Pulmonary Journal Club September 2026 (Articles from August 2026)

Presented by
Dr. Ying-Chun Lo, Associate Professor of Laboratory Medicine and Pathology
Mayo Clinic, Rochester, MN

Articles for Discussion

(1) Biopsies Can Predict Lung Adenocarcinoma IASLC Grade: A New Proposal and Grading Pitfalls
JTO Clin Res Rep. 2026 Jun 5;7(8):101032.

Introduction:

- The IASLC grading system for resected invasive lung adenocarcinoma provides robust prognostic stratification for recurrence risk and overall survival.
- However, most patients present at advanced stages, where only small biopsy samples are available, leaving no established prognostic tool for such cases.
- The authors propose a practical biopsy-based grading method for pulmonary adenocarcinoma.

Methods:

- The authors analyzed 267 paired biopsies and resections.
- Two biopsy grading (bxG) models were tested:
    1. Model 1: Based on the predominant pattern-grade 1 (lepidic), grade 2 (acinar/papillary), grade 3 (solid/micropapillary/complex glandular).
    2. Model 2: Any percentage of high-grade patterns classified as grade 3, regardless of predominance.
- BxG 1 and 2 are defined as predominant patterns as described.For analysis, grades 1 and 2 were combined (G1-2), and grade 3 was considered a separate category.
- Diagnostic performance was assessed using resections as the reference standard. Interobserver reliability was evaluated, and discrepant cases were reviewed.

Results:

- Model 1 achieved 79.8% accuracy (sensitivity 57%, specificity 98.6%, positive predictive value [PPV] 97.2%, negative predictive value 73.5%, area under the curve 0.78).
- Model 2 performed better, with 88.4% accuracy (sensitivity 83.5%, specificity 92.5%, PPV 90.2%, negative predictive value 87.1%, area under the curve 0.89), and was used for further analysis.
- Discrepancies (n = 21) were primarily due to sampling limitations and artifacts, such as tangential sectioning.
- Adjusting for these factors improved interobserver agreement from moderate to almost perfect.

Conclusion:

- Biopsy grading using the presence of any high-grade pattern correlates well with IASLC -based resection grading.

- Although bxG1 to 2 biopsies may underestimate tumor grade, bxG3 biopsies demonstrate more than 90% specificity and PPV for predicting G3 resections, supporting their potential utility as a clinical prognostic marker.

(2) Baseline Tumor Proliferation and Ki-67 Are Associated With Pathological Response to Neoadjuvant Chemoimmunotherapy in Non–Small Cell Lung Cancer
Mod Pathol. 2026 Aug;39(8):101028.

Introduction:

- Heterogeneity in the pathological response to neoadjuvant chemoimmunotherapy underscores the need for predictive biomarkers in resectable non-small cell lung cancer (NSCLC).
- This study identified baseline molecular features-particularly tumor proliferation signatures-associated with pathological response.

Methods:

- Two retrospective cohorts (test, n = 81; validation, n = 107) of patients with NSCLC who received neoadjuvant chemoimmunotherapy were analyzed.
- Bulk RNA sequencing was performed on baseline biopsies from the test cohort, with immunohistochemistry (IHC) for PD-L1 and Ki-67 in both cohorts.
- Outcomes included major pathological response (MPR), pathological complete response (pCR), and event-free survival.

Results:

- In the test cohort, transcriptomic analysis showed that responders had significant upregulation of proliferation-related genes (eg, TP63, SOX2, NTRK2, and HMGA2) and activation of proliferation signatures (eg, chromosomal instability signature and core embryonic stem cell-like module), without activation of canonical immune-inflamed pathways. PD-L1 expression had limited predictive value (area under the curves [AUCs], 0.56-0.59 for MPR and 0.52-0.54 for pCR).
- In contrast, proliferation markers demonstrated higher performance: MKI67 messenger RNA predicted both MPR and pCR with an AUC of 0.71, and the Ki-67 IHC index yielded AUCs of 0.71 for MPR and 0.64 for pCR. The predictive value of the Ki-67 IHC index was validated in the independent cohort, with AUCs of 0.74 for MPR and 0.70 for pCR, and this association was generally consistent across squamous cell carcinoma and adenocarcinoma.
- A Ki-67 index ≥50% was significantly correlated with improved event-free survival in both cohorts (both Ps < .05).

Conclusion:

- These findings indicate baseline tumor proliferation, particularly MKI67/Ki-67, as predictors of pathological response in NSCLC patients receiving neoadjuvant chemoimmunotherapy, supporting its potential clinical utility for patient selection.

(3) YAP1 Defines an Emergent, Plastic Population of Relapsed SCLC
J Thorac Oncol. 2026 Aug;21(8):103730.

Introduction:

- SCLC is an aggressive neuroendocrine malignancy characterized by rapid onset of chemoresistance and poor clinical outcomes.
- Transcriptional heterogeneity among treatment-naive SCLC tumors underlies four transcriptional subtypes, each with distinct clinical vulnerabilities.
- Though previously hypothesized to delineate a distinct subtype, expression of YAP1 is largely absent from treatment-naive, pure SCLC.

Methods:

- To characterize relapsed SCLC, circulating tumor DNA, circulating tumor cells, and core needle biopsies from patients with SCLC and preclinical models following resistance to standard-of-care therapies were analyzed.

Results:

- In contrast to treatment-naive SCLC, these analyses reveal an emergent YAP1-positive cell population that coincides with treatment resistance.
- These YAP1-positive cells exhibit characteristics of drug-tolerant persister cells, including senescence, stemness, and plasticity, as YAP1-positive cells largely abandon features characteristic of SCLC to adopt those of large cell neuroendocrine carcinoma.
- As a result of this SCLC-like to large cell neuroendocrine carcinoma-like evolution, YAP1-positive cells lack several clinically relevant SCLC surface targets (i.e., DLL3, SEZ6) but are enriched for others (i.e., B7-H3, TROP2).

Conclusion:

- The authors propose a model where YAP1-expressing cells emerge with SCLC treatment resistance and characterize a tenacious subpopulation capable of diverging from the treatment-naive lineage and adopting features to evade therapeutic response.

(4) Subphenotypes of pneumonia defined by pulmonary histopathological features
Am J Respir Crit Care Med. 2026 Aug 1;212(8):1778-1792.

Introduction:

- Establishing subphenotypes of pneumonia based on host biology will be a step toward using host-directed therapies (to complement microbe-directed therapies) more rationally and precisely.
- Pneumonia is a pulmonary pathophysiology, but histopathological changes within the lungs have not been leveraged for subphenotyping.

Objective:

- To determine whether pneumonia includes distinct subphenotypes based on pulmonary histopathology.

Methods:

- The authors scored 20 histopathology features (eg, type 2 cell hyperplasia or necrosis) across rapid autopsy lung samples from 276 elderly participants with pneumonia.
- Statistical analyses were used to define associations among histopathological features, and clustering segregated participants into groups of similar histopathologies.
- Lung leukocytes were quantified using multispectral immunofluorescence.
- Lung samples from mice with varied infections were similarly examined to assess generalizability of findings and utility of experimental models.

Results:

- Participants with pneumonia clustered into 7 subphenotypes with distinct histopathology signatures.
- Some histopathological features tended to associate with others, and each of the leukocytes measured (including macrophages, neutrophils, T cells, and B cells) associated with select histology features and pulmonary pathology subphenotypes.
- Corollary subphenotypes were observed in mouse models, although some histology features observed in human lungs were never observed in mice.

Conclusion:

- By illuminating a spectrum of histopathologies and discriminating discrete subphenotypes of pneumonia, these studies provide a framework that may prove useful for developing and testing host-directed therapies for subsets of pneumonia patients.

At a Glance Commentary Scientific Knowledge on the Subject: Distinguishing subphenotypes of critical illnesses including pneumonia, ARDS, and sepsis is being pursued as a promising step towards optimizing application of host-directed therapies. Pneumonia is a pulmonary pathophysiology, making lung-specific data especially meaningful for establishing subphenotypes. While pneumonia associates with multiple different pathologic features in the lung, whether pneumonia subphenotypes can be distinguished by segregating sets of pulmonary histopathology features has yet to be directly addressed.What This Study Adds to the Field: Using unbiased machine learning to interrogate pathological assessments of lung tissues from people who died with pneumonia, seven different patterns of pulmonary pathology are discriminated. These pathological subphenotypes involve different types of immune cells in the lungs, and they can be partially captured with mouse models of lower -respiratory infection. Recognition of distinct pulmonary pathology subphenotypes of pneumonia suggests new opportunities for associating discriminatory biomarkers, defining underlying mechanisms, and testing responses to therapies.

Articles for Notation – Neoplastic

Pulmonary Neuroendocrine Tumor Artificial Intelligence—Assisted Prediction of Postoperative Recurrence From Tumor Biopsy Specimens

Mod Pathol. 2026 Aug;39(8):101027.

The current World Health Organization (WHO) (2021) classification of lung neuroendocrine tumors (LNETs) into typical carcinoids (TC) and atypical carcinoids (AC) relies on resection material and is not applicable to small biopsies. However, accurate risk stratification at the preoperative stage remains clinically important.

In this study, we developed an artificial intelligence (AI) model to predict postoperative recurrence in LNET patients directly from hematoxylin and eosin (H&E)-stained tissue fragments, including diagnostic biopsies, independent of the WHO classification. A multiscale vision transformer was trained and evaluated to predict disease recurrence following curative resection using a population-based cohort of pathologically confirmed stage I to III patients.

H&E slides of tissue microarrays (TMAs) from 452 LNET patients (TC, 414; AC, 38; nonrecurrence, 381; and recurrence, 71) were included. For external validation, an independent TMA cohort of 120 surgically treated LNETs (TC, 91; AC, 29; nonrecurrence, 109; and recurrence, 11) was used. To evaluate clinical applicability, 93 routine preoperative biopsies (TC, 80; AC, 13; nonrecurrence, 76; and recurrence, 17) were analyzed. The AI model demonstrated robust cross-cohort performance with balanced accuracy of 0.79 to 0.89 and area under the curve of 0.84 to 0.95. Despite few recurrence cases, the model achieved high sensitivity (0.82-0.94), reliably identifying high-risk patients. Specificity was 0.70 to 0.85, and negative predictive value was consistently 0.98 across all data sets, enabling confident recognition of low-risk patients.

Overall, the AI model outperformed the WHO-based recurrence prediction, correctly identifying 91 of 99 (92%) versus 31 of 99 (31%) high-risk cases. Performance improvements were statistically significant in the TMA cohorts (Wilcoxon signed-rank test; $P < .05$). This is the first AI-based approach capable of predicting recurrence in LNETs using only H&E-stained biopsies. These findings support AI-driven histopathological assessment as a complementary tool to improve preoperative risk stratification and guide clinical management of LNET patients.

ERBB2-Activating Mutations and Co-Occurring Genomic Alterations Contribute to Disease Heterogeneity in Patients With ERBB2-Mutant Lung Cancer

J Thorac Oncol. 2026 Aug;21(8):103708.

Introduction: ERBB2 mutations occur in 1% to 4% of all NSCLCs. Trastuzumab-deruxtecan and the novel ERBB2 tyrosine kinase inhibitors zongertinib and sevabertinib are approved by the Food and Drug Administration for the treatment of metastatic ERBB2-mutant NSCLC based on data from tumors harboring tyrosine kinase domain (TKD) mutations. The clinico-genomic characteristics of NSCLC tumors with ERBB2 mutations beyond the TKD remain largely unexplored.

Methods: Patients with NSCLC with oncogenic ERBB2 mutations included in two independent cohorts (American Association for Cancer Research Project GENIE database and the U.S.-based deidentified Flatiron Health-Foundation Medicine advanced NSCLC Clinico-Genomic Database [FH]) were studied. The clinico-genomic characteristics of patients with tumors harboring TKD, extracellular domain (ECD), or transmembrane domain (TMD)-juxtamembrane domain (JMD) ERBB2 mutations were compared, and clinical outcomes with chemoimmunotherapy were evaluated.

Results: A total of 483 patients (GENIE [Genomics Evidence Neoplasia Information Exchange] cohort) and 286 patients (FH cohort) with ERBB2-mutant NSCLC were included. In both cohorts, most patients had tumors harboring TKD (75% and 71%), followed by ECD (18% and 24%) and TMD-JMD mutations (7% and 5%). In both cohorts, male patients ($p < 0.05$), patients with squamous NSCLC tumors ($p = 0.0001$ and $p = 0.0002$), and patients with a smoking history ($p = 0.01$ and $p < 0.0001$) were more likely to have ECD-mutant tumors. In the GENIE cohort with detailed genomic information available, ECD- versus TKD-mutant tumors had a higher median tumor mutation burden ($p < 0.0001$) and higher rates of co-mutations in EGFR ($p < 0.0001$), KRAS ($p < 0.0001$), STK11 ($p < 0.0001$), KEAP1 ($p < 0.0001$), and SMARCA4 ($p < 0.0001$). TMD-JMD-mutant tumors had high rates of PIK3CA (24%) and RBM10 (18%) co-mutations. In the FH cohort with detailed outcome data available, among patients with advanced ERBB2-mutant NSCLC treated with first-line chemoimmunotherapy, those with ECD-mutant tumors had longer 12-month progression-free survival compared with those with TKD mutations (35% versus 18%; hazard ratio, 0.72; confidence interval, 0.54-0.94, $p = 0.026$). This difference persisted in a multivariate Cox regression model accounting for other variables.

Conclusion: NSCLCs harboring ECD-ERBB2 mutations are associated with a unique clinico-genomic phenotype and improved outcomes with first-line chemoimmunotherapy. These findings have implications for optimizing treatment strategies in this disease.

Enrichment of SMARCA4 mutations in lung carcinomas presenting as cancer of unknown primary

Lung Cancer. 2026 Aug:218:109502.

Objectives: Identifying the primary tumor in cancer of unknown primary (CUP) remains a major clinical challenge. While WGS-based tissue-of-origin (TOO) prediction has improved diagnostic precision, its use is constrained by cost and availability. We investigated whether a low-complexity surrogate, combining SMARCA4 mutations and smoking history, can identify a lung cancer origin in CUP (CUP-Lung).

Methods: We retrospectively identified 305 provisional CUP cases from two Dutch CUP referral centers (2022-2025). Integration of whole-genome sequencing (WGS)-based TOO prediction with clinicopathological data identified 58 patients (18.9%) with CUP-Lung. Associations between SMARCA4 mutations, smoking history, and CUP-Lung were assessed using comparative and regression analyses.

Results: SMARCA4 mutations were present in 36.2% of CUP-Lung cases, significantly higher than in the overall CUP cohort (10.7%) and TCGA lung cancer datasets (6-8%). CUP-Lung cases had higher tumor mutational burden (median 21.5 vs. 12.6 mut/Mb, $p < 0.001$) and enriched smoking-related mutational signatures ($p < 0.001$). Smoking history was reported in 87.9% of cases. Smoking history (OR 4.9, 95% CI 2.2-10.9, $p < 0.001$) and SMARCA4 mutation (OR 10.3, 95% CI 4.5-23.8, $p < 0.001$) independently predicted CUP-Lung, together conferring a 76.0% probability of lung origin. No statistical differences were found between cases with and without detectable pulmonary involvement.

Conclusion: Combined smoking history and SMARCA4 mutations support lung cancer classification even in the absence of detectable pulmonary involvement enabling organ-directed treatment when WGS is unavailable.

Genome-wide copy number analysis identifies AKT as a novel therapeutic target in pleural mesothelioma

Lung Cancer. 2026 Aug:218:109512.

Purpose: Targeting aberrantly activated kinases in pleural mesothelioma (PM) is a promising therapeutic strategy. To identify potential candidates, we characterized recurrent chromosomal gains in PM and subsequently evaluated the specific inhibition of kinases that were activated by amplification and/or overexpression.

Methods: 42 primary PM were screened for chromosomal alterations using OncoScan technology and AKT expression was assessed using immunohistochemistry. The impact of Ipatasertib (pan-AKT inhibitor) and Sapanisertib (mTOR inhibitor) on cell survival, apoptosis induction, AKT/mTOR signaling, glycolysis was investigated in cell lines and primary cells. Preclinical anti-tumor efficacy was further assessed in a PDX model selected for AKT and mTOR expression.

Results: OncoScan profiling identified eleven regions of significant chromosomal gains. Among them, 14q32.33 and 19q13.2 gains affected AKT1 and AKT2, members of the AKT serine/threonine protein kinase family. AKT1 protein was expressed in 66 % (60/91), AKT2 in 80 % (73/91) and AKT3 in 94 % (86/91) PM. 57 % PM co-expressed AKT1/AKT2/AKT3. Treatment with Ipatasertib impaired cell viability in PM cell lines and induced apoptosis. Combined treatment with Ipatasertib and Sapanisertib had a synergistic cytotoxic effect in all three cell lines and primary cells from two PM patients, even in Cisplatin-resistant cells. We also noted an improved response to the combination in a PDX model. Mechanistically, the combined

treatment acted synergistically to inactivate AKT/mTOR downstream signaling, suppress glycolysis, and trigger ATP depletion.

Conclusions: Our study demonstrates recurrent activation of AKT kinases by copy number gains and upregulated expression in PM. Pharmacological AKT and mTOR inhibition is a promising therapeutic alternative for mesothelioma.

Limited predictive value of PD-L1 TPS for pathological response in NSCLC is not attributable to interobserver variability

Lung Cancer. 2026 Aug:218:109510.

Background: PD-L1 tumor proportion score (TPS) is used to guide immunotherapy in non-small cell lung cancer (NSCLC), yet its ability to predict pathological response in the neoadjuvant setting remains limited.

Methods: Thirty pathologists from 11 countries independently assessed PD-L1 TPS in pre-treatment biopsies and residual viable tumor (RVT) in matched resection specimens after neoadjuvant chemoimmunotherapy in 30 digitized cases from the ReGraDE (regression grading in Germany) study. Interobserver agreement was evaluated using intraclass correlation coefficients (ICC) and Fleiss' kappa. Associations between TPS and RVT were analyzed using Pearson correlation, and correlations derived from single-rater and averaged TPS were compared using the Williams test.

Results: Interobserver agreement was moderate for both TPS and RVT (ICC = 0.74, 95% CI 0.60-0.87, and ICC = 0.74, 95% CI 0.62-0.85, respectively) and became near-perfect when mean scores per case were calculated across observers (ICC = 0.99, for both). However, TPS remained poorly correlated with RVT for both single-rater assessment ($r = -0.17$, $p = 0.38$) and averaged TPS ($r = -0.16$, $p = 0.39$) with no significant difference between these approaches ($p = 0.96$). Differences in interpretation thresholds were observed particularly in borderline cases around the 1% TPS cut-off and in distinguishing 0% from minimal RVT, but did not account for the lack of association between TPS and RVT. Systematic differences were observed depending on individual professional experience, particularly in borderline cases.

Conclusion: Interobserver variability does not explain the limited predictive value of PD-L1 TPS in the neoadjuvant setting, suggesting an intrinsic limitation of the biomarker.

Prevalence and characteristics of NTRK fusions in 25,946 patients with non-small cell lung cancer

Lung Cancer. 2026 Aug:218:109514.

Background: Functional NTRK1-2-3 fusions are rare, tumor-agnostic, targetable alterations. Accurate detection is essential to ensure optimal treatment. We investigated the prevalence of NTRK fusions in two cohorts of patients with NSCLC.

Methods: The Lungscape Cohort, comprising of tissue microarrays from 1703 resected stage I-III NSCLC cases (52% adenocarcinomas, 40% squamous cell carcinomas), was screened using pan-TRK immunohistochemistry (IHC, EPR17341, Ventana) and positive cases were confirmed by next-generation sequencing (NGS). The NGS Cohort of 24,243 NSCLC was screened by NGS within the European Lungscape Center Network and positive cases were retested using IHC. Functional fusions were defined as in-frame fusions containing an intact NTRK kinase domain.

Results: In the Lungscape Cohort of resected NSCLC panTRK IHC was found positive in 69 (60squamous cell carcinoma, 5 adenocarcinoma, 4 large cell carcinoma) of 1703 patients (4%, median H-score: 37, range 5-200). Sixty-five samples underwent confirmatory testing by NGS and one fusion was found, which after manual review was classified as non-functional. The NGS Cohort yielded 11 fusions in tumors of 24,243 patients of which eight were functional (0.03%; 5 in NTRK1, 1 in NTRK2 and 2 in NTRK3) and five were retested using IHC (median H score 200, range 50-300). Of the three non-functional fusions, two were IHC negative and 1 weakly positive (H-score 30).

Conclusion: Pan-TRK IHC has a false-positive rate of ~4%, particularly in squamous cell carcinomas, underscoring the need for confirmatory NGS to validate IHC findings and assess fusion functionality. Functional NTRK1/2/3 fusions remain exceedingly rare in NSCLC, with a detection rate of 0.03% across our combined cohorts.

Prognostic impact of the 9th vs 8th TNM classification in small-cell lungcancer. a population-based study

Lung Cancer. 2026 Aug:218:109515.

Background: Small cell lung cancer (SCLC) is an aggressive malignancy with poor prognosis. The traditional limited and extensive-stage classification does not adequately capture disease heterogeneity. The tumor-node-metastasis (TNM) system has prognostic value in SCLC and is increasingly used, but the relevance of the 9th TNM edition in SCLC remains uncertain.

Materials and methods: This retrospective, population-based study included patients with pathologically confirmed SCLC treated at Karolinska University Hospital, Sweden, between 2008 and 2022. Patients were reclassified according to the 8th and 9th TNM classifications. Survival was analyzed using Kaplan-Meier estimates and Cox proportional hazards regression.

Results: The cohort encompassed 893 patients with a median age of 68 years; 58% were female. Stage migration between the 8th and 9th TNM classifications occurred in 49 (5.5%) patients and consisted exclusively of downstaging. Subdivision of mediastinal nodal disease showed a clear prognostic separation, with a median overall survival (mOS) of 11.7 months for N2a and 6.5 months for N2b (HR 1.8, 95% CI 1.4-2.2,$p < 0.001$); outcomes for N2b were comparable to N3 disease. Metastatic subclassification showed a modest but statistically significant prognostic difference, with mOS of 6.9 months for M1c1 and 4.8 months for M1c2 (HR 1.3, 95% CI 1.1-1.5,$p = 0.008$). Both N2 and M1c subclassifications showed independent associations with survival in multivariate analysis.

Conclusions: The 9th TNM classification provided additional prognostic stratification in SCLC. Refined nodal and metastatic subclassifications showed clear separation between groups. while stage migration was limited and had modest impact on stage-specific survival.

Refining N1 classification: prognostic validation of N1 subdivision in resected non-small cell lung cancer

Lung Cancer. 2026 Aug:218:109474.

Introduction: Accurate evaluation of nodal metastasis is essential for staging and prognostication of non-small cell lung cancer (NSCLC). The 9th edition of the TNM classification subdivided N2 into single station(N2a) and multi-station(N2b) involvement, however, pathological N1 disease remains a unified category. This study aimed to evaluate whether subdivision of N1 into N1a and N1b provides meaningful prognostic discrimination.

Methods: Patients who underwent surgery for NSCLC between 2005 and 2022 at the Asan Medical Center were retrospectively analyzed. Patients were categorized into N1a (n = 811), N1b (n = 215), N2a (n = 797), and N2b (n = 507). Overall survival (OS) and Recurrence-free survival (RFS) were compared using Kaplan-Meier estimates and multivariable Cox models. Prognostic performance of the 9th TNM model (N1, N2a, N2b) was evaluated against a proposed model incorporating N1 subdivision using Akaike information criterion (AIC), R2, and Harrell's C-index.

Results: A total of 11,047 patients (1,026 with pN1 and 1,304 with pN2) were included. Adjuvant therapy use, extracapsular extension, and extent of nodal involvement increased with advancing N stage. Subdividing N1 showed clear prognostic separation: 5-year OS was 66.2% for N1a vs 53.0% for N1b, and 5-year RFS was 49.6% vs 29.9%, respectively. In multivariable analysis, N1b independently increased mortality risk (HR 1.56 vs N1a), and its outcomes were comparable to N2a. Model incorporating N1 subdivision showed improved prognostic performance, with lower AIC, slightly higher corrected R^2, and a modestly higher C-index.

Conclusions: Subdividing N1 into single- and multi-station provides meaningful prognostic discrimination in resected NSCLC and provides complementary prognostic information beyond the current TNM staging.

Articles for Notation - Non-Neoplastic

Single-cell sequencing unveils a profibrotic macrophage and infiltrating monocyte niche in the bronchoalveolar lavage of patients with chronic obstructive pulmonary disease

Am J Respir Crit Care Med. 2026 Aug 1;212(8):1710-1720.

Rationale: Chronic obstructive pulmonary disease (COPD) is characterized by global immune dysregulation. The most abundant immune cells in the distal airways and alveolar compartments are macrophages and lymphocytes. These cells have been poorly characterized in human airways due to their plasticity and numerous subtypes. There is a marked scarcity of information in the COPD airway, limiting our understanding of the inflammatory process that drives COPD progression.

Objectives: The primary aim of this study was to characterize the differences in composition of the immune cells in the alveolar space of patients with COPD versus healthy controls and the relation with severity of airflow limitation at a single-cell resolution.

Methods: Individuals with and without COPD were recruited. All participants underwent bronchoscopy, where a single-cell suspension was created from the retrieved bronchoalveolar lavage and then sequenced using single-cell RNA sequencing technology. Full pulmonary function tests, thoracic computed tomography (CT), and xenon-129 hyperpolarized gas magnetic resonance imaging (MRI) were performed on participants for phenotyping.

Measurements and main results: From 17 participants, a total of 97 254 cells were recovered, with 52 840 cells belonging to the COPD group (N = 10). The COPD immune landscape was perturbed and characterized by an expansion of non-typable macrophages, increased neutrophils and classical monocytes, and significant changes in regulatory and double-negative T lymphocytes compared to controls (FDR < 0.05). The percentage of these cells was further altered with increasing GOLD (Global Initiative for Chronic Obstructive Lung Disease) severity stages. The percentage of double-negative T cells in BAL was significantly related to airway luminal area on CT, whereas that of regulatory T cells was inversely related to MRI gas transfer and DLCO of COPD patients.

Conclusions: The immune cell transcriptomic profile of COPD BAL reveals global immune dysregulation, with increased abundance of proinflammatory and profibrotic macrophages, monocytes, and neutrophils, potentially driving airway remodeling. Regulatory T cells may play a significant role in gas exchange perturbations of COPD.

Letters, Brief Communications, Case Reports

(1) **Brief Report: Low Delta-Like Ligand 3 Expression and T-Cell Exhaustion Drive Resistance to Tarlatamab Combined With Anti–Programmed Cell Death Protein 1 in SCLC**
J Thorac Oncol. 2026 Aug;21(8):103693.

(2) Characterization of a rare EGFR resistance mutation in a lung cancer patient with a long response to osimertinib: case report
Lung Cancer. 2026 Aug:218:109489.

(3) HER2-targeting zongertinib shows early activity in untreated advanced HER2-mutant NSCLC
Cancer. 2026 Aug 1;132(15):e70489.

Reviews

(1) New biomarkers for antibody-drug conjugates in lung cancer the pathologist's perspective
Lung Cancer. 2026 Aug:218:109507.

(2) Intratumour, anatomical and temporal heterogeneity in mesothelioma
Thorax. 2026 Jul 15;81(8):796-805.