.0%)	< 0.001
Gene alteration/driver-gene abnormality	268 (30.8%)	33 (44.0%)	235 (29.5%)	0.009

Smoking percentages are based on patients with available smoking history (n = 675).

Table 4
Baseline status and treatment exposures in the development cohort

Variable	Overall (n = 871)	ILD (n = 75)	Non-ILD (n = 796)	P value
Any comorbidity	486 (55.8%)	50 (66.7%)	436 (54.8%)	0.047
Underlying pulmonary disease	108 (12.4%)	9 (12.0%)	99 (12.4%)	0.913
Prior lung surgery	362 (41.6%)	13 (17.3%)	349 (43.8%)	< 0.001
Prior thoracic/pulmonary radiotherapy	102 (11.7%)	10 (13.3%)	92 (11.6%)	0.648
Immunotherapy exposure	272 (31.2%)	49 (65.3%)	223 (28.0%)	< 0.001
Chemotherapy exposure	539 (61.9%)	56 (74.7%)	483 (60.7%)	0.017
Targeted therapy exposure	211 (24.2%)	25 (33.3%)	186 (23.4%)	0.054

Treatment categories were allowed to overlap.

Table 5
Inflammatory indicators in the development cohort

Indicator	Overall	ILD	Non-ILD	P value
Abnormal white blood cell count	168 (19.7%)	18 (25.7%)	150 (19.2%)	0.190
Abnormal neutrophil percentage	284 (33.4%)	39 (55.7%)	245 (31.4%)	< 0.001
Abnormal CRP	219 (32.8%)	34 (52.3%)	185 (30.7%)	< 0.001
Inflammatory abnormality (CRP and/or neutrophils)	389 (44.7%)	51 (68.0%)	338 (42.5%)	< 0.001

Individual laboratory variables were calculated among patients with available measurements.

Logistic regression and four-factor model

In univariable analysis, smoking history was strongly associated with ILD (OR 3.99, 95% CI 2.41–6.59; P < 0.001). Older age, male sex, advanced-stage disease, gene alterations, chemotherapy exposure, immunotherapy exposure, and inflammatory abnormality were also associated with ILD in univariable analyses.

Several additional univariable associations were clinically notable. Age was associated with a modest increase in odds per year, male sex was more frequent among ILD cases, and advanced-stage/extensive-

stage disease, gene alterations, chemotherapy exposure, and immunotherapy exposure were associated with higher odds of ILD. Prior lung surgery was associated with lower univariable odds of ILD. This inverse association was not interpreted as a protective biological effect of surgery; rather, it was considered likely to reflect resectability, earlier-stage disease, fewer subsequent treatment lines, and other treatment-pathway differences that separate surgical candidates from patients managed predominantly with systemic therapy.

Among the 675 development patients with known smoking status, the four-factor multivariable model showed that smoking history remained independently associated with ILD (aOR 3.37, 95% CI 1.99–5.69; P < 0.001). Immunotherapy exposure (aOR 3.77, 95% CI 2.23–6.39; P < 0.001) and inflammatory abnormality (aOR 2.25, 95% CI 1.31–3.86; P = 0.003) also retained independent associations. Any comorbidity remained directionally associated but did not reach the conventional significance threshold (aOR 1.66, 95% CI 0.97–2.84; P = 0.066). Comorbidity was retained in the integer score as the host-susceptibility component of the four-domain clinical framework (Table 6).

Table 6
Logistic regression analysis in the development cohort

Variable	Univariable N	Univariable OR (95% CI)	P value	Four-factor aOR (95% CI)	P value
Age, per year	870	1.03 (1.01–1.06)	0.018	—	—
Male sex	871	2.52 (1.39–4.59)	0.002	—	—
Smoking history	675	3.99 (2.41–6.59)	< 0.001	3.37 (1.99–5.69)	< 0.001
Stage III–IV/extensive stage	833	5.27 (1.89–14.69)	0.001	—	—
Gene alteration/driver abnormality	871	1.88 (1.16–3.03)	0.010	—	—
Prior lung surgery	871	0.27 (0.15–0.50)	< 0.001	—	—
Prior thoracic/pulmonary radiotherapy	871	1.18 (0.58–2.37)	0.648	—	—
Any comorbidity	871	1.65 (1.00–2.72)	0.049	1.66 (0.97–2.84)	0.066
Underlying pulmonary disease	871	0.96 (0.46–1.99)	0.913	—	—
Immunotherapy exposure	871	4.84 (2.94–7.98)	< 0.001	3.77 (2.23–6.39)	< 0.001
Chemotherapy exposure	871	1.91 (1.11–3.28)	0.019	—	—
Targeted therapy exposure	871	1.64 (0.99–2.72)	0.056	—	—
Inflammatory abnormality	871	2.88 (1.74–4.77)	< 0.001	2.25 (1.31–3.86)	0.003

The four-factor multivariable model used smoking-complete development cases (n = 675).

Performance and risk stratification of the four-factor integer score

The four-factor score achieved an AUC of 0.771 (95% CI 0.720–0.820) in the development cohort and 0.756 (95% CI 0.661–0.845) in the formal external validation cohort. The external validation calibration intercept was − 0.113 and the calibration slope was 1.080, indicating broadly preserved calibration when the score was applied to the independent validation center without re-estimating its weights (Table 7; Fig. 3).

The Brier score was 0.089 in the development cohort and 0.083 in the formal external validation cohort, providing a supplementary indication that overall prediction error remained similar after transport. The external validation calibration intercept of -0.113 and slope of 1.080 were close to the ideal values of 0 and 1, respectively. These calibration results do not imply perfect individual-level probability estimation, but they support the conclusion that the score did not undergo a major systematic shift when applied to the independent validation center.

Observed ILD incidence increased markedly across risk strata. In the development cohort, ILD incidence was 3.44% in the low-risk group, 8.72% in the intermediate-risk group, and 29.38% in the high-risk group. Corresponding rates in the external validation cohort were 3.64%, 4.59%, and 25.84%. At a score threshold ≥ 2, sensitivity was 85.3% and 87.5%, and the negative predictive value was 96.6% and 96.4%, respectively. The relatively low specificity and positive predictive value indicate that the score is more appropriate for monitoring triage than for diagnosing ILD (Table 8; Fig. 4).

The practical value of the score was most evident in the absolute separation of observed event rates. In both the development and formal validation cohorts, low-risk patients had ILD rates of only approximately 3–4%, whereas high-risk patients reached approximately 26–29%. Thus, the score did not simply produce a modest statistical improvement in AUC; it reorganized patients into clinically distinct monitoring groups. The intermediate-risk group was less consistent across centers, which is one reason the score should not be viewed as a precise probability calculator and why the main intended use is a pragmatic threshold for heightened surveillance.

At the third independent center, the risk gradient remained directionally ordered (3.45%, 9.09%, and 12.00% from low to high risk), but the exploratory AUC was only 0.608. Given the small number of events and the absence of smoking among the eight ILD cases, this center was not used to update the model and was interpreted as evidence of residual transportability limitations rather than a formal failure of the external validation.

Table 7
Cross-center performance of the four-factor integer score

Cohort	n (ILD)	AUC (95% CI)	Brier score	Sensitivity*	Specificity*	PPV*	NPV*
Development center	675 (75)	0.771 (0.720–0.820)	0.089	85.3%	51.5%	18.0%	96.6%
External validation center	308 (32)	0.756 (0.661–0.845)	0.083	87.5%	38.4%	14.1%	96.4%
Third independent validation center†	98 (8)	0.608 (exploratory)	0.083	87.5%	31.1%	10.1%	96.6%

*Score ≥ 2 used as the intensified-monitoring threshold. †Exploratory because only eight ILD events occurred.

Table 8
Observed ILD incidence across four-factor risk strata

Cohort	Low risk 0–1: n/ILD (rate)	Intermediate risk 2: n/ILD (rate)	High risk 3–4: n/ILD (rate)
Development center	320/11 (3.44%)	195/17 (8.72%)	160/47 (29.38%)
External validation center	110/4 (3.64%)	109/5 (4.59%)	89/23 (25.84%)
Third independent validation center†	29/1 (3.45%)	44/4 (9.09%)	25/3 (12.00%)

Low risk = 0–1 point; intermediate risk = 2 points; high risk = 3–4 points. †Exploratory third-center analysis.

Third independent-center clinical profile

The third independent center included 99 patients after deduplication. Eight developed ILD. All eight had at least one comorbidity, five had received immunotherapy, seven had received chemotherapy, and none had a documented smoking history. Chemotherapy exposure was higher in the ILD group than in the non-ILD group (87.5% vs 42.9%, P = 0.023), whereas immunotherapy and pulmonary comorbidity showed directionally higher proportions without statistical significance (Table 9).

The clinical profile of the eight third-center ILD cases illustrates the complexity of real-world attribution. Five cases occurred in adenocarcinoma, two in squamous cell carcinoma, and one in small-cell lung cancer. Seven of eight patients were male, all had at least one comorbidity, three had an underlying pulmonary disease, five had received immunotherapy, seven had received chemotherapy, and two had received targeted therapy. Structured symptom fields documented cough in four patients, sputum production in three, and chest tightness or dyspnea in two, although some symptom fields were incomplete. Outcomes were recorded as improved in two, stable in two, progressed in three, and incompletely documented in one (Table 10).

Five of the eight ILD cases were classified as NSIP, one as UIP, and two were not further classified. The small number of events prevented stable center-specific multivariable modeling.

Table 9
Characteristics of patients with and without ILD at the third independent center

Variable	Overall (n = 99)	ILD (n = 8)	Non-ILD (n = 91)	P value
Age, years	69.9 ± 10.0	72.5 ± 6.5	69.6 ± 10.2	0.284
Male sex	67 (67.7%)	7 (87.5%)	60 (65.9%)	0.431
Smoking history (n = 98 available)	15/98 (15.3%)	0/8 (0.0%)	15/90 (16.7%)	0.352
Histology: adenocarcinoma	62 (62.6%)	5 (62.5%)	57 (62.6%)	1.000
Histology: squamous cell carcinoma	25 (25.3%)	2 (25.0%)	23 (25.3%)	1.000
Histology: small-cell lung cancer	9 (9.1%)	1 (12.5%)	8 (8.8%)	0.547
Histology: other/unknown	3 (3.0%)	0 (0.0%)	3 (3.3%)	1.000
Stage III–IV/extensive stage	90 (93.8%)	6 (85.7%)	84 (94.4%)	0.373
Any comorbidity	80 (80.8%)	8 (100.0%)	72 (79.1%)	0.347
Underlying pulmonary disease	19 (19.2%)	3 (37.5%)	16 (17.6%)	0.178
Immunotherapy exposure	31 (31.3%)	5 (62.5%)	26 (28.6%)	0.104
Chemotherapy exposure	46 (46.5%)	7 (87.5%)	39 (42.9%)	0.023
Targeted therapy exposure	29 (29.3%)	2 (25.0%)	27 (29.7%)	1.000
Prior lung surgery	19 (19.2%)	3 (37.5%)	16 (17.6%)	0.178
Prior thoracic/pulmonary radiotherapy	4 (4.0%)	1 (12.5%)	3 (3.3%)	0.290

Categorical variables were compared with Fisher's exact test; age was compared with Welch's t test.

Table 10
Clinical profile of the eight ILD cases at the third independent center

Characteristic	Result
ILD pattern	NSIP, 5; UIP, 1; not further classified, 2
Histology	Adenocarcinoma, 5; squamous cell carcinoma, 2; small-cell lung cancer, 1
Sex	Male, 7; female, 1
Smoking history	0/8
Any comorbidity	8/8
Underlying pulmonary disease	3/8
Immunotherapy exposure	5/8
Chemotherapy exposure	7/8
Targeted therapy exposure	2/8
Cough	4/8
Sputum production	3/8
Chest tightness/dyspnea	2/8; some records missing
Outcome	Improved, 2; stable, 2; progressed, 3; incomplete, 1

Symptom counts are based on structured fields; missing records were not interpreted as absence.

Discussion

This multicenter study evaluated ILD occurring during systemic treatment for lung cancer from the perspective of overall clinical risk rather than the toxicity of a single drug. Across all observation periods, 1382 patients were included and 118 developed ILD, corresponding to an overall incidence of 8.54%. In the prespecified primary-analysis population, the incidence was 9.00%, and event rates were similar across the three participating centers. The principal finding was that risk could be organized into three clinically recognizable domains—host susceptibility, treatment exposure, and inflammatory activation—and that four routinely available variables derived from these domains provided a practical risk-stratification framework. The resulting score showed moderate discrimination in the development cohort and, importantly, maintained similar performance in the independent external validation cohort (Fig. 5).

The consistency of ILD incidence across centers is clinically relevant. Although the diagnosis and attribution of treatment-associated ILD can vary in routine practice, the development, external validation, and third independent centers had broadly comparable event rates. This argues against the overall signal being driven by an unusually high- or low-incidence institution and supports the clinical relevance of ILD

as a recurring complication of contemporary lung cancer treatment. An event frequency of approximately 8–10% is high enough to affect treatment planning and monitoring, particularly because even a relatively uncommon severe pulmonary event can lead to treatment interruption, hospitalization, glucocorticoid exposure, or deterioration in respiratory reserve[18,19].

These findings also support a broader view of treatment-associated ILD. In real-world care, patients may move through surgery, radiotherapy, platinum-based chemotherapy, pemetrexed or taxanes, immune checkpoint inhibition, antiangiogenic treatment, and molecularly targeted therapy in different combinations and sequences[20–22]. The pulmonary event observed at one time point is therefore not necessarily explained by the most recent drug alone. Baseline host characteristics may determine susceptibility, previous treatment may reduce pulmonary reserve, ongoing systemic therapy may act as a trigger, and inflammatory activation may accompany or precede clinically apparent lung injury[23,24]. A risk model that integrates these dimensions is therefore more consistent with routine clinical decision making than a simple ranking of individual drugs by pulmonary toxicity.

Host susceptibility was represented in the score by smoking history and the presence of comorbidity. Smoking history emerged as a strong statistical risk factor in the development cohort and was independently associated with ILD after adjustment for the other score components. The same direction of association was observed in the formal external validation cohort, where smoking history was complete and was substantially more frequent among patients with ILD than among those without ILD. This consistency across the development and formal validation cohorts supports smoking as a clinically useful marker of baseline pulmonary vulnerability, but it should be interpreted as one component of a broader host-risk profile rather than as the central cause of treatment-associated ILD[25–27].

Several mechanisms may link smoking to treatment-related pulmonary vulnerability. Long-term tobacco exposure can be accompanied by chronic airway inflammation, emphysematous or fibrotic change, impaired mucociliary clearance, reduced pulmonary reserve, and altered local immune responses. Some of these abnormalities may be present even without a formal diagnosis of chronic lung disease, so smoking history may capture cumulative pulmonary injury not fully represented by diagnostic labels. Nevertheless, smoking remains a coarse exposure measure; future studies should distinguish current from former smoking, quantify pack-years, and consider time since cessation[27].

The third independent center illustrates why smoking should not be overinterpreted. None of the eight ILD cases at that center had a recorded smoking history, despite the strong associations observed in the larger development and external validation cohorts. With only eight events, a center-specific estimate is extremely unstable and may be influenced by patient mix, regional smoking patterns, documentation, histologic distribution, or chance. This discordance does not negate the externally reproduced association in the larger cohorts, but it demonstrates that smoking is neither necessary nor sufficient for ILD to occur and that a multivariable risk framework is preferable to any single-factor interpretation.

Histologic subtype provided additional clinical context. The overall distribution of histology differed significantly between patients with and without ILD, and squamous cell carcinoma represented a higher

proportion of the ILD group. Because squamous histology is closely related to tobacco exposure, stage, treatment selection, and underlying pulmonary injury, this association should not be interpreted as independent causality. We therefore regard histology as part of the clinical phenotype associated with ILD rather than as an additional component of the bedside score.

Treatment exposure formed the second major risk domain. Immunotherapy was one of the strongest independent factors in the multivariable model. Immune checkpoint inhibitors can produce a spectrum of immune-mediated pulmonary injury, including organizing-pneumonia-like changes, NSIP-like patterns, ground-glass abnormalities, and severe diffuse alveolar damage[28,29]. The association identified in this study is therefore clinically coherent, but it should not be interpreted to mean that all ILD events were caused by immunotherapy. Many patients received combined or sequential therapies, and immune activation may act as one trigger within a susceptible host rather than as a sufficient explanation for every pulmonary event.

Chemotherapy exposure was also more common among patients with ILD in the development cohort and was particularly frequent among ILD cases at the third independent center. However, chemotherapy did not enter the final four-factor score. This distinction is important. A categorical chemotherapy variable may represent not only drug-related pulmonary toxicity but also disease stage, treatment intensity, cumulative cycles, combination with immunotherapy, and the clinical trajectory of patients requiring multiple lines of therapy. The third-center finding is therefore better interpreted as a signal of treatment burden than as proof that chemotherapy independently causes ILD. Future analyses with detailed drug names, cumulative exposure, number of cycles, combination regimens, and treatment sequence will be required to separate direct drug effects from treatment-intensity confounding.

Inflammatory activation was the third major domain and remained independently associated with ILD. Abnormal CRP and neutrophil measures were more frequent among patients who developed ILD, and the composite inflammatory abnormality retained independent information in the multivariable model. These markers are intentionally interpreted as warning signals rather than diagnostic biomarkers. CRP and neutrophil abnormalities may accompany infection, tumor-related inflammation, tissue injury, glucocorticoid exposure, or other systemic processes. Their value in the present model lies in identifying a patient whose inflammatory state has changed in the setting of systemic treatment, thereby lowering the threshold for respiratory reassessment and imaging when other clinical risk factors are present.

Comorbidity provided an additional host-susceptibility component. Although its adjusted association was borderline, the direction of effect remained clinically consistent with reduced physiologic reserve increasing vulnerability to pulmonary injury. The variable intentionally captured overall chronic disease burden rather than one specific pulmonary diagnosis. Cardiovascular disease, diabetes, renal impairment, chronic pulmonary conditions, and previous infection may affect treatment tolerance through different mechanisms. All eight ILD cases at the third independent center had at least one comorbidity, which supports the clinical concept but cannot establish an independent effect given the small event count.

The four-factor integer score translated these clinical observations into a simple risk-stratification tool. The AUC was 0.771 in the development cohort and 0.756 in the independent external validation cohort, indicating moderate discrimination with little loss of performance after transport to another hospital. This stability is more informative than maximizing the development-center AUC through additional variables or complex weighting. The score was deliberately constructed from variables that can be obtained from routine medical records and interpreted at the bedside. Its external performance suggests that the selected domains capture a reproducible risk signal despite differences in patient characteristics and treatment practice between centers.

The observed risk gradient further supports the clinical usefulness of the score. ILD incidence increased from 3.44% in the low-risk group to 29.38% in the high-risk group in the development cohort, and from 3.64% to 25.84% in the formal external validation cohort. Thus, a complication occurring in fewer than one in ten patients overall was enriched to approximately one in four to one in three patients in the highest-risk stratum. At a threshold of at least 2 points, sensitivity and negative predictive value were high in both cohorts, whereas specificity and positive predictive value were more modest. This pattern is appropriate for a screening and monitoring tool: the score is better suited to identifying patients who merit intensified surveillance than to determining which patient already has ILD.

A practical clinical workflow can therefore be based on monitoring intensity rather than therapeutic exclusion. Before treatment, smoking history and comorbidity can be recorded as baseline host-risk features. Planned immunotherapy contributes a treatment-exposure signal, while inflammatory abnormalities arising before or during treatment add a dynamic clinical warning. Patients accumulating multiple factors could undergo more systematic assessment of new cough or dyspnea, resting and exertional oxygen saturation, and interval inflammatory changes, with a lower threshold for chest computed tomography when abnormalities emerge[30]. Importantly, a high score alone should not trigger a diagnosis of ILD or automatic discontinuation of an otherwise effective anticancer regimen. Once pulmonary abnormalities are suspected, infection, tumor progression, cardiogenic causes, radiation-related injury, and other differential diagnoses remain essential considerations[31,32].

The third independent center and the 2026 temporal cohort provide complementary but more limited information. At the third center, the direction of the risk-strata gradient was preserved, but discrimination was lower and the number of ILD events was small. These findings are most appropriately considered exploratory evidence of transportability rather than a second formal external validation. The 2026 temporal cohort contained only three ILD events and substantial missingness in smoking history; consequently, a reliable four-factor temporal performance estimate could not be obtained. Keeping these cohorts separate from the formal external validation prevents overstatement of precision and preserves the distinction between confirmatory and supportive evidence.

This study has several strengths. It included patient-level data from three independent tertiary hospitals and preserved a clear hierarchy of model development, formal external validation, third-center transportability assessment, and temporal follow-up. Duplicate admissions and overlapping records

were resolved at the patient level, reducing the risk of counting the same individual more than once. The final score is deliberately parsimonious and clinically interpretable, and the comparable AUCs in development and formal external validation argue against substantial overfitting. The study also examined ILD across real-world systemic treatment rather than restricting the question to a single anticancer drug, improving applicability to multimodal care.

Several limitations should be acknowledged. The retrospective design resulted in missingness and heterogeneous documentation; smoking history was unavailable for 22.5% of the development cohort, so the four-factor model relied on complete cases. Smoking was recorded as a binary lifetime history rather than by pack-years or cessation status. Centralized blinded HRCT review was not performed, and ILD pattern or severity may have varied among centers. Treatment categories overlapped and did not fully capture specific drugs, cumulative dose, cycles, or treatment sequence. Inflammatory abnormalities were based on routine clinical measurements and are not specific for ILD. Finally, the third independent center and temporal cohort contained few events, limiting the precision of exploratory validation. Future prospective studies should standardize smoking exposure, imaging, lung-function measures, dynamic inflammatory markers, treatment sequence, and time to ILD onset, while evaluating whether score-guided surveillance improves clinical net benefit.

Conclusions

ILD during systemic treatment for lung cancer appears to arise from the interaction of host susceptibility, treatment exposure, and inflammatory activation rather than from a single clinical factor. Smoking history, immunotherapy exposure, and inflammatory abnormality were independently associated with ILD in the development cohort, while comorbidity provided additional host-related information. A simple four-factor integer score showed moderate and stable discrimination in formal independent external validation and identified a substantially higher-risk group for whom intensified respiratory monitoring may be appropriate. The score is intended to support pretreatment and early-treatment risk stratification and should complement, not replace, clinical assessment, chest imaging, exclusion of alternative diagnoses, and specialist judgment.

Declarations

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Jiangnan University Medical Center (Approval No. 2025-Y-121), which also granted a waiver of informed consent for all participating centers. A waiver of informed consent was granted by the committee, given the retrospective nature of this analysis and the use of data that did not include any individual-level personal information. The study design and reporting were performed in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

De-identified study data may be made available from the corresponding author on reasonable request, subject to ethics and institutional data-management requirements.

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Figures

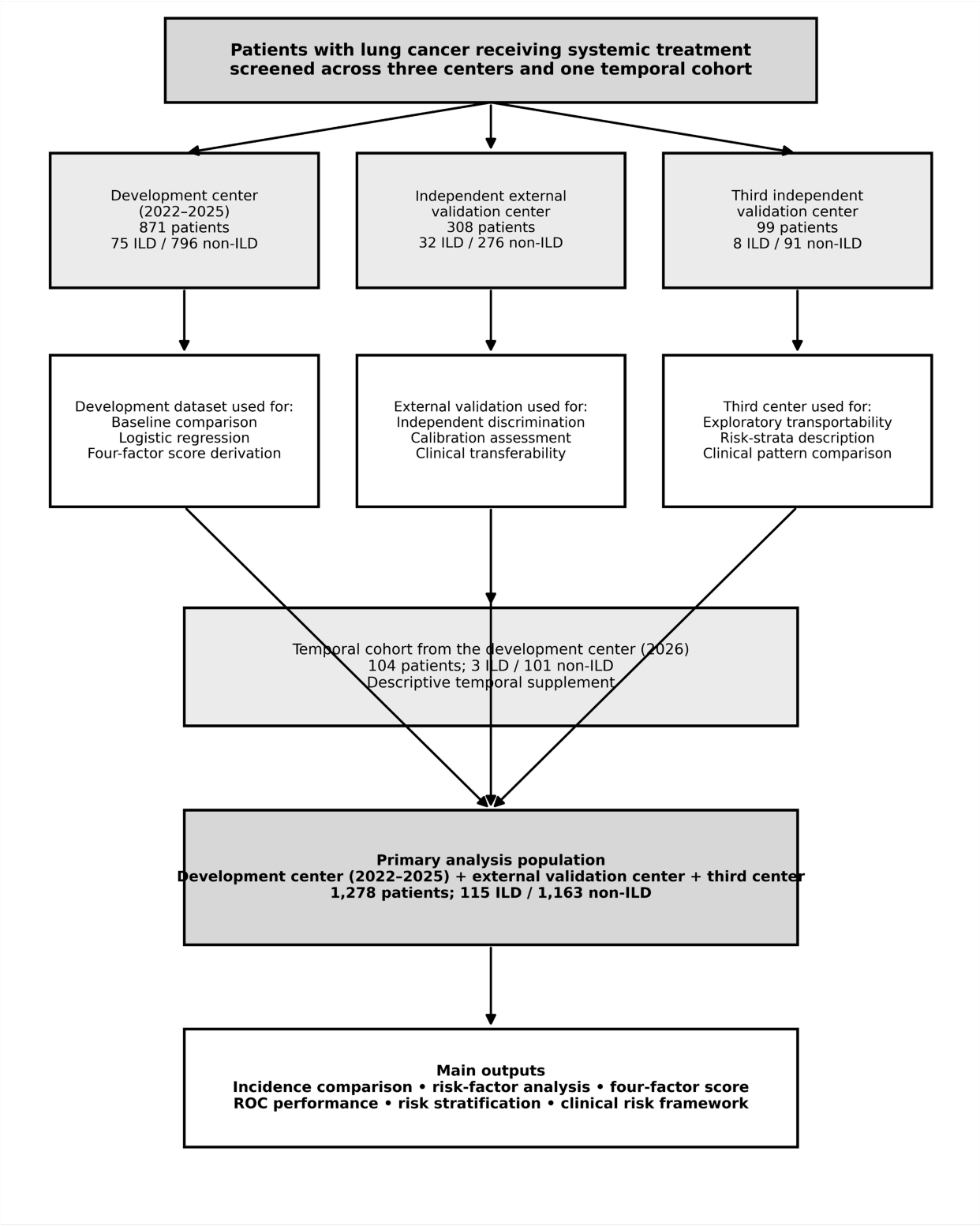


Figure 1

Study flowchart. The 2022–2025 development cohort was used for model development, the second center for formal independent external validation, the third center for exploratory transportability assessment, and the 2026 development-center cohort for temporal description.

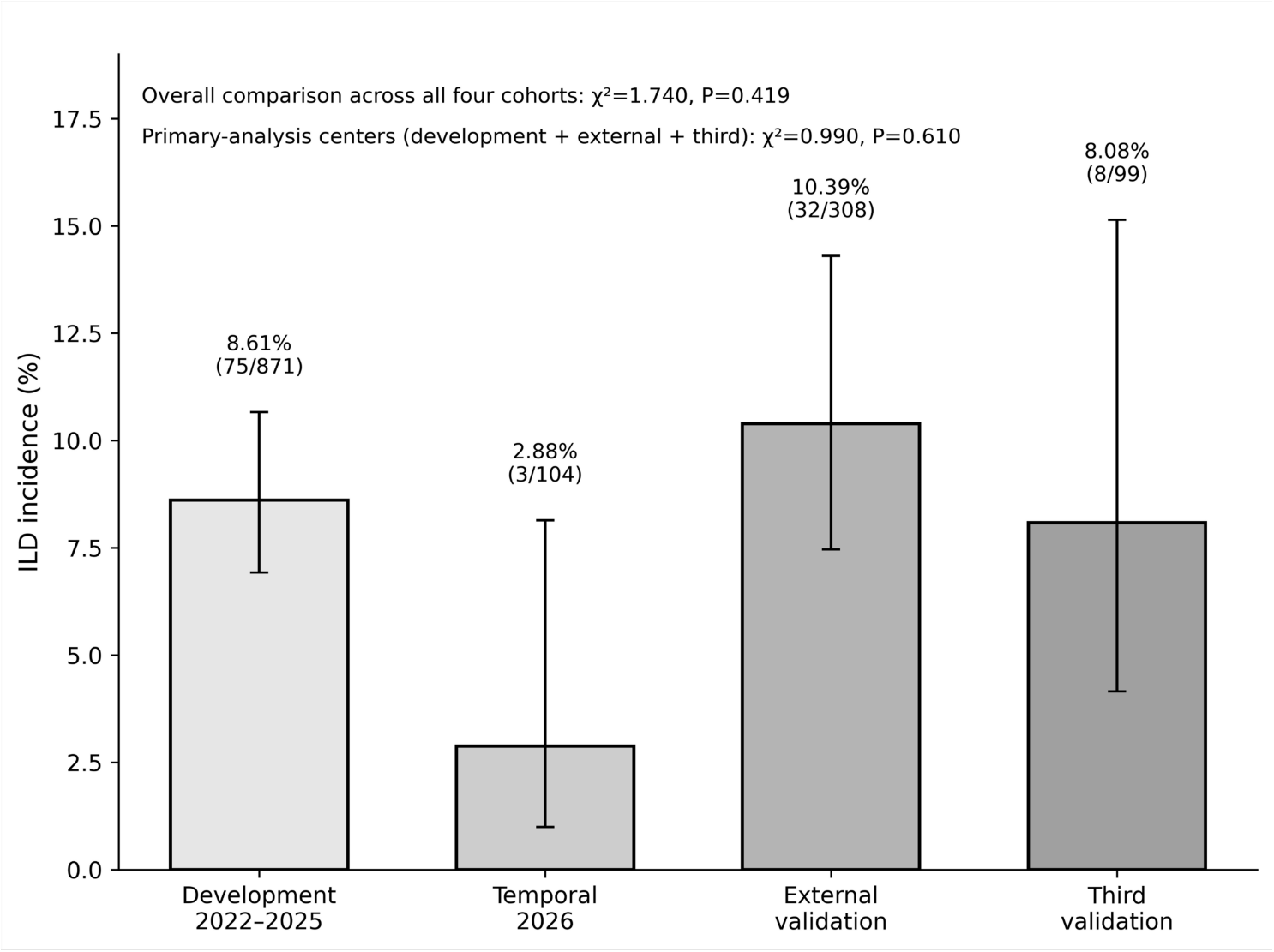


Figure 2

ILD incidence across the three primary-analysis centers. Error bars indicate 95% confidence intervals; χ^2=0.990, P=0.610.

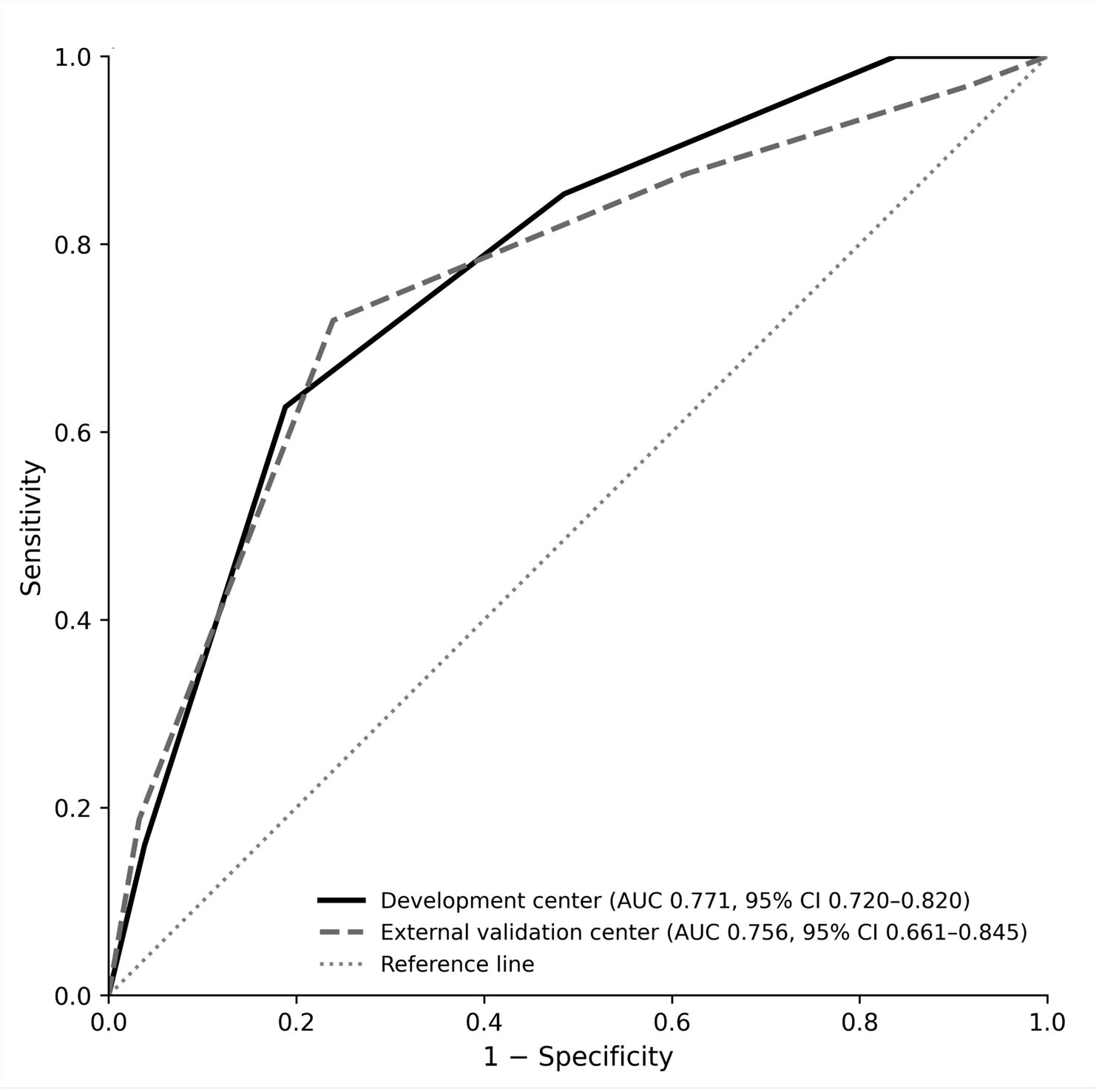


Figure 3

ROC curves of the four-factor integer score in the development and formal external validation cohorts. AUCs were 0.771 and 0.756, respectively.

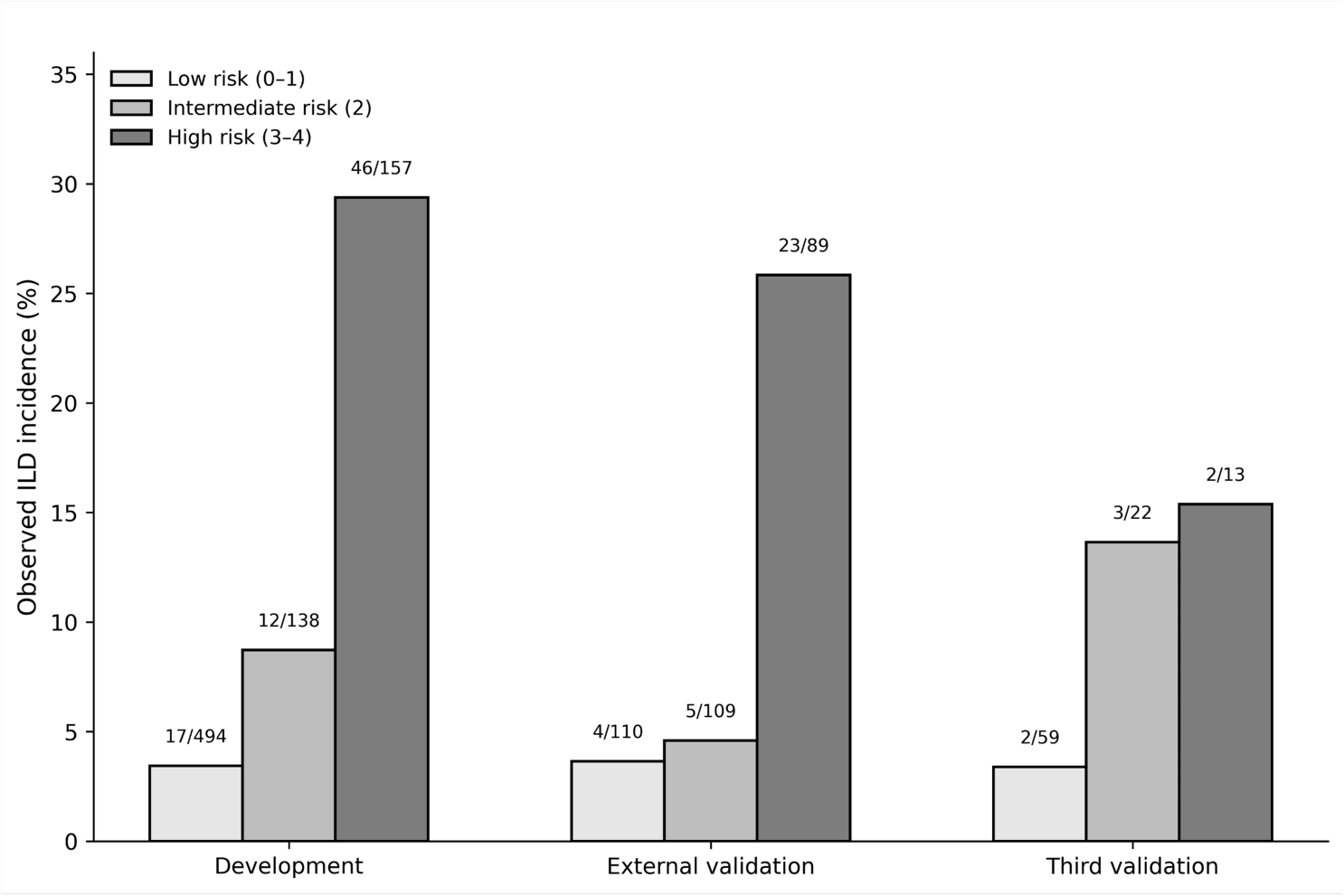


Figure 4

Observed ILD incidence across four-factor risk strata. Low risk=0–1 point, intermediate risk=2 points, and high risk=3–4 points.

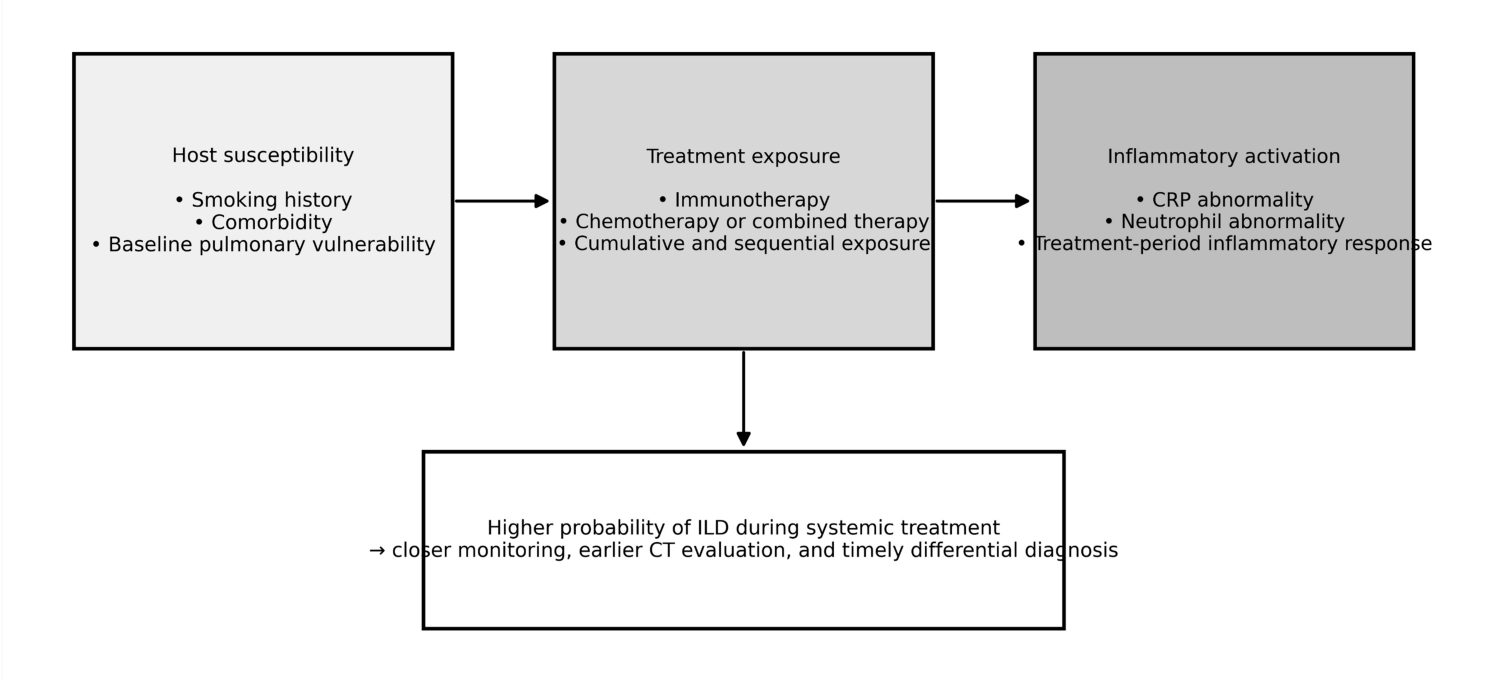


Figure 5

Clinical risk framework for ILD during systemic treatment of lung cancer. The four score components are organized within broader clinical domains: smoking history and comorbidity represent host susceptibility, immunotherapy represents treatment exposure, and inflammatory abnormality represents inflammatory activation. The score is intended for monitoring stratification and does not replace clinical diagnosis of ILD.