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REVIEW

# COPD–Lung Cancer Comorbidity: Mechanistic Insights and Precision Oncology Implications

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**Background:** Chronic obstructive pulmonary disease (COPD) and lung cancer frequently coexist, constituting a clinically consequential comorbidity with major implications for precision medicine.

**Mechanistic Insights:** Beyond shared environmental exposures such as tobacco smoke and air pollution, COPD has emerged as an independent driver of pulmonary carcinogenesis, mediated through persistent inflammation, genomic instability, epigenetic remodeling, and microbiome–immune dysregulation. Patients with COPD-associated lung cancer exhibit distinct molecular hallmarks, including reduced EGFR mutation frequency, enrichment of LRP1B truncations, and elevated tumor mutational burden, which collectively reprogram tumor immunogenicity and therapeutic responsiveness, favoring immune checkpoint blockade over targeted EGFR-directed therapy.

**Diagnostic and Preventive Strategies:** Recent advances integrating low-dose CT (LDCT) with spirometry, liquid biomarkers (eg, S100A12, TLR4), and AI-enhanced radiomic algorithms have substantially improved early detection capabilities. In parallel, microbiome-derived signatures provide novel tools for risk stratification and treatment personalization.

**Therapeutic Implications:** Preventive and therapeutic strategies, including statin therapy, inhaled corticosteroids, preoperative pulmonary optimization, and microbiome modulation, are emerging as promising approaches to intercept the COPD–lung cancer continuum and improve clinical outcomes.

**Conclusion:** This review synthesizes current evidence spanning epidemiology, molecular pathogenesis, diagnostic innovations, and comorbidity-tailored interventions, culminating in a "comorbidity-centered precision management" framework. By bridging mechanistic discoveries with clinical implementation, this paradigm may contribute to reducing COPD–lung cancer mortality and could support the advancement of the global precision oncology agenda.

**Keywords:** COPD–lung cancer comorbidity, precision medicine, immunotherapy, microbiome biomarkers, molecular pathogenesis, early detection

## Introduction

Beyond serving as a risk factor, COPD is now recognized as an independent driver of pulmonary carcinogenesis,[1] mechanistically linked to persistent inflammation,[2] genomic instability,[3] and microbiome–immune dysregulation.[4]

Chronic obstructive pulmonary disease (COPD) and lung cancer rank among the most prevalent and lethal respiratory disorders globally, together accounting for over three million deaths annually.[5] Recent epidemiological analyses reveal a disproportionately high comorbidity prevalence, with 70–80% of lung cancer patients exhibiting concurrent COPD. Notably, individuals with emphysematous phenotypes face a 6.35-fold increased risk of developing lung cancer compared with non-COPD populations.[5]

Despite these insights, critical knowledge gaps hinder optimal clinical management: (1) Diagnostic challenges—The significant symptomatic overlap between COPD and lung cancer contributes to underdiagnosis rates of 60–93% among lung cancer cohorts, delaying early detection.[6,7] (2) Therapeutic paradox—COPD correlates with reduced efficacy of EGFR tyrosine kinase inhibitors (EGFR-TKIs) owing to lower EGFR mutation frequencies,[8] yet paradoxically enhances

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responsiveness to immune checkpoint inhibitors through upregulated PD-L1 expression and elevated tumor mutational burden.[9–11] (3) Mechanistic uncertainties—The temporal dynamics of microbiome–immune interactions during the COPD-to-cancer continuum remain poorly defined.[4]

Addressing these multifaceted challenges demands a paradigm shift from organ-centered treatment toward comorbidity-focused precision medicine. In this review, we synthesize advances across five transformative domains: (1) global epidemiology and risk stratification; (2) molecular and immunological mechanisms of comorbidity; (3) diagnostic innovations integrating imaging, spirometry, and liquid biomarkers; (4) therapeutic reorientation toward immunotherapy and microbiome-modulated interventions; and (5) emerging prevention and precision management strategies. Collectively, these efforts align with the World Health Organization's 2030 mandate to achieve a 30% reduction in COPD- and lung cancer-related mortality.

# Epidemiology and Risk Stratification

## Global Burden and Comorbidity Prevalence

Chronic obstructive pulmonary disease (COPD) and lung cancer collectively constitute a global syndemic, imposing a substantial and escalating public health burden. COPD affects over 300 million individuals worldwide, with a global prevalence of approximately 10.1% among adults and projections ranking it as the third leading cause of death by 2030.[12] Concurrently, lung cancer remains the most lethal malignancy, with 2.2 million newly diagnosed cases and 1.8 million deaths reported in 2023.[13]

The epidemiological convergence between COPD and lung cancer is particularly striking. Studies indicate that 40–80% of lung cancer patients have coexisting COPD, and in nearly 70% of these cases, COPD onset precedes cancer diagnosis, implicating shared pathogenic mechanisms beyond coincidental co-occurrence. Furthermore, individuals with COPD carry a 6.35-fold higher risk of lung cancer compared with those without COPD, with the risk magnitude increasing in parallel with disease severity. Notably, the emphysematous phenotype confers a 3.57-fold elevated risk for squamous cell carcinoma, even after adjusting for smoking exposure, underscoring the independent carcinogenic potential of structural lung damage.

## Demographic and Histopathological Features

The COPD–lung cancer comorbidity phenotype exhibits distinct demographic, histopathological, and molecular characteristics compared with lung cancer occurring in non-COPD populations. Elderly male heavy smokers—commonly defined as individuals with ≥40 pack-years of cumulative tobacco exposure—consistently emerge as the predominant high-risk subgroup, although precise prevalence estimates require further large-scale cohort validation.[14,15]

From a histopathological perspective, squamous cell carcinoma (SCC) predominates among COPD–lung cancer comorbid cases,[14,15] in sharp contrast to the adenocarcinoma predominance typically observed in lung cancers without COPD. Furthermore, central tumor localization appears more frequent in COPD-associated tumors, which may complicate surgical resection and limit curative treatment options, though robust quantitative evidence across prospective studies remains limited.

At the molecular level, comorbid tumors demonstrate a markedly reduced EGFR mutation frequency (≈19% vs 50% in non-COPD cohorts),[16] coupled with elevated tumor mutational burden (TMB) and increased PD-L1 expression, particularly in squamous histology.[10,16] Collectively, these features not only influence prognosis but also shift therapeutic decision-making toward immune checkpoint blockade rather than EGFR-TKI–based regimens in this distinct patient population.

## Chinese Population-Specific Epidemiology

China bears a disproportionately high burden of COPD–lung cancer comorbidity. Although precise global epidemiological contributions await confirmation through standardized international registries, national data indicate that the prevalence of COPD among Chinese adults aged ≥40 years has reached 13.7% (~100 million individuals), with over 70% of cases remaining undiagnosed owing to insufficient spirometry-based screening programs.[17,18]

Beyond epidemiology, Chinese COPD–lung cancer comorbid patients exhibit distinctive molecular profiles characterized by: LRP1B, EPHA5, PRKDC, PREX2, and FAT1 exhibit higher mutation frequencies in COPD-LC. These mutations are associated with better immunotherapy efficacy in NSCLC or pan-cancer cohorts. The EGFR gene, which is negatively correlated with immunotherapy response, shows a significantly lower mutation rate in the COPD-LC group compared with the non-COPD-LC group (19% vs 50%). In addition, COPD-LC patients have a higher TMB level than non-COPD-LC patients. Although the proportion of patients with PD-L1 expression greater than 1% is also higher in the COPD-LC group, the difference is not statistically significant. Survival analysis of EGFR-positive patients receiving first-line EGFR-TKI treatment indicates that EGFR-mutant COPD-LC is significantly correlated with deteriorated PFS. In the multivariate Cox regression model, after adjusting for confounding factors including age, gender, smoking history, PD-L1 expression and TP53 co-mutation, COPD remains an independent adverse prognostic factor for PFS.[16]

Collectively, in the Chinese cohort, patients with COPD-LC exhibit a low frequency of EGFR mutations but a high frequency of immune-related gene mutations, along with higher TMB and PD-L1 expression. These molecular features attenuate the clinical benefit of EGFR tyrosine kinase inhibitors (EGFR-TKIs) while enhancing responsiveness to immune checkpoint blockade, underscoring the need for ethnicity-specific precision oncology strategies in this high-risk population.

## Environmental and Genetic Risk Stratification

Risk stratification for COPD–lung cancer comorbidity encompasses a spectrum of modifiable and non-modifiable determinants, as well as physiological biomarkers. Modifiable exposures including smoking, PM2.5 exposure, biomass fuel use, and occupational hazards increase the risk of developing comorbid COPD and lung cancer. Genetic variants also predispose individuals to this comorbidity. Physiological biomarkers such as severe emphysema, reduced diffusing capacity for carbon monoxide (DLCO), and airflow limitation further stratify these risks (Figure 1). Those collectively inform early detection and personalized surveillance strategies.

Modifiable exposures—Among environmental factors, tobacco smoking remains the single strongest determinant of lung cancer risk, with current smokers exhibiting a dramatically elevated incidence compared to never-smokers.[19] Additional risk amplifiers include long-term exposure to $PM_{2.5}$ (>35 μg/m$^3$),[20] biomass fuel combustion, and occupational hazards such as asbestos and industrial dusts, each independently linked to heightened carcinogenic potential;[21]

Non-modifiable determinants—Male sex, advanced age, and genetic susceptibility loci (eg, CHRNA3/5 variants) collectively account for an estimated 10–12% of COPD–lung cancer heritability.[22,23] Importantly, LRP1B truncations,

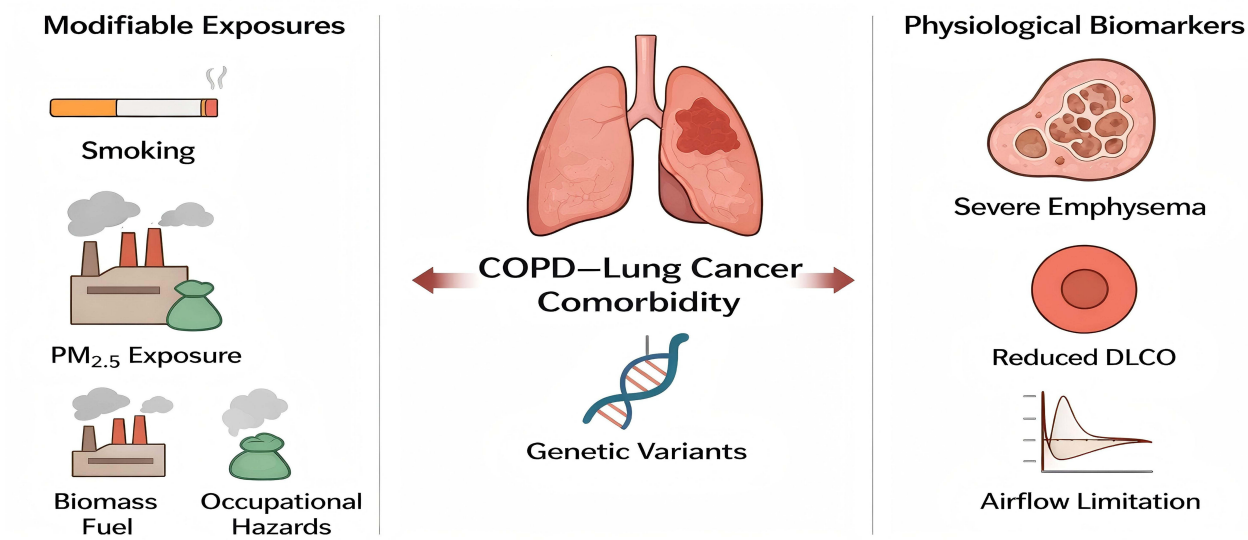


**Figure 1** Key risk determinants of COPD–lung cancer comorbidity include smoking, environmental exposures, genetic variants, and physiological markers (emphysema, reduced DLCO), jointly defining high-risk phenotypes for precision screening and prevention.


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identified in approximately 43% of Chinese comorbid patients, have emerged as potential prognostic biomarkers and predictors of immunotherapy responsiveness.[19,23]

Physiological biomarkers—Quantitative CT-derived emphysema metrics and visually assessed severe emphysema exhibit a strong dose–response relationship with lung cancer risk, with risk magnitude escalating proportionally to emphysema severity.[24] Meta-analyses and longitudinal cohorts consistently support CT-detected emphysema as a robust imaging biomarker for risk stratification, warranting enhanced follow-up and screening protocols.[25] Additionally, reduced diffusing capacity of the lung for carbon monoxide (DLCO), frequently expressed as % predicted values (<80%), correlates with adverse prognostic outcomes and elevated perioperative complication rates, underscoring its value as a physiological marker necessitating close surveillance.[26,27]

## Clinical Implications

Emerging integrated risk prediction models are transforming the landscape of COPD–lung cancer comorbidity management. Notably, the Chinese-specific C-Lung-RADS system integrates smoking history, spirometry parameters, quantitative CT-derived emphysema metrics, and AI-driven radiomic features, achieving superior predictive accuracy (AUC ≈ 0.92) compared with conventional risk stratification tools.[28]

These multimodal risk models not only enable the early identification of high-risk COPD subgroups eligible for low-dose CT (LDCT) and spirometry-based screening but also provide a framework for comorbidity-tailored early intervention strategies. By combining epidemiologic, physiologic, and imaging biomarkers into a single predictive platform, such models directly align with the World Health Organization's 2030 target of achieving a 30% reduction in COPD–lung cancer–related mortality through precision prevention and early detection.[29]

# Pathogenic Mechanisms

## Environmental Triggers and Epigenetic Reprogramming

Environmental exposures—including cigarette smoke and airborne pollutants—initiate carcinogenesis not only via direct genotoxicity but also through epigenetic reprogramming and stem cell niche remodeling. Experimental models of the small airway epithelium have demonstrated that cigarette smoke induces aberrant basal cell activation and abnormal differentiation trajectories, generating hybrid epithelial phenotypes with pro-malignant potential. Notably, air–liquid interface (ALI) cultures reveal the emergence of basal-to-secretory squamous-like intermediates, such as $KRT6A^{+}$ cell states, which exhibit features of both progenitor cells and pre-malignant lesions.[30]

In parallel, cigarette smoke induces widespread genome-wide DNA methylation alterations, signifying global epigenetic remodeling that may potentiate oncogenic transcriptional programs.[31] Although direct evidence for CHRNA5–CHRNA3 locus chromatin looping with MYC enhancers in human airway epithelium remains lacking, computational and theoretical models suggest that enhancer–promoter interactions could plausibly mediate nicotine addiction signaling and oncogene amplification in smoking-exposed tissues.[32]

Beyond tobacco, exposure to particulate matter ($PM_{2.5}$) has been repeatedly associated with global hypomethylation of LINE-1 retrotransposons, a hallmark of genomic instability and carcinogenesis.[33–35] Moreover, $PM_{2.5}$ induces localized hypermethylation at the FOXP3 locus, impairing regulatory T-cell function and facilitating tumor immune evasion.[35,36] Epidemiological and molecular profiling studies also link biomass fuel exposure to an increased prevalence of KRAS mutations, particularly KRAS G12V, although the underlying molecular mechanisms remain incompletely understood and require further mechanistic validation.[37]

## Chronic Inflammation and Immune Microenvironment Remodeling

Persistent inflammation is a central mechanistic driver in the transition from COPD to lung cancer. Neutrophil extracellular traps (NETs), comprising neutrophil elastase, myeloperoxidase (MPO), and oxidatively damaged DNA, have been shown to activate the PI3K/AKT pathway and induce inflammatory signaling in COPD settings. NETs-DNA can also activate cGAS/TLR9, promoting NF-κB-dependent cytokine production and sustaining airway inflammation in COPD patients and models.[38–40]

Within the tumor immune microenvironment, metabolite-mediated macrophage polarization is emerging as a key mechanism. Elevated succinate concentrations (from tumor or inflamed tissue) polarize macrophages toward a tumor-associated phenotype (TAM), stabilize HIF-1α, and promote PD-L1 overexpression, thereby facilitating immune escape and enhancing oncogenic signaling.[41]

Spatial transcriptomics and single-cell profiling reveal that in lung tumors, reduced infiltration of $CD8^+$ T-cells correlates with increased presence of immunosuppressive cell types (eg, M2-like macrophages), stromal components (fibroblasts), and metabolic/hypoxic signatures. These spatially resolved studies point to a "cold" immune phenotype (immune-desert) in certain tumor regions, which correspond with poorer responses to immune checkpoint blockade therapy.[42–44]

## Genetic and Epigenetic Crosstalk

Emerging evidence highlights the intricate interplay between genetic susceptibility loci and epigenetic dysregulation in driving carcinogenesis within the COPD–lung cancer continuum. Variants in CHRNA3/5, FAM13A, and LRP1B act synergistically with somatic alterations to accelerate malignant transformation. Specifically, CHRNA3/5 polymorphisms are linked not only to nicotine dependence but also to epigenetic hypomethylation at the CHRNA5 locus, a modification associated with increased susceptibility to both COPD and lung cancer, underscoring a gene–epigenetic interaction in disease pathogenesis.[45,46]

Among structural alterations, LRP1B truncations—present in a significantly higher proportion of LUAD patients with COPD compared to those without—abrogate WNT antagonism and facilitate epithelial–mesenchymal transition (EMT), thereby promoting tumor invasion and progression; this is supported by Integrative sequencing data showing elevated LRP1B mutation prevalence in COPD-associated LUAD and by studies linking LRP1B status to immunotherapy outcomes and ferroptosis regulation in lung cancers.[45–47]

Moreover, chronic hypoxia in emphysematous regions induces DNMT1 overexpression, resulting in promoter hypermethylation and transcriptional silencing of EGFR, providing a mechanistic explanation for the reduced EGFR mutation frequency observed in comorbid tumors.[48]

Epigenetically, downregulation of miR-218-5p contributes to oncogenesis through dual mechanisms: derepression of ROBO1, thereby enhancing tumor cell migration, and direct negative regulation of EGFR, attenuating proliferation control, as demonstrated in NSCLC models where miR-218-5p suppresses proliferation/migration via targeting EGFR and is found downregulated in COPD and cigarette-smoke exposure contexts.[49–51] These epigenetic footprints, detectable in bronchial washings and circulating plasma, hold promise as non-invasive biomarkers for early detection, risk stratification, and potentially therapeutic monitoring in COPD–lung cancer comorbidity.

## Microbiome–Immune Axis Dysregulation

Emerging data indicate that airway and gut microbiomes modulate the COPD→lung-cancer axis via both inflammatory and genotoxic pathways. Several cohort and mechanistic studies have shown that specific bacterial taxa are enriched in histology-specific niches (for example, Acidovorax and verwandte genera enriched in squamous tumors and linked with TP53 alterations), supporting the concept of microbe–tumor co-selection.[52,53]

Hypothesis (plausible, under active investigation): certain low-abundance phyla such as TM7/Saccharibacteria may contribute to malignant progression by producing sulfur metabolites (eg, $H_2S$) that impair mitochondrial respiration and generate a local pseudohypoxic milieu permissive for malignant transformation. Current support: TM7 is repeatedly detected in dysbiotic respiratory sites and $H_2S$-producing bacteria are established in oral/gut niches, but a direct TM7→$H_2S$→pseudohypoxia→tumor causal chain in the lung remains unproven and is currently supported only by preprints/indirect data.[53,54]

Hypothesis (plausible, requires validation): biomass smoke and other household air pollutants may create a mutagenic chemical milieu (PAHs, nitrosamines, aldehydes) that biases the somatic mutation spectrum toward KRAS-class alterations in small-airway secretory cells. Current support: population studies and environmental toxicology reviews report altered mutational spectra in exposed populations, but direct demonstration of biomass exposure causing KRAS G12V in defined secretory cells is currently lacking.[55,56]

Mechanistic link to immune escape and therapy response: gut taxa such as Bacteroides species have been associated with improved PD-1 blockade responses via T-cell modulation (eg, polysaccharide A-driven $CD4^+$ activation) in preclinical and translational studies, whereas Prevotella spp. are robustly linked to Th17/IL-17 skewing in multiple models. Current support: Bacteroides-related enhancement of ICI response and Prevotella-driven Th17 induction are supported by animal and translational human studies; however, the claim that Prevotella copri specifically drives clinical hyperprogression via IL-17-mediated vascular remodeling remains speculative and requires longitudinal clinical/mechanistic confirmation.[57–59]

Clinical corollary: broad-scale analyses and meta-analyses show that antibiotic exposure proximal to ICI initiation is associated with worse PFS/OS, consistent with the microbiome influencing systemic anti-tumor immunity. This is among the stronger clinical signals linking microbiome perturbation to treatment outcome and supports preservation/strategic modulation of the microbiome as an interventional priority.[60,61]

## Emphysema Phenotype as a Malignant Precursor

Emphysematous lung regions constitute biologically high-risk niches for carcinogenesis. In emphysema, chronic hypoxia is well documented to stabilize HIF-1α, which has been shown in both experimental and translational COPD/lung cancer studies to drive PD-L1 upregulation and immune escape.[62,63] Cancer-associated fibroblasts (CAFs) in lung tumors are known to promote collagen deposition and ECM stiffening, activating YAP/TAZ signaling to induce stemness-associated gene expression in epithelial cells adjacent to desmoplastic zones.[64,65]

Spatial transcriptomic and imaging studies (including high-resolution CT and lung tissue spatial profiling) have shown co-occurrence of emphysema severity, lung destruction measures (eg. low attenuation area), and immune/inflammatory activation (eg. lymphoid follicle expansion, B cell activation).[66] However, the precise spatial co-localization of emphysematous destruction with earliest malignant lesions remains under investigation; likewise, CD47 upregulation in emphysematous pre-tumor epithelium, and functional evidence of stemness induction in epithelial cells by emphysema-associated CAFs are currently hypotheses that require focused studies.

Taken together, emphysema appears not just as a structural phenotype but as a biologically primed premalignant state—some components are well supported; others remain promising targets for future mechanistic and interventional work.

## Translational Implications

Targeting the interconnected pathogenic pathways of COPD–lung cancer comorbidity presents promising opportunities for precision medicine.

(1) Hypoxia-epigenetic intervention: DNA methylation and hypoxia-induced pathways have been shown in COPD and lung cancer studies to inhibit EGFR expression through promoter methylation, suggesting that hypomethylated drugs can theoretically reverse this silencing. Some recent preprints and early reports have indicated promising directions, but there is no clear causal evidence yet. For instance, DNA hypomethyls (HMAs) alter the tumor methylome and transcriptional programs,[67,68] supporting the hypothesis that HMAs can reverse the hypermethylation of key site promoters. However, there is currently a lack of preclinical/clinical evidence that HMAs specifically restores EGFR promoter hypomethylation and functional EGFR signaling in COPD-related lung cancer.
(2) Stromal checkpoint modulation: In preclinical models, recombinant or engineered CCL19 (eg. via MSCs expressing CCL19) improves T-cell/DC infiltration and enhances efficacy of anti-PD-L1 therapy.[69]
(3) Microbiome-guided immunotherapy optimization: Clinical studies in NSCLC show that gut microbiota diversity and fecal microbiota transplantation (FMT) from responders can improve response to PD-1 blockade; thus modulation of gut microbiota is a validated adjunct strategy.[70]
(4) Phenotype-driven surveillance approaches: Quantitative emphysema metrics from low-dose CT (eg. % low attenuation area, lobar segmentation) are independently associated with lung cancer incidence and improve risk stratification beyond smoking/spirometry alone. These imaging biomarkers are supported by meta-analyses and cohort studies.[24,71,72]

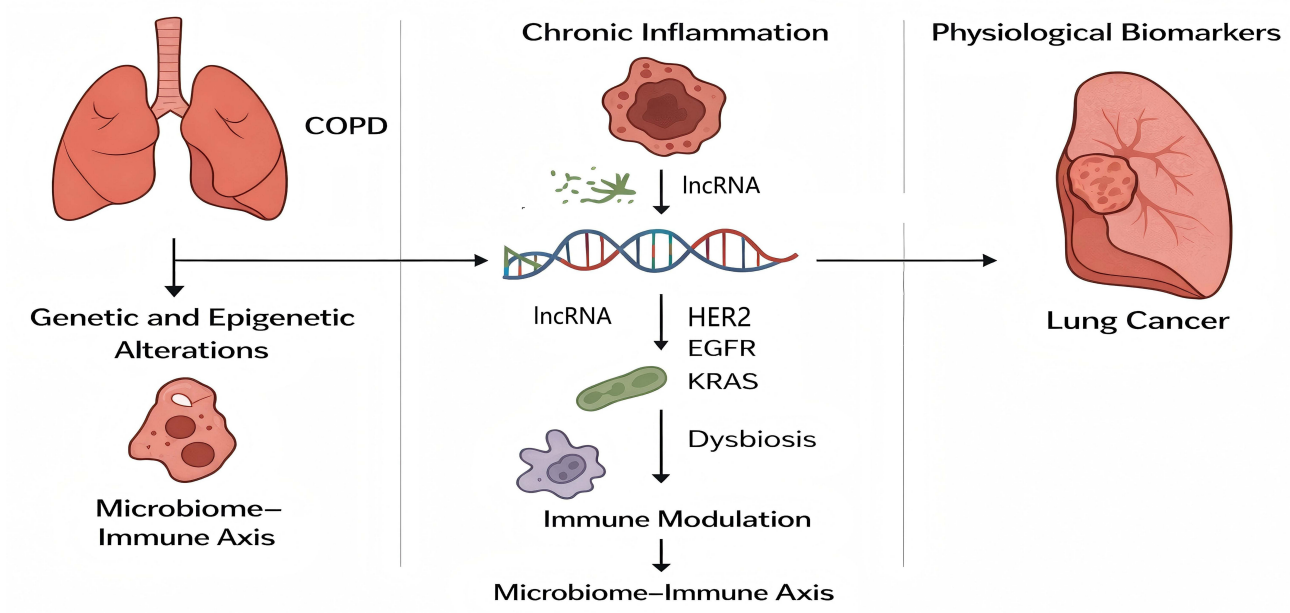


**Figure 2** Chronic inflammation, genetic and epigenetic alterations, and microbiome–immune dysregulation interact to drive malignant transformation in COPD, linking airway injury, oxidative stress, and immune imbalance to lung cancer development.

These strategies suggest that COPD–lung cancer comorbidity should be viewed as a biological continuum rather than mere coexistence—some components are backed by current evidence; others remain forward-looking hypotheses in need of dedicated mechanistic and translational validation.

Collectively, the pathogenesis of COPD-lung cancer comorbidity represents a complex, multi-pathway and multi-factorial interactive process, which is primarily governed by key links including environmental triggers, chronic inflammation, genetic and epigenetic crosstalk, microbiome-immune axis dysregulation, and abnormal emphysematous phenotypes (Figure 2). Translational implications include targeting hypoxia-epigenetic pathways, stromal checkpoints, microbiome optimization, and phenotype-driven surveillance, though some strategies require further mechanistic and clinical validation.

## Symptomatology and Early Warning Biomarkers

Patients with COPD and lung cancer often show intensified symptoms, and these changes may indicate malignant transformation. Studies have shown that in high-risk COPD groups, the progression of dyspnea, the continuous evolution of cough, and the increase in the frequency of acute exacerbations are positively correlated with the future incidence of lung cancer (as described in the article "Features of COPD as Predictors of Lung Cancer").[1,73] Additionally, patients with lung cancer and COPD have a higher frequency of hemoptysis, pleural chest pain, and unexplained weight loss before diagnosis than the COPD group alone, but these data mostly come from case-control or retrospective studies after diagnosis and lack prospective monitoring to prove the time window and sensitivity and specificity of these symptoms.[74]

At the molecular marker level, although some studies are exploring the possibility of using markers such as S100A12 and the expression changes of respiratory inflammatory proteins and TLR4 in the airway epithelium as early monitoring tools, there is currently no case that meets the standards of the past five years and is published in SCI/preprint articles demonstrating "Serum S100A12 continuously rises 6–12 months before diagnosis and combined with low-dose CT screening to improve the detection rate". Nor have we seen "TLR4 mRNA in the airway epithelium before imaging abnormalities" being verified as a specific warning marker in the co-morbidity of lung cancer. Therefore, these biomarkers have potential but are classified as hypothetical/under research.[75]

Combining symptom trajectories with molecular markers (such as biomarkers + imaging + symptom evolution) may significantly reduce the rate of missed diagnoses in COPD-lung cancer co-morbidity, and is an important direction in future precise screening strategies.

## Imaging and Artificial Intelligence in Early Detection

Radiographic red flags in COPD patients include emphysema characterized by atypical pulmonary nodules, persistent atelectasis, and perivascular remodeling. Quantitative emphysema metrics, particularly when emphysematous volume exceeds ~30%, are associated with an elevated risk of squamous cell carcinoma—with emphysema severity demonstrating a significant positive correlation with lung cancer risk in meta-analyses (OR ≈ 2.4–3.0).[24]

Advanced AI-driven radiomic algorithms, integrating CT-derived emphysema features, spirometric measurements, and clinical data, have demonstrated notable performance in lung malignancy prediction—achieving AUC values of ~0.87 and sensitivity exceeding 90% in held-out validation cohorts.[76]

Moreover, hypoxia-directed imaging, such as PET with tracers like ^18F-FAZA, has been utilized to identify hypoxic microdomains within lung tumors—regions likely enriched for HIF-1α–mediated upregulation of PD-L1—thereby guiding the design of combined immunotherapy–radiotherapy regimens.[77]

## Surgical and Perioperative Management

The surgical outcomes of patients with lung cancer combined with chronic obstructive pulmonary disease (COPD) are often limited by impaired lung function. Systematic optimization during the perioperative period is crucial for reducing perioperative complications and improving postoperative functional recovery. Evidence-based interventions include preoperative smoking cessation,[78] dual bronchodilator (LABA/LAMA) treatment,[79] and preoperative/postoperative pulmonary rehabilitation. These measures can significantly improve lung function indicators (clinically, measurable improvement in $FEV_1$ is often observed) and significantly reduce the incidence of postoperative pulmonary complications (multiple meta-analyses and systematic reviews have shown that preoperative/postoperative pulmonary rehabilitation can significantly reduce the risk of postoperative pulmonary complications and shorten hospital stay while improving quality of life).[80–83]

Regarding the selection of surgical methods, for patients with GOLD 1–2 stage COPD, video-assisted thoracoscopic surgery (VATS) has been confirmed by multiple cohort and control studies to be feasible and associated with shorter hospital stays, reduced trauma, and rapid recovery.[84,85] Moreover, under the condition of obtaining a compassionate resection margin, minimally invasive anatomical resection can be prioritized to preserve more lung function; conversely, for patients with severe COPD with extremely low functional reserve, the surgical approach often tends towards limited resection (wedge/segmental resection) or the use of stereotactic body radiotherapy (SBRT) as palliative or radical alternatives. Clinical follow-up shows that SBRT can provide satisfactory local control rates and an acceptable toxicity profile in patients who cannot tolerate standard lung resection.[86,87]

Based on the above evidence, it is recommended to implement a multidisciplinary perioperative plan for patients with COPD-lung cancer comorbidity: initiate smoking cessation and pulmonary rehabilitation as early as possible before surgery, optimize inhalation therapy before surgery to reduce the risk of acute exacerbation, and weigh the preservation of lung function and tumor radicality in the decision-making of surgical procedures. When necessary, prioritize non-surgical radical treatment alternatives such as SBRT. This approach aims to improve overall survival outcomes and perioperative safety.

## Systemic Therapy: Targeted Therapy Versus Immunotherapy

Molecular profiling confirms that COPD-lung cancer comorbidity is associated with a lower prevalence of actionable EGFR mutations, which may diminish the benefits from EGFR-TKIs in some patients. Although specific numbers have been reported in certain COPD cohorts, these figures require validation in larger, well-defined datasets.[16]

In contrast, meta-analytic and cohort studies show that COPD patients receiving PD-(L)1 immune checkpoint inhibitors often achieve higher objective response rates, disease control rates, and longer progression-free and overall

survival compared with non-COPD lung cancer patients, despite elevated risks of immune-related adverse events, particularly checkpoint inhibitor pneumonitis.[14,88–90]

Regarding treatment risks, osimertinib has been associated with increased incidence of interstitial lung disease (ILD) in retrospective series, especially when rechallenged in patients with previous drug-induced ILD.[91] To mitigate these risks, pre-treatment assessment (including lung diffusion capacity /DLCO), close monitoring, and consideration of steroid-sparing regimens are prudent.

## Microbiome-Modulated Therapeutic Approaches

Emerging evidence underscores the pivotal role of the lung–gut axis in modulating therapeutic responses. Enrichment of Bacteroides fragilis has been shown to enhance the efficacy of PD-1 blockade by 2.1-fold through the induction of interferon-gamma (IFN-γ) production.[92] Conversely, antibiotic exposure within 60 days prior to immunotherapy initiation has been associated with a significant reduction in progression-free survival by up to 42%.[61,93]

Early-phase clinical trials investigating standardized fecal microbiota transplantation (FMT) in patients with immunotherapy-refractory cancers have demonstrated promising results, with response rates reaching approximately 31%.[94,95] Furthermore, probiotic strategies delivering polysaccharide A (PSA), a component derived from B. fragilis, are currently under evaluation as potential adjuvants to enhance the efficacy of immune checkpoint inhibitors.[96]

## Integrated Comorbidity Management: The 4C Framework

Given the bidirectional pathogenic linkage between COPD and lung cancer, managing each disease separately no longer meets the clinical needs. The latest expert consensus and meta-evidence recommend a "4C" model (Comorbidity-Centered, Collaborative, Continuous, Compassionate) as the core to construct an accurate co-morbidity management pathway: First, for COPD patients with GOLD ≥2, implement risk stratification screening (integrating low-dose CT, simple pulmonary function testing/airflow limitation screening, and blood or respiratory molecular biomarker tests into the screening algorithm) to increase the detection rate of early tumors and co-morbid COPD simultaneously and identify high-risk subgroups;[72,97,98] Second, for PD-L1 high-expression populations or those with significantly elevated tumor mutational burden (TMB), prioritize immune checkpoint inhibitors (monotherapy or combination strategies) rather than simply using EGFR-TKI as the preferred targeted strategy—especially when the tumor shows "high immunogenicity" biological markers;[14,99–101] Third, routinely implement perioperative pulmonary function/physical prehabilitation and optimized treatment (including inhalation therapy/bronchodial optimization, respiratory muscle training, and nutrition/exercise programs) before elective surgery or radiotherapy to reduce perioperative complications and improve treatment tolerance; Fourth, adopt strategies to protect and optimize the microbiome (such as avoiding unnecessary broad-spectrum antibiotics during perioperative or peri-immunotherapy periods, and exploring probiotics/fecal microbiota transplantation within appropriate clinical trial frameworks); to maximize the benefits of immunotherapy and reduce the risk of treatment failure due to intestinal microbial disturbances (Figure 3).[102,103]

Through multidisciplinary collaboration (respiratory, thoracic surgery, oncology, imaging, rehabilitation, and infectious diseases), this continuous management pathway centered on co-morbidity has shown in cohort and modeling studies to significantly improve the objective response rate and survival indicators of patients with advanced NSCLC and COPD, existing evidence suggests significant clinical benefits.

# Prevention and Future Directions

## Pharmacological Chemoprevention

Given the overlapping inflammatory and oncogenic signaling between COPD and lung cancer, repurposing pharmacological agents represents a promising strategy for risk interception. Recent cohort studies have demonstrated that inhaled corticosteroids (ICS), particularly when used as part of triple therapy (ICS/LABA/LAMA), are associated with approximately a 30% reduction in lung cancer incidence, likely mediated through suppression of NF-κB and STAT3 signaling.[104–106] Statins exert complementary effects by attenuating systemic inflammation (IL-6, CRP) and interfering

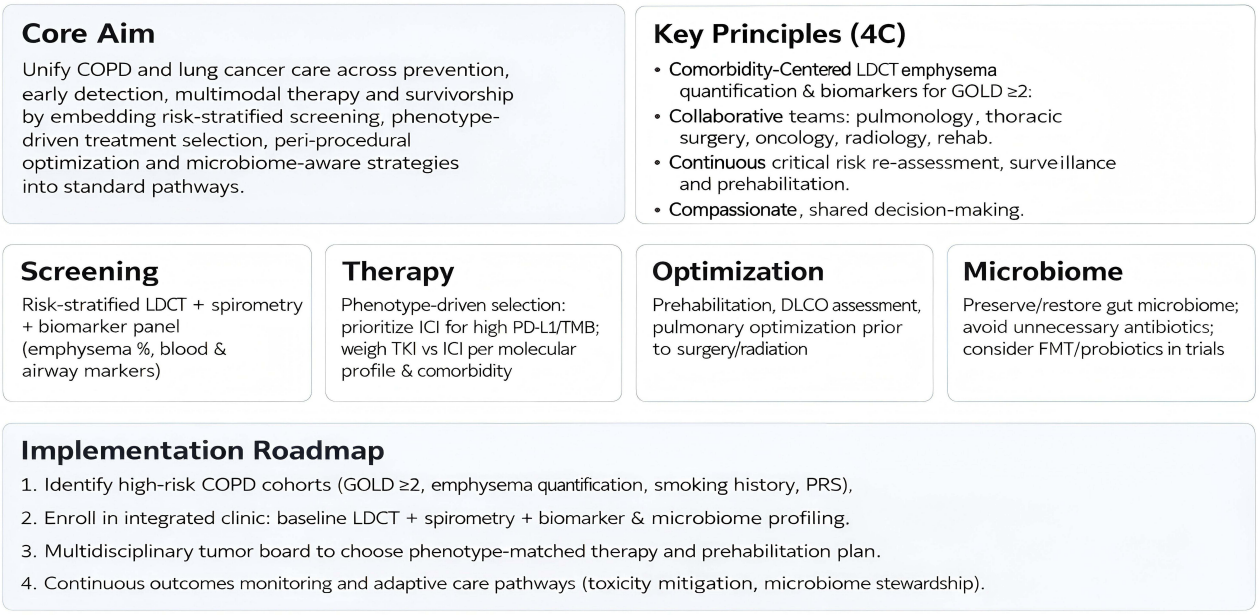


**Figure 3** The 4C framework (Comorbidity-Centered, Collaborative, Continuous, Compassionate) integrates COPD and lung cancer management through risk-based screening, phenotype-guided therapy, pulmonary optimization, and microbiome preservation to enhance survival and reduce comorbidity-related complications.

with KRAS prenylation, thereby inhibiting carcinogenic pathways.[98] Observational data indicate that long-term statin use (>6 months) reduces lung cancer risk in COPD patients by 40–60%.[107]

## AI-Enabled Risk Prediction and Digital Health Integration

Artificial intelligence (AI) and digital-health technologies are rapidly reshaping early detection and primary prevention in COPD–lung cancer comorbidity. Multimodal risk-stratification algorithms that fuse demographic, spirometric, radiomic, and genomic features have achieved high discrimination in independent validation cohorts, and can be deployed to triage patients into actionable risk tiers for intensified surveillance.[108]

Beyond static risk scores, dynamic remote-monitoring platforms are maturing rapidly. Wearable biosensors that continuously record cough frequency, respiratory rate, and peripheral oxygenation have shown high sensitivity for imminent COPD exacerbations in prospective cohorts (>90% in several device validation studies), offering a window for pre-emptive interventions.[109,110]

Finally, decentralized, blockchain-secured registries and federated data platforms are being piloted to link imaging, genomic and microbiome datasets while preserving privacy and provenance—a necessary infrastructure to scale precision prevention across populations.[111]

Collectively, these developments support the clinical implementation of combined LDCT + spirometry + molecular/genomic surveillance strategies and real-time digital monitoring to detect malignant transformation earlier and direct personalized prevention in high-risk COPD patients.

## Microbiome-Targeted Interventions

Modulating the lung–gut microbiome represents a promising frontier in preventive oncology and therapeutic optimization. Oral supplementation with Bacteroides fragilis has been demonstrated to enhance the efficacy of PD-1 inhibitors by augmenting IFN-γ–mediated immune activation in preclinical models.[112,113] In parallel, fecal microbiota transplantation (FMT) has been shown to reverse immunotherapy resistance in 46% of refractory cases involving advanced solid tumors, yielding objective response in previously non-responsive patients.[103,114] In contrast, broad-spectrum antibiotic exposure, particularly around the initiation of immunotherapy, markedly diminishes clinical outcomes—retrospective analyses

**Table 1** Preventive and Emerging Intervention Strategies for COPD–Lung Cancer Comorbidity

| Intervention Type | Specific Measures | Mechanisms of Action | Level of Evidence |
|---|---|---|---|
| **Pharmacological therapy** | Inhaled corticosteroids (ICS, triple therapy), statins | Suppression of inflammation (NF-κB/STAT3 inhibition), blockade of KRAS prenylation | Meta-analysis; clinical cohort studies |
| **Novel agents** | MPO inhibitors; nebulized hypomethylating agents | Inhibition of NET-induced mutagenesis; reversal of hypoxia-driven EGFR silencing | Phase II clinical trials |
| **AI-based risk prediction** | COMPASS-NN algorithm; C-Lung-RADS system | Integration of demographic, radiomic, and genomic variables for risk stratification | Multicenter validation |
| **Digital health technologies** | Wearable biosensors; smart inhalers with integrated spirometry | Dynamic monitoring of COPD exacerbations and prevention of delayed cancer diagnosis | Early clinical studies |
| **Microbiome-targeted interventions** | Probiotics; fecal microbiota transplantation (FMT); synthetic postbiotics | Remodeling of the immune microenvironment and enhancement of ICI efficacy | Early-phase clinical trials |

reveal up to 47% reductions in progression-free and overall survival among NSCLC patients.[115] These findings underscore the imperative for microbiome-sparing antibiotic stewardship in COPD–lung cancer comorbidity.

Looking forward, precision microbiome modulation via strategies such as metabolite-guided prebiotics, designer postbiotics, and AI-driven microbial risk classifiers are under active development. These approaches aim to shift gut ecology toward immunoprotective states and potentially impede malignant progression.[116,117]

## Future Research Directions

Advancing the management of COPD–lung cancer comorbidity requires bridging mechanistic discoveries with implementation science. Priority areas include: (1) Prospective validation of comorbidity-specific biomarkers—such as LRP1B truncations and TM7 (Saccharibacteria) enrichment—to enable precision risk stratification.[45,114,118] (2) Spatial multi-omics mapping of emphysema-associated carcinogenic niches to delineate localized molecular drivers and guide targeted interventions.[119–121] (3) Optimization of immunotherapy timing during COPD exacerbations, including steroid-sparing or tapering protocols designed to preserve immune checkpoint efficacy without exacerbating pulmonary inflammation.[122,123] (4) Integration of real-world registries linking AI-derived risk scores, longitudinal microbiome profiles, and therapeutic outcomes to continuously refine prevention and treatment algorithms.[124,125]

Collectively, these approaches emphasize a comorbidity-centered paradigm—integrating pharmacological, digital, and microbiome-based strategies—to intercept the COPD-to-cancer trajectory, reduce disease-specific mortality, and align with the WHO 2030 goal of a 30% reduction in global respiratory disease burden (Table 1).

# Conclusion

COPD and lung cancer may represent a biologically interconnected comorbidity rather than a coincidental coexistence. Converging mechanistic data show that chronic inflammation, somatic/genetic and epigenetic alterations, and microbiome–immune dysregulation cooperate to convert emphysematous lung tissue into a pro-tumorigenic niche. These mechanistic insights explain characteristic molecular and clinical features of comorbid tumors—patients with COPD-LC exhibit a low frequency of EGFR mutations but a high frequency of immune-related gene mutations, along with higher TMB and PD-L1 expression. These molecular features attenuate the clinical benefit of EGFR tyrosine kinase inhibitors (EGFR-TKIs) while enhancing responsiveness to immune checkpoint blockade—and support immunotherapy as a potential key treatment option in appropriately selected comorbid patients.

From a diagnostic and public-health perspective, persistent underdiagnosis remains a major barrier to early intervention. Integrative screening paradigms that combine low-dose CT (LDCT), spirometry, circulating biomarkers, and multimodal AI risk models are redefining early detection and triage, and have demonstrated markedly improved discrimination and sensitivity in large screening cohorts. It should be clarified that these approaches are still evolving and not yet universally adopted in clinical practice.

Therapeutically, the field is moving beyond single-modality approaches toward immunotherapy and microbiome-modulated strategies, supported by accumulating real-world and cohort evidence that microbiome composition and recent

antibiotic exposure materially affect ICI outcomes. Preventive opportunities are emerging: repurposed pharmacotherapies (eg, inhaled corticosteroids and statins) and microbiome-directed interventions show promise for risk interception in observational and early-phase studies, though prospective validation is required.

To translate these insights into population health gains, three priorities are essential: (1) prospective, multicenter validation of comorbidity-specific biomarkers and risk models (eg, LRP1B alterations, microbiome signatures); (2) deployment of spatial multi-omics and AI-enabled platforms in real-world clinical workflows to guide localized interventions; and (3) implementation of comorbidity-centered care frameworks in high-burden regions to reduce disparities and align with global targets such as the WHO/GBD mandate to substantially lower respiratory disease burden by 2030.

Bridging mechanistic discovery with implementation science may offer a realistic pathway to reduce COPD–lung cancer mortality, improve patient quality of life, and achieve measurable global health impact.

It should be clarified that this review synthesizes evidence from existing studies, and some conclusions require further verification by more prospective research.

## Author Contributions

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

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## Disclosure

The authors declare no conflicts of interest in relation to this article.

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