



Beyond airway obstruction: restrictive lung physiology as an independent risk factor for lung cancer in tuberculosis survivors

Sang Hoon Chun

Division of Medical Oncology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea

See Article on Page 721-730

Lung cancer remains the leading cause of cancer-related mortality worldwide. Over the past two decades, treatment of advanced lung adenocarcinoma has changed substantially. Targeted therapies against EGFR, ALK, ROS1, and RET, together with immune checkpoint inhibitors, have more than doubled median overall survival in metastatic disease. Nevertheless, outcomes in advanced-stage disease remain poor, and early detection, accurate risk stratification, and timely screening continue to provide the greatest opportunity for cure and improved survival.

In countries with a high historical burden of tuberculosis (TB), such as the Republic of Korea, clinicians face a distinct epidemiological challenge. Although active TB incidence has steadily declined, many survivors continue to live with chronic and often irreversible structural and functional sequelae of prior infection. These manifestations, collectively termed post-tuberculosis lung disease (PTLD), include parenchymal scarring, bronchovascular distortion, pleural thickening, and bronchiectasis [1]. Prior TB infection is consistently associated with increased lung cancer risk [2]; however, the subgroup of survivors at greatest risk for malignant transformation remains poorly defined because recovery after active TB varies substantially.

In the current issue of *The Korean Journal of Internal Medicine*, Lee et al. [3] address this question through a cohort analysis of 9,734 TB survivors from the Kangbuk Samsung Health Study (2011–2021), followed for a median of 12.3 years. Restrictive lung function, defined by spirometry as forced expiratory volume in 1 s/forced vital capacity (FEV¹/

FVC) ≥ 0.7 with FVC $< 80\%$ predicted, was independently associated with incident lung cancer (adjusted hazard ratio [aHR] 2.94, 95% confidence interval [CI] 1.00–8.65; $p = 0.050$). Obstructive lung function (FEV¹/FVC < 0.7), although strongly associated with lung cancer in unadjusted analysis (HR, 6.48), was no longer significant after adjustment for age and cumulative smoking exposure (aHR 2.29, 95% CI 0.51–10.26; $p = 0.279$), suggesting confounding by smoking.

These findings should be interpreted cautiously for two reasons. First, the lower bound of the 95% CI for restrictive lung function was exactly 1.00, and the p-value reached the conventional significance threshold, indicating statistical fragility and supporting interpretation as hypothesis-generating rather than definitive. Second, restrictive physiology defined by spirometry alone, without measurement of total lung capacity, approximates the preserved ratio impaired spirometry (PRISm) phenotype. However, the standard PRISm definition uses FEV¹ $< 80\%$ predicted with preserved FEV¹/FVC ratio rather than FVC $< 80\%$. PRISm is increasingly recognized as a phenotype associated with elevated all-cause and cardiovascular mortality [4]. Interpreting these findings within the PRISm framework clarifies the mechanistic ambiguity and aligns the study with a rapidly expanding literature.

Another mechanistic limitation is the absence of histological subtyping in the cancer registry. Classical scar carcinoma has historically been linked to peripheral adenocarcinoma, which also predominates among never-smoker lung cancers in Korea. Although the present cohort could not directly evaluate this association, the restrictive phenotype identified by Lee et al. [3] aligns more closely with adenocarcinoma

arising in fibrotic parenchyma than with smoking-related squamous histology. PTLD may therefore represent an infection-driven analogue of the fibrosis–cancer relationship observed in idiopathic pulmonary fibrosis (IPF), in which lung cancer incidence is approximately four- to sevenfold higher than in the general population [5]. Whether carcinogenic pathways in PTLD parallel those in IPF or follow distinct mycobacteria-related trajectories remains uncertain.

Despite these limitations, the study has important implications for the biology and clinical management of lung cancer in TB survivors. From a medical oncology perspective, the findings suggest pathophysiological pathways linking structural lung damage to oncogenesis that differ from those involved in chronic obstructive pulmonary disease (COPD). COPD is an independent lung cancer risk factor, even among never-smokers [6]; however, obstructive airway disease is primarily airway-centered and strongly associated with cigarette smoking. In contrast, the restrictive physiology observed in TB survivors more directly reflects parenchymal injury, persistent fibrotic remodeling, and scarring. Lee et al. [3] therefore suggest that, in post-TB sequelae, the fibrotic parenchymal microenvironment may contribute more directly to oncogenesis than airway-centered processes.

These findings provide clinical support for the longstanding concept of scar carcinoma [7]. Post-TB scar tissue is characterized by chronic low-grade inflammation, persistent cellular proliferation, and localized hypoxia. Aberrant wound healing sustains release of profibrotic and proinflammatory cytokines, including transforming growth factor- β , tumor necrosis factor- α , and interleukin-1 β , which promote myofibroblast activation and collagen deposition while inducing epithelial–mesenchymal transition, genomic instability, and DNA damage in adjacent epithelium. Hypoxia within fibrotic foci upregulates hypoxia-inducible factor-1 α , supporting angiogenesis, cellular survival, and metabolic reprogramming. Persistent mycobacterial antigens within granulomas may also produce chronic antigenic stimulation, contributing to a field-cancerization-like microenvironment extending beyond the scar itself.

The cumulative incidence curves for abnormal lung function diverged from those for normal lung function within the first 5 years of follow-up, suggesting that elevated risk is not restricted to the late post-treatment period. This early divergence supports initiating active surveillance soon after completion of TB therapy rather than delaying it until a remote post-cure interval.

The findings also have implications for lung cancer screening and risk stratification. Current guidelines, including the 2021 US Preventive Services Task Force recommendation (aged 50–80 years with ≥ 20 pack-years) [8] and the Korean National Lung Cancer Screening Program (aged 54–74 years with ≥ 30 pack-years), rely primarily on age and cumulative smoking exposure to determine eligibility for low-dose computed tomography. In TB-endemic regions such as Korea, however, 30–40% of lung cancers occur in never-smokers, particularly in female patients, leaving many patients outside current screening criteria. By demonstrating that restrictive lung function independently confers an approximately threefold increased risk of lung cancer in TB survivors, Lee et al. [3] identify screening spirometry as an accessible and objective biomarker that could be incorporated into risk-stratification models. TB survivors with restrictive ventilatory defects, including those with minimal smoking exposure, warrant heightened clinical suspicion. From a policy perspective, these findings support consideration of a distinct risk-eligible category for TB survivors with restrictive spirometric patterns who otherwise would not qualify for screening despite clinically meaningful cancer risk.

Several limitations warrant consideration. Despite a cohort of nearly 10,000 participants, only 22 lung cancer events occurred, reflecting the relatively young, health-screened population (mean age, 41.2 yr). Consequently, the wide confidence intervals require cautious interpretation. The cancer registry also lacked histological subtyping, precluding assessment of whether the scar–cancer association is stronger for adenocarcinoma, as prior evidence suggests. Restrictive physiology may arise from obesity, chest wall disease, or interstitial lung disease, and the absence of chest computed tomography (CT) data prevented direct attribution of the spirometric pattern to TB-induced parenchymal scarring. Spirometry also remains a relatively crude surrogate for PTLD severity. Quantitative high-resolution CT (HRCT) measures, such as fibrotic lung volume and traction bronchiectasis scoring, would more accurately characterize structural disease burden. Diffusing capacity for carbon monoxide (DLco), arguably the most sensitive functional marker of parenchymal injury in PTLD, was not evaluated. Pulmonary function testing incorporating DLco and static lung volumes would likely refine risk estimation. In addition, the cohort was predominantly male (65.4%), and only four lung cancer events occurred in female patients, leaving the relationship between PTLD-related restrictive physiology and lung cancer in

Korean female patients largely unresolved.

Future studies should include prospective multicenter cohorts of older TB survivors, the population in whom lung cancer incidence is concentrated. Combining quantitative HRCT with spirometry may allow direct correlation between fibrotic burden and subsequent cancer development, while molecular or inflammatory biomarkers in sputum or blood could further improve risk prediction in TB survivors with restrictive physiology.

Lee et al. [3] advance understanding of post-TB oncology by identifying restrictive lung physiology as an independent risk factor for lung cancer, thereby shifting clinical attention from airway obstruction toward the oncogenic potential of parenchymal scarring. These findings emphasize that the clinical course of patients with TB does not end with microbiological cure; long-term surveillance incorporating simple lung function testing may identify a subgroup in whom early lung cancer detection is most likely to improve outcomes.

REFERENCES

1. Seo W, Kim HW, Kim JS, Min J. Long term management of people with post-tuberculosis lung disease. *Korean J Intern Med* 2024;39:7-24.
2. Hwang SY, Kim JY, Lee HS, et al. Pulmonary tuberculosis and risk of lung cancer: a systematic review and meta-analysis. *J Clin Med* 2022;11:765.
3. Lee YG, Gil HI, Seo D, et al. Restrictive lung function and smoking increase lung cancer risk in tuberculosis survivors: a cohort study. *Korean J Intern Med* 2026;41:721-730.
4. Wan ES, Fortis S, Regan EA, et al. Longitudinal phenotypes and mortality in preserved ratio impaired spirometry in the COPDGene study. *Am J Respir Crit Care Med* 2018;198:1397-1405.
5. Karamitsakos T, Tzilas V, Tringidou R, et al. Lung cancer in patients with idiopathic pulmonary fibrosis. *Pulm Pharmacol Ther* 2017;45:1-10.
6. Park HY, Kang D, Shin SH, et al. Chronic obstructive pulmonary disease and lung cancer incidence in never smokers: a cohort study. *Thorax* 2020;75:506-509.
7. Yu YY, Pinsky PF, Caporaso NE, et al. Lung cancer risk following detection of pulmonary scarring by chest radiography in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. *Arch Intern Med* 2008;168:2326-2332; discussion 2332.
8. US Preventive Services Task Force; Krist AH, Davidson KW, et al. Screening for lung cancer: US Preventive Services Task Force recommendation statement. *JAMA* 2021;325:962-970.

Received : May 26, 2026

Accepted : May 29, 2026

Correspondence to

Sang Hoon Chun, M.D., Ph.D.
Division of Medical Oncology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06591, Korea
Tel: +82-32-340-7140
E-mail: rowett@catholic.ac.kr
<https://orcid.org/0000-0002-5847-7317>

Conflicts of interest

The author discloses no conflicts.

Funding

None