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REVIEW

# COPD and Immune Checkpoint Inhibitors for Cancer: A Literature Review

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**Purpose:** Immune checkpoint inhibitors are a standard treatment option for many patients with cancer and are most frequently used to treat lung cancer. Chronic obstructive pulmonary disease (COPD) is the most common comorbidity of patients with lung cancer. As the cancer-specific survival of patients with lung cancer continues to increase with modern treatments, it is critical to optimize comorbidities to improve overall survival. This literature review aimed to summarize current research on the impact of COPD upon immunotherapy outcomes.

**Methods:** A comprehensive search was conducted in the PubMed database using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Inclusion criteria focused on peer-reviewed articles published between 2010 and 2024 that addressed COPD, cancer, and immune checkpoint inhibitors. The study team screened the studies for relevance and then synthesized them narratively.

**Results:** This review identified 37 studies that met the inclusion criteria. Findings suggest that COPD is predictive of improved efficacy but slightly worse toxicity from immune checkpoint inhibitor therapy. The chronic inflammation of COPD leads to immune exhaustion including the overexpression of immune checkpoints on T-cells. Particularly within "hot" tumors that have higher concentrations of tumor-infiltrating lymphocytes, the COPD-related increase in programmed cell death protein 1 (PD-1) signaling likely creates sensitivity to immune checkpoint inhibitors. However, COPD can also lead to respiratory dysfunction, debility, and interstitial lung disease; each of which increases the severity of immune-related adverse events.

**Conclusion:** COPD is a critical comorbidity that has a significant impact on many patients with cancer who receive treatment with immune checkpoint inhibitors. Future research is needed to design interventions to optimize COPD care in this high-risk patient population.

**Keywords:** lung cancer, COPD, immunotherapy, immune checkpoint inhibitors

## Introduction

The routine use of immune checkpoint inhibitors for cancer treatment has rapidly expanded over the past ten years. Contrary to cytotoxic chemotherapy's immunosuppressive effect, these drugs block inhibitory signals that allow cancer cells to evade the immune system.[1] The most common cancer types treated with these drugs are associated with tobacco abuse (eg lung cancer),[2] and a personal history of smoking is associated with improved immunotherapy efficacy.[3–6] Among patients with a history of inhaled tobacco dependence, chronic obstructive pulmonary disease (COPD) is frequently underdiagnosed and undertreated in the general population and among patients with cancer.[7–9] The prevalence of smoking remains unacceptably high and remains the major modifiable risk factor for cancer-related mortality in the United States.[10] As novel interventions incrementally prolong survival in patients with cancer, it becomes increasingly essential to manage toxicity and the comorbidities, such as COPD, of the many patients treated for two years or more with a maintenance immune checkpoint inhibitor.[11]

There are many reasons why a patient can develop respiratory symptoms while receiving immunotherapy for cancer. Checkpoint inhibitor pneumonitis (CIP) is one of the most common dose-limiting toxicities of these drugs and can sometimes be fatal. COPD patients may be at higher risk for developing immune-related adverse events, which can lead

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to treatment interruption or discontinuation, potentially compromising the effectiveness of immunotherapy. It has been hypothesized that COPD complicates the safe administration of immune checkpoint inhibitors by worsening bronchial inflammation,[12,13] necessitating corticosteroids, which may suppress the efficacy of immunotherapy,[14] and potentially increase the risk of CIP via an unknown mechanism.[15] Besides CIP and comorbidities, bulky tumors within the lung parenchyma are another frequent cause of respiratory symptoms. In addition to lung cancer, which by definition has respiratory involvement, other types of cancer that are frequent indications for immunotherapy (eg, head and neck squamous cell carcinoma, kidney cancer, melanoma) have high rates of metastases to the lungs.[16] Thoracic tumors can cause respiratory symptoms by developing central airway obstruction, post-obstructive pneumonia, pulmonary emboli, and radiation pneumonitis if the tumors have been targeted with external beam radiotherapy.

It is critical to better understand the impact of COPD comorbidity on clinical outcomes among patients receiving immunotherapy for cancer, given its high prevalence. However, COPD data collection has been limited in cancer research due to the variable phenotypes of COPD and the restrictive eligibility criteria of registration clinical trials. This paper aims to systematically review the existing literature to explore the relationship between COPD and clinical outcomes in cancer patients receiving immunotherapy. Our hypothesis is that COPD is associated with improved treatment efficacy in terms of cancer control but a higher incidence and increased severity of respiratory adverse events. The findings of this review will provide insights into future clinical trial design to inform the development of strategies to optimize immunotherapy administration of patients with COPD and cancer.

# Methods

The search strategy for our review focused on the National Center for Biotechnology Information (NCBI)/PubMed database and was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[17] We used the following search terms in different combinations within medical subject headings, titles, and abstracts: “pulmonary disease, chronic obstructive”, “immune checkpoint inhibitors”, “lung neoplasms/drug therapy”, “COPD”, “pneumonitis”, and “immunotherapy”. All unfiltered results were entered into Covidence, a web-based collaboration software platform that streamlines the production of systematic reviews (Veritas Health Innovation, Melbourne, Australia). The study team then conducted a systematic literature review, summarized the findings in a narrative synthesis, and developed a conceptual model to organize the relationships between key variables. Backward snowballing by citation tracking was used during the review to identify additional relevant sources.

# Results

## Literature Review

The PubMed and citation searches identified 270 studies published up to August 2024, which then underwent review by the co-investigators as shown in the PRISMA flow diagram (Supplementary Figure 1). The study team screened the titles and abstracts of all the studies and included only the studies that referenced immune checkpoint inhibition, cancer, and obstructive lung disease (n = 93) as relevant. The study team then assessed the full text of these studies for eligibility, with 56 studies excluded due to the wrong study population (ie, participants without either COPD or cancer; n = 26), wrong intervention (ie, participants did not receive an immune checkpoint inhibitor; n = 15), wrong study design (ie, review, expert opinion, or commentary; n = 14), or lack of availability in the English language (n = 1). Additional studies were identified among references, particularly from a recent meta-analysis.[18] The 42 studies identified by this systematic literature review were included in the narrative synthesis, conceptual model, and table summary of key findings (Table 1).

## Narrative Synthesis

### COPD Pathophysiology and Immunotherapy

#### Neutrophils and Macrophages

Neutrophils and macrophages are the innate immune cells that are the primary mediators of the chronic inflammatory damage of COPD.[60] Neutrophils and macrophages also have a supplementary role in the mechanism of immune checkpoint inhibitors, as the adaptive immune response leads to increased levels of inflammatory mediators which

**Table 1** Summary of Key Findings from Studies

| Topic | n | Key COPD-related Finding | Citation |
|---|---|---|---|
| Innate immunity | | | |
| Prospective | 156 | Low IL-8 and IL-2R were associated with better outcomes. | [19] |
| Prospective | 95 | Immunotherapy increased FeNO in some patients with COPD. | [20] |
| Prospective | 82 | COPD was associated with increased Treg and Th17 cells. | [21] |
| Other immunity | | | |
| Prospective | 101 | ICI response was associated with CD8+ MAIT cells. | [22] |
| Prospective | 31 | ICI response was associated with active natural killer cells. | [23] |
| Mouse study | n/a | Lipopolysaccharide-induced inflammation helps ICI activity. | [24] |
| Adaptive immunity | | | |
| Prospective | 230 | COPD down-regulated HHLA2, increased memory T cells. | [25] |
| Retrospective | 125 | COPD has expanded Th1 cells associated with ICI response. | [26] |
| Retrospective | 39 | COPD has increased sensitivity of CD8 T lymphocytes. | [27] |
| Pneumonitis | | | |
| Meta-analysis | n/a | COPD was associated with higher risk of pneumonitis. | [18] |
| Prospective | 138 | Baseline symptoms and obstruction were associated with ILD. | [28] |
| Prospective | 99 | Severe COPD was associated with immunotoxicity. | [29] |
| Retrospective | 284 | FEV1 was not associated with pneumonitis incidence. | [30] |
| Retrospective | 164 | COPD was associated with pneumonitis. | [31] |
| Retrospective | 123 | Baseline pulmonary fibrosis was associated with pneumonitis. | [32] |
| Retrospective | 122 | COPD was not associated with higher risk of pneumonitis. | [33] |
| Retrospective | 88 | CPFE had similar toxicity but worse ICI efficacy than COPD. | [34] |
| Retrospective | 83 | COPD was associated with incidence of pneumonitis. | [35] |
| Retrospective | 43 | Baseline spirometry was associated with pneumonitis risk. | [36] |
| Retrospective | 34 | COPD was associated with lack of ICI after chemoradiation. | [37] |
| Acute exacerbations of COPD | | | |
| Retrospective | 234 | COPD had similar ICI outcomes with or without pneumonitis. | [38] |
| Retrospective | 11 | Immunotherapy was associated with stable COPD control. | [39] |
| Case series | 6 | Patients on ICI can have worsening COPD exacerbations. | [40] |
| Case series | 2 | ICI can cause tracheobronchitis. | [41] |
| Other complications of COPD | | | |
| Retrospective | 958 | Intratumoral Escherichia DNA had improved ICI efficacy. | [42] |
| Retrospective | 298 | COPD had higher risk of hospitalization. | [43] |
| Retrospective | 166 | COPD was a risk factor for venous thromboembolism. | [44] |
| Predictive marker of clinical outcomes | | | |
| Retrospective | 447 | COPD was associated with worse immunotoxicity. | [45] |
| Retrospective | 133 | Spirometry-defined COPD had improved ICI outcomes. | [46] |
| Retrospective | 74 | COPD was associated with improved ICI outcomes. | [47] |
| Retrospective | 39 | Frail patients with COPD can tolerate attenuated treatments. | [48] |
| Radiomics | | | |
| Retrospective | 240 | COPD had lower uptake on PET/CT imaging. | [49] |
| Retrospective | 257 | Primary tumor adjacent to COPD bullae improved outcomes. | [50] |
| Retrospective | 153 | Radiographic emphysema improved some ICI outcomes. | [51] |

(*Continued*)

**Table 1** (Continued).

| Topic | n | Key COPD-related Finding | Citation |
|---|---|---|---|
| Retrospective | 90 | COPD did not predict pneumonitis after adapted radiotherapy. | [52] |
| Retrospective | 56 | Emphysema was associated with improved ICI outcomes. | [53] |
| Prospective | 39 | COPD predicted for pneumonitis after adapted radiotherapy. | [54] |
| Genetic profiling | | | |
| Retrospective | 435 | COPD had different patterns of tumor genetic alterations. | [55] |
| Retrospective | 151 | COPD had upregulated ZNF143 expression. | [56] |
| Retrospective | 139 | COPD was associated with higher tumor mutational burden. | [57] |
| Future directions | | | |
| Retrospective | 13,113 | COPD was documented in 27% of the patient population. | [58] |
| Mouse study | n/a | Tumor growth was decreased in Il-17c deficient mice. | [59] |

**Abbreviations**: COPD, chronic obstructive pulmonary disease; Treg, regulatory T cells; Th17, T helper cell 17; IL, interleukin; ICI, immune checkpoint inhibitor; CD, cluster of differentiation; MAIT, mucosal-associated invariant T; HHLA2, HERV-H LTR-associating protein; ILD, interstitial lung disease; CPFE, combined pulmonary fibrosis/emphysema; PET/CT, combined positron emission and computed tomography.

activate innate immune cells to cause inflammation in the tumor microenvironment.[61] Peripheral blood tests to measure the levels of these mediators are minimally invasive, can be collected longitudinally as part of routine lab draws, and seem to change in response to immunotherapy. However, changes in levels often seem to be non-specific and therefore difficult to interpret. A prospective observational study of 82 patients with both COPD and lung cancer found that programmed cell death protein 1 (PD-1) inhibitors increased levels of interleukin (IL)-17, IL-6, and tumor necrosis factors (eg, TNF-α and TGF-β), several of the critical mediators of neutrophilic inflammation in COPD.[21] Increased baseline blood levels of two other key mediators, IL-8 and IL-2 receptors, were also associated with longer responses to immunotherapy.[19] Another retrospective study found that a higher baseline level of IL-8 was associated with a lower incidence of checkpoint inhibitor pneumonitis.[31] In contrast, a retrospective cohort of 178 patients found that baseline high levels of inflammatory markers (including IL-8) were associated with worse progression-free survival for immunotherapy.

### Other Innate Immune Cells

Other innate immune cells (eg, natural killer T-cells, eosinophils, mast cells) have supplementary roles in the progression of COPD.[60] In a prospective study that collected peripheral blood from patients receiving the PD-1 inhibitor nivolumab, high levels of natural killer T-cells were associated with COPD and with improved progression-free survival.[23]

Mucosal-associated invariant T (MAIT) cells are a large subset of T lymphocytes that are innate immune cells with some adaptive characteristics. In patients with COPD, MAIT cells tend to have dysfunctional signaling with an exaggerated inflammatory response to healthy bronchial epithelial cells and a decreased response to infected bronchial epithelial cells.[62] A study that collected surgically resected lung cancer after neoadjuvant (ie, pre-operative) immunotherapy found that higher concentrations of tumor-infiltrating MAITs were associated with a major pathologic response to immunotherapy. The presence of COPD was found to be associated with markers of immune exhaustion, including higher levels of PD-1 and lower levels of cluster of differentiation (CD) 69, Granzyme B (GZMB), and interferon gamma (IFN-γ) as compared to samples collected from patients without COPD. The investigators also found that in a mouse model, the stimulation of MAIT cells using 5-(2-oxopropylideneamino)-6-D-ribitylaminouracil (5-OP-RU) increased antitumor efficacy of an anti-PD1 immune checkpoint inhibitor.[22]

Eosinophilic COPD is another phenotype of chronic airway inflammation and is associated with a higher risk of acute exacerbations.[63] A prospective observational study of 95 patients with lung cancer found that four cycles of nivolumab slightly increased the levels of eosinophils in peripheral blood (171 to 229 cells/$mm^3$), but this difference was seen primarily among the subset of patients without COPD (142 to 226 cells/$mm^3$) and less in patients with COPD (208 to 233

cells/mm$^3$). The overall cohort had improvements in functional testing (increased FVC, FEV1) and no worsening of symptoms by dyspnea scale or incidence of acute exacerbations.[20] Among patients with COPD, there was an increase in the fraction of exhaled nitric oxide (FeNO) that was not seen among patients without COPD. The FeNO is a surrogate marker of local inflammation in the small airways[64] (eg, asthma, eosinophilic pneumonia) which may be exacerbated by immune checkpoint inhibitors.

### Adaptive Immune Cells

The primary mechanism of action of immune checkpoint inhibitors is through the activation of adaptive immune cells. The most used immunotherapies are monoclonal antibodies that target the PD-1 axis of adaptive immune cells; an immunosuppressive signaling pathway that can be pirated by cancer but is more commonly up-regulated as the body's response to control the severity of chronic inflammation.[1] In COPD pathophysiology, adaptive immune cells have a supplementary role through the stimulation of innate immune cells to cause chronic inflammation in the lungs.[26,63,65] In lung tissue, COPD is associated with increased PD-1 expression among T-cells along with a diminished response to viral infection.[66] The immune dysregulation of COPD can lead to T-cell exhaustion and may contribute to lung carcinogenesis.[67]

The key distinction for when COPD has an impact on immunotherapy efficacy may be limited to the patients that have higher concentrations of tumor-infiltrating lymphocytes (so-called "hot" tumors).[68] A retrospective study analyzing surgical pathology from 435 patients with lung cancer found that COPD was associated with similar immune cell density in the tumor microenvironment, similar programmed death-ligand 1 (PD-L1) expression in tumor cells, and similar tumor mutational burden as compared to patients without COPD. But among the patients who had higher concentrations of CD8+ tumor-infiltrating lymphocytes, there was increased expression of T-cell immunoglobulin and mucin domain-containing protein 3 (TIM-3), co-expression of PD-1/TIM-3, and functional exhaustion among CD8+ tumor-infiltrating lymphocytes.[27] These COPD-associated tumor-infiltrating lymphocytes are likely a mechanism for immunotherapy response. A study of resected lung tumors after neoadjuvant immunotherapy found that COPD was associated with higher levels of CD8+ CD103+ tissue-resident memory T cells and also with a treatment response to immunotherapy.[25] A previously noted prospective study of patients receiving the PD-1 inhibitor nivolumab found that COPD was associated with higher levels of CD8+ T-cells expressing PD-L1 in tumor tissue and in the peripheral blood and was also associated with improved progression-free survival.[23]

### Other Triggers of Airway Inflammation

The lung microbiome of patients with COPD tends to have higher rates of bacterial colonization, most notably with Gram-negative bacteria, as compared to patients without COPD.[69,70] The presence of lung cancer likely also changes the lung microbiome.[71,72] Bacterial colonization of the airway may contribute to chronic inflammation and improved immunotherapy efficacy. An observational study of 958 patients with lung cancer found that 52% of patients had intratumoral DNA consistent with Escherichia coli colonization. The presence of intratumoral Escherichia was associated with improved survival of single-agent immunotherapy.[42] Airway colonization by *Pseudomonas aeruginosa* is found in a high-risk subset of patients with COPD (~4%)[73,74] and was tested in a preclinical study to see if its presence modulated immunotherapy efficacy.[24] A mouse model of lung cancer found that repeated exposure to lipopolysaccharide from *Pseudomonas aeruginosa* led to a stronger tumor response to immune checkpoint inhibitors over the short term. The immune gene signatures from these mice correlated with the gene signatures from a retrospective cohort of human patients with lung cancer who responded to immunotherapy.

## COPD as a Complicating Comorbidity of Immunotherapy

### Overview

Compared to cytotoxic chemotherapies, immune checkpoint inhibitors typically have improved quality of life, less risk of toxicity, and similar or even enhanced treatment efficacy. As a result, patients with debility due to COPD may be better suited to receive attenuated systemic therapy with single-agent immunotherapy.[75] But COPD may conversely increase the risk of immunotoxicity; as a retrospective cohort of patients found that patients with a documented history of COPD

(n = 40) had a higher treatment-related discontinuation rate compared to the patients without COPD (n = 407).[45] It is likely that if COPD increases immunotoxicity, it is in the form of respiratory complications. In some cases, uncontrolled respiratory symptoms due to COPD may complicate or even preclude immunotherapy, both because of the potential increased risk of CIP but also due to the difficulty differentiating whether an increased symptom burden is secondary to poorly controlled COPD or the onset of CIP.[37]

### Pneumonitis

Observational and some limited clinical trial data have indicated that the presence of COPD increases the risk of developing CIP.[18] For example, the KEYNOTE-001 registration trial of pembrolizumab for non-small cell lung cancer found a higher incidence of CIP among patients with a history of either COPD or asthma as compared to patients without either of those diagnoses (5.4% vs 3.1%).[76] A prospective cohort study of 138 patients with lung cancer found that obstruction on pre-treatment spirometry (i.e, decreases in forced expiratory volume in one second [FEV1] or forced vital capacity [FVC]) or daily symptoms of dyspnea measured using the modified Medical Research Council (mMRC) scale were associated with a higher risk of pneumonitis.[28] A retrospective cohort study of 315 patients who received either nivolumab or pembrolizumab for lung cancer found that the presence of any one of the three indicators of COPD: (i) a recorded history of COPD in the medical record, (ii) emphysema on baseline chest computed tomography (CT) scan, or (iii) obstruction on pre-treatment spirometry (ratio of FEV1/FVC less than lower limit of normal) was associated with a higher incidence of CIP.[77] Another retrospective cohort study of 164 patients that used the above diagnostic criteria and added the presence of clinical symptoms of COPD (ie, chronic cough, expectoration, and exertional dyspnea) also found a higher incidence of CIP.[31] When stratifying COPD by functional severity using the predicted FEV1 (ie, mild ≥80%, moderate 50–79%, severe 30–49%, extremely severe <30%), another retrospective cohort of 99 patients with lung cancer found a higher rate of immune-related adverse events (56%) among patients with severe or extremely severe COPD, as well as an indication of decreased efficacy.[29,78] Another retrospective cohort of 43 patients also found an association between worse FEV1 and higher incidence of CIP.[36] When COPD is defined solely by reported medical history (ie, not confirmed by spirometry or indicated by symptoms/imaging), several retrospective studies have failed to show an association between COPD and pneumonitis risk.[35,36] While a diagnosis of COPD may indicate a modestly increased risk of CIP, there are subgroups of COPD that have increased risk.[79] Interstitial lung abnormalities (eg, interlobular septal thickening, honeycombing) and emphysema (eg, low-attenuation areas indicative of reduced tissue density) are common radiographic changes among patients with COPD.[80,81] A retrospective cohort of 123 patients with lung cancer treated with programmed cell death protein 1 (PD-1) inhibitors found that pre-treatment fibrotic changes (but not emphysematous changes) had a higher risk of CIP.[32] A retrospective study of 122 patients did not find a higher incidence of CIP (16% vs 18%) among patients with COPD but found an indication of higher risk among patients with pulmonary fibrosis evident on baseline CT.[33] Another retrospective study found that the radiographic evidence of combined pulmonary fibrosis and emphysema as per Cottin's 2005 criteria[82] appeared to have a higher rate of respiratory immune-related adverse events as compared to patients with clinically diagnosed COPD (5/28 [18%] vs 7/78 [9%]).[34]

Prior radiation therapy involving the lungs is an additional cause of pneumonitis among patients being treated with immunotherapy. The typical treatment course for unresectable stage III lung cancer is thoracic chemoradiation followed by the anti-programmed death-ligand 1 (PD-L1) inhibitor durvalumab for one year. Among patients with lung cancer receiving post-radiation immunotherapy, it is possible that patients with COPD are at higher risk for CIP as compared to patients without COPD.[18] A small prospective study (n = 39) found a higher risk of CIP among patients with COPD.[54] A larger retrospective study (n = 264) did not find an association between pretreatment FEV1 and the incidence of CIP.[30]

### Acute Exacerbations of COPD (AECOPD)

A multidisciplinary panel recommended that if a patient develops an AECOPD that immunotherapy should be suspended until symptoms have improved and performance status has recovered.[83] Based on low-level data, it is possible that immunotherapy may worsen the frequency and severity of AECOPDs in some patients. Defined by responsiveness to corticosteroids but in the absence of radiographic signs of pneumonitis, AECOPD have been described in case series among patients started on immunotherapy.[40,41] Other competing factors may contribute to this – most notably, the loss of

functional airspace by tumor and the continued natural progression of COPD – and further research is needed to delineate the course of COPD among patients who live for years with advanced lung cancer. Interestingly, a retrospective cohort study of 142 patients with COPD found that the 34 patients who had immune-related adverse events did not have a higher frequency of AECOPD than the 108 patients who did not have immunotoxicity.[38] A small retrospective study (n = 82) found that the 11 patients who received immune checkpoint inhibitors had a similar frequency of AECOPD but did have different changes to their maintenance inhaler regimens as compared to patients who received other cancer treatments.[39] Immune checkpoint inhibitors can also cause immune-related respiratory dysfunction (eg, tracheobronchitis)[41] and it is not clear how to distinguish this from worsening COPD control. A meta-analysis of 22 randomized controlled trials did not find evidence that immunotherapy can increase the risk of developing new onset of COPD.[84] There are clinical trials currently in progress (eg, National Clinical Trial registrations NCT04253964, NCT05696782) that are collecting validated COPD patient-reported outcome measures (eg, the COPD Assessment Test and the modified Medical Research Council tool); these data should provide additional insight into COPD control during immunotherapy.[85]

It is not certain which signaling pathway mediates immunotherapy and worsening control of COPD. One possible pathway is through toll-like receptors (TLRs); proteins that detect microbial antigens and activate the innate immune system. In particular, double-stranded DNA of respiratory viruses activates TLR3 which decreases the expression of immune checkpoints (eg, PD-1),[86] contributes to airway remodeling,[87] and worsens COPD control.[88,89] In this way it is possible that patients who are receiving immune checkpoint inhibitors are sensitized to immune activation by respiratory viral infections.

### Pulmonary Embolism

Thrombotic risk is increased among patients with active cancer, and pulmonary embolism is one of the most common respiratory problems in patients being treated with an immune checkpoint inhibitor. A meta-analysis of 22 randomized controlled trials did not find evidence that immune checkpoint inhibitors increase the risk of pulmonary embolism,[84] and likely have a relatively lower thrombotic risk compared to other systemic cancer therapies (eg, anti-angiogenic therapy, chemotherapy).[44] However, COPD is associated with a higher risk of pulmonary embolism among the general population[90,91] and among patients with cancer treated with immunotherapy.[44]

### Infections

Mechanistically, the alleviation of immunosuppression by immune checkpoint inhibitors should allow effector T-cells to respond more aggressively to bacterial antigens and clear respiratory infections, a common cause of AECOPDs.[92,93] However, it is not clear whether this proposed mechanism has any clinical relevance. A retrospective cohort of 298 patients treated with immunotherapy with or without chemotherapy had a slim majority of patients (162, 54%) diagnosed with an infection at any point from initiation of treatment until three months after treatment discontinuation.[43] Patients with COPD had a higher incidence of hospitalization for infection, and patients who recently received corticosteroids (likely as treatment for AECOPD) had a higher risk of admission to an intensive care unit. Interestingly, the investigators found that the inability to discern between infection and an immune-related adverse event (40, 12%) was also associated with hospitalization, a clinical challenge that was previously identified in another review.[94]

## COPD as a Predictive Marker for Immunotherapy

### Overview

The chronic inflammation of COPD often leads to immune exhaustion, including the overexpression of immune checkpoints on T-cells; within the tumor microenvironment, this reliance on PD-1/PD-L1 signaling likely creates sensitivity to immune checkpoint inhibitors.[95] Several retrospective studies have reported that the presence of COPD (whether symptom-defined or spirometry-based) is associated with improved progression-free and overall survival among patients with non-small cell lung cancer treated with an immune checkpoint inhibitor.[19,27,46,96] Two retrospective studies found a benefit in progression-free but not overall survival,[26] and one of these studies also found a benefit in tumor response rate.[51] In the neoadjuvant setting, a retrospective cohort found a higher pathological complete response

rate among patients with spirometry-confirmed COPD (n = 30, 43%) as compared to patients without COPD (n = 44, 21%).[47] Among patients with COPD, the development of an immune-related adverse event was not associated with worse outcomes in terms of incidence of AECOPDs, hospitalization, or cancer progression.[38] Even among higher-risk patients (eg, elderly, decreased performance status, multiple comorbidities), the presence of COPD is not an absolute contraindication to the use of an immune checkpoint inhibitor as part of an attenuated treatment plan for lung cancer.[48]

### Radiomics

Since nearly all patients with lung cancer have serial thoracic imaging for response assessment, radiomics is a promising predictive biomarker for immune checkpoint inhibitors. The presence of emphysematous changes on baseline chest CT (whether using a low attenuation area cut-off value of either >1% or >25% of the total surface area) was associated with better efficacy in two retrospective cohorts.[51,53] A retrospective cohort of 257 patients with lung cancer treated in Japan with either nivolumab, pembrolizumab, or atezolizumab monotherapy tested the predictive value of lung tumors being physically adjacent to emphysematous bullae (n = 55), a radiographic finding associated with smoking.[50] The investigators found that adjacent bullae were an independent predictor of progression-free and overall survival after controlling for age, sex, and smoking history. This finding was not previously seen with another cohort of patients treated with chemotherapy.[97] Therefore, the investigators hypothesized that emphysematous bullae were likely a surrogate marker for heavier smoking exposure and a greater accumulation of genetic alterations by cancer, which enhanced the targeting ability of immunotherapy. Cancer staging typically requires a pre-treatment [18F]FDG-PET/CT scan which visualizes the uptake of glucose by tumors as well as non-tumorous lung tissue, which may be predictive of increased inflammation and a higher risk of drug-induced pneumonitis. A retrospective study found that patients with COPD (n = 57) had decreased glucose uptake at baseline as compared to patients without COPD (n = 183), likely due to the emphysematous loss of density in lung tissue.[49]

Novel imaging techniques may provide further insight into the association between COPD and immunotherapy outcomes. Flakus et al collected functional ventilation imaging (ie, four-dimensional computed tomography) and found that radiation treatments to higher functional lung volumes – which differed from static three-dimensional lung volumes – were associated with a higher risk of radiation pneumonitis and that the subgroup of patients who received adjuvant immunotherapy did not have a higher risk than patients who did not receive adjuvant immunotherapy.[52] Thomas et al collected functional perfusion imaging (ie, Technetium-99m macro-aggregated albumin SPECT/CT) and found that patients reported to have COPD had increased volumes of perfused lung compared to patients not reported to have COPD.[54]

### Genetic Profiling

In patients with COPD, lung tumors often have different profiles of gene expression and mutations as compared to patients without COPD. The recognition of tumor mutations that are related to smoking is well established in lung cancer care.[98] Retrospective cohort studies have shown that COPD is associated with an increased prevalence of mutations that may be targetable (eg, Kirsten Rat Sarcoma Viral Oncogene Homolog [KRAS]) or informative (eg, Serine/Threonine Kinase 11 [STK11], Kelch-like ECH-associated protein 1 [KEAP1], Retinoblastoma 1 [RB1]); and a lower prevalence of other "driver" mutations associated with non-small cell lung cancer in never-smokers (eg, Epidermal Growth Factor Receptor [EGFR]). Two commonly used biomarkers for immunotherapy, PD-L1 expression and tumor mutational burden, are not associated with COPD.[55,57,59,99]

Human endogenous retrovirus-H long terminal repeat-associating 2 (HHLA2, also known as B7-H7), is an inhibitory immune checkpoint that may be a novel PD-L1-independent pathway for tumors to evade the immune system and is being evaluated as a potential target for cancer drug development.[100] An observational study of resected lung tumors after neoadjuvant immunotherapy (n = 62) found that COPD was associated with decreased HHLA2 expression, higher levels of CD8+ tissue-resident memory T cells and with a major pathologic response to immunotherapy. This study found COPD-related differences in the expression levels of 10 other genes as well.[25] Zinc finger protein 143 (ZNF143) is another gene with higher levels of expression associated with both COPD and lung cancer, as compared to patients with

lung cancer alone or without either condition. Known to be related to COPD, higher expression of ZNF143 was correlated with PD-L1 and other predictive biomarkers of immunotherapy efficacy.[56]

### Future Directions

The mechanisms by which COPD increases the efficacy of immunotherapy may have insights into the development of novel cancer drugs. The pro-inflammatory cytokine IL-17C is overexpressed in airway epithelial cells of patients with COPD and contributes to lung cancer progression. The knockout of the IL-17C gene in a mouse model of KRAS-mutated lung cancer led to the increased expression of PD-L1 and improved tumor responsiveness to anti-PD-1 treatment.[101] The investigators hypothesized that blocking of IL-17C may augment the response of some lung cancers to immune checkpoint inhibitors. One literature review discussed how the long-standing success of inhaled immunomodulating therapies for COPD (eg, corticosteroids, PDE3/4 inhibitors) can inform the development of inhaled immunotherapies for cancer.[102] In particular, the review cites nanoparticles as a potential means to deliver immunotherapies to the lung microenvironment,[103] an avenue of drug development that could provide a safer option for patients with extra-thoracic immune comorbidities (eg, transplanted kidney, inflammatory bowel disease). Additionally, it is likely that some future immunotherapies for cancer will have a higher risk of COPD-related complications via shared signaling pathways (eg, TLR3 agonists[104,105]).

The presence and severity of COPD are important variables among patients receiving immunotherapy and should be consistently assessed as a baseline comorbidity using validated diagnostic criteria. One clinical trial currently in progress is specifically testing immunotherapy efficacy and safety among patients with lung cancer and a confirmed diagnosis of COPD.[85] Clinical trials testing neoadjuvant or shorter pre-operative "window of opportunity" regimens will allow for the procurement of surgical lung specimens after neoadjuvant immunotherapy; this will allow for better studies of the immune microenvironment.[106] Retrospective studies should address the presence of underlying lung disease as a potential confounder, for example, by matching cases and controls.[58]

## Conceptual Model

We developed a conceptual model (Figure 1) to provide an overarching graphical description of this literature review. COPD was selected as the independent variable due to its much greater prevalence than lung cancer. Immunotherapy outcomes, defined as the response rate of the cancer treatments, progression-free survival, and risk of immunotherapy-

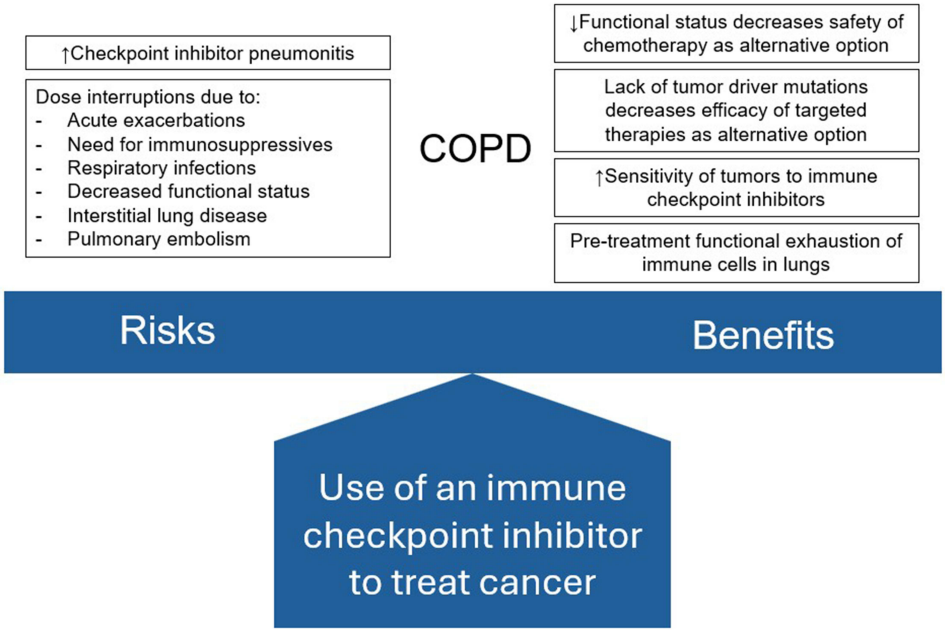


**Figure 1** Conceptual model for immunotherapy outcomes among patients with COPD and cancer.

related toxicity, were chosen as the dependent variable because it is clinically meaningful and readily measurable. This model can help to inform the design of immunotherapy research studies so that they can better account for each of these variables.

## Discussion

This review found that although current evidence supports the routine use of immune checkpoint inhibitors to treat lung cancer among patients who have COPD, there is a critical need for data to inform interventions to reduce their risk to cause respiratory failure or worsen the underlying disease control. In general, the presence of COPD complicates the course of immunotherapy by increasing the risk of respiratory failure and modestly increasing the risk of CIP. However, it also predicts improved efficacy by the immune checkpoint inhibitor in treating lung cancer for progression-free and overall survival. Given the high prevalence of COPD among patients with lung cancer (40–80%),[107] even among participants enrolled in clinical trials for immunotherapy (25%),[108] the presence of uncomplicated COPD should not preclude this standard-of-care modality of cancer treatment. Even among patients with COPD and interstitial lung abnormalities (10–30%), immunotherapies can be considered.[80,109,110] But a notable exception is the presence of COPD complicated by interstitial lung disease with severe features – eg, radiographic honeycombing (<1%),[80] requiring anti-fibrotic therapies – which conveys an exceptionally high risk of CIP and should be considered a relative contraindication to immunotherapy.

Despite nearly all of the studies being concordant with their findings, there was an overall low level of evidence supporting these conclusions. Surprisingly, despite the large scope and high acuity of this medical problem, we found few studies on it. Lung cancer is the leading cause of cancer death in the United States, and COPD is its most common comorbidity and by itself the sixth leading cause of death in the United States.[111] Yet there were only 176 studies identified that studied the management of these two problems together. As a relatively new drug modality, that has emerged in the last decade, the inclusion of immunotherapy narrowed the review down to just 61 relevant studies. With the increased utilization of immune checkpoint inhibitors to treat lung cancer, there will likely be growing opportunities to study this patient population in the future. Secondly, apart from two prospective observational studies,[19,20] all studies were either retrospective or animal models. Many of the retrospective studies were case series or single-institution cohorts. Although treatment trials nearly always collect past medical history from participants, there has been little data analysis on COPD as a pre-treatment comorbidity among registration trials testing the use of immune checkpoint inhibitors in lung cancer. Additionally, lung cancer treatment trials have not routinely collected measures of COPD phenotype (self-reported, radiographic changes), severity (eg, spirometry), or outcomes (eg, incidence of acute exacerbations while on study).

We propose that future studies designed to optimize the care of COPD among patients receiving immunotherapy for lung cancer should focus on the risk reduction of acute respiratory failure due to any cause. This review found that uncontrolled COPD contributes to acute respiratory failure via a wide variety of mechanisms, either direct (eg, acute exacerbations, pneumonia, worsening obstruction) or indirect (eg, CIP, missed doses of cancer-directed therapy contributing to the progression of cancer, debility contributing to pulmonary embolism). Therefore, focusing on only one of these outcomes does not address the full impact of COPD on patients. Additionally, the ability to discern between etiologies of acute respiratory failure is challenging at the point of care. Even after diagnostic testing and follow-up, the retrospective determination of the specific etiology of acute respiratory failure is often subjective.[112] Therefore, lumping these causes together as a syndrome of acute respiratory failure is likely the best approach for research.

Several future aims identified by the narrative synthesis would benefit from additional study. One open question is whether the categorization of COPD by clinical phenotype (eg, chronic bronchitis, emphysema, overlap COPD-asthma), inflammatory phenotype (eg, neutrophilic, eosinophilic), and severity (eg, high or low risk for exacerbation, high or low FEV1) could be predictive markers for immunotherapy. The above studies indicate that the presence of individual markers of COPD (eg, airway colonization by *Pseudomonas*, emphysematous bullae) can be predictive so it stands to reason that clinical categorization of COPD could be a valuable tool at the point of care. Given the high prevalence of this comorbidity among patients receiving immune checkpoint inhibitors, this information could be tested and then validated with an observational cohort study at a single institution.

Another opportunity for further study is the routine inclusion of COPD-related variables and outcomes in registration trials for lung cancer. COPD-related variables would start with confirmation and severity assessment of COPD functionally (ie, by spirometry) and quantification of symptoms by validated questionnaires such as the COPD assessment tool (CAT) and the mMRC dyspnea index. These could be expanded to include its phenotype radiographically as airway dominant or emphysematous patterns. COPD-related outcomes would start with additional characterization of the acute and chronic respiratory failure syndromes. The incidence of this life-threatening adverse event is always measured as the routine safety monitoring of treatment trials, but study analysis and reporting often provide limited information on the type of acute respiratory failure and its attribution. This would benefit from protocol standardization for defining the etiology of acute respiratory failure on a case-by-case basis. Finally, lung cancer research should include COPD therapies as possible confounders of immunotherapy efficacy and toxicity, given the frequent use of corticosteroids and the emerging use of long-term immunomodulating drugs (eg, dupilumab) for COPD.[113] This would provide valuable prospective toxicity data to supplement what is already known.

## Conclusion

COPD is the most common comorbidity among patients with lung cancer, and it is predictive of improved efficacy but slightly worse toxicity from immune checkpoint inhibitor therapy. Further research is needed to design interventions to optimize the diagnosis and management of COPD to reduce the risk of acute respiratory failure in this high-risk patient population.

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## References

1. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer*. 2012;12(4):252–264. doi:10.1038/nrc3239
2. Haslam A, Gill J, Prasad V. Estimation of the percentage of US patients with cancer who are eligible for immune checkpoint inhibitor drugs. *JAMA Network Open*. 2020;3(3):e200423. doi:10.1001/jamanetworkopen.2020.0423
3. Kim JH, Kim HS, Kim BJ. Prognostic value of smoking status in non-small-cell lung cancer patients treated with immune checkpoint inhibitors: a meta-analysis. *Oncotarget*. 2017;8(54):93149–93155. doi:10.18632/oncotarget.18703
4. Dai L, Jin B, Liu T, Chen J, Li G, Dang J. The effect of smoking status on efficacy of immune checkpoint inhibitors in metastatic non-small cell lung cancer: a systematic review and meta-analysis. *EClinicalMedicine*. 2021;38:100990. doi:10.1016/j.eclinm.2021.100990
5. Kim J, Ha H, Park J, Cho J, Lim JH, Lee MH. Association of smoking status with efficacy of first-line immune checkpoint inhibitors in advanced non-small cell lung cancers: a systematic review and meta-analysis. *J Cancer*. 2022;13(2):364–372. doi:10.7150/jca.65374
6. Wang X, Ricciuti B, Alessi JV, et al. Smoking history as a potential predictor of immune checkpoint inhibitor efficacy in metastatic non-small cell lung cancer. *J National Cancer Inst*. 2021;113(12):1761–1769. doi:10.1093/jnci/djab116
7. Parron Collar D, Pazos Guerra M, Rodriguez P, et al. COPD is commonly underdiagnosed in patients with lung cancer: results from the RECOIL study (retrospective study of COPD infradiagnosis in lung cancer). *Int J Chron Obstruct Pulmon Dis*. 2017;12:1033–1038. doi:10.2147/copd.s123426
8. Braman SS, Carlin BW, Hanania NA, et al. Results of a pulmonologist survey regarding knowledge and practices with inhalation devices for COPD. *Respiratory Care*. 2018;63(7):840–848. doi:10.4187/respcare.05717
9. Gershon AS, Thiruchelvam D, Chapman KR, et al. Health services burden of undiagnosed and overdiagnosed COPD. *Chest*. 2018;153(6):1336–1346. doi:10.1016/j.chest.2018.01.038
10. Shiels MS, Lipkowitz S, Campos NG, et al. Opportunities for achieving the cancer moonshot goal of a 50% reduction in cancer mortality by 2047. *Cancer Discov*. 2023;13(5):1084–1099. doi:10.1158/2159-8290.Cd-23-0208
11. Howlader N, Forjaz G, Mooradian MJ, et al. The effect of advances in lung-cancer treatment on population mortality. *New Engl J Med*. 2020;383(7):640–649. doi:10.1056/NEJMoa1916623

12. Filho MM, Aguiar PN, de Mello RA. Chronic obstructive pulmonary disease alters immune cell composition and immune checkpoint inhibitor efficacy in non-small cell lung cancer. *Ann Transl Med*. 2019;7(Suppl 1):S42. doi:10.21037/atm.2019.02.27
13. Wilkinson TMA. Immune checkpoints in chronic obstructive pulmonary disease. *Eur Respir Rev*. 2017;26(144). doi:10.1183/16000617.0045-2017
14. Remon J, Passiglia F, Ahn MJ, et al. Immune checkpoint inhibitors in thoracic malignancies: review of the existing evidence by an IASLC expert panel and recommendations. *J Thoracic Oncol*. 2020;15(6):914–947. doi:10.1016/j.jtho.2020.03.006
15. Gershner KA. Immunotherapy-induced pneumonitis: a review of diagnostic workup and treatment guidelines. *Clin Pulm Med*. 2020;27(5):141–147.
16. Budczies J, von Winterfeld M, Klauschen F, et al. The landscape of metastatic progression patterns across major human cancers. *Oncotarget*. 2015;6(1):570–583. doi:10.18632/oncotarget.2677
17. Rethlefsen ML, Kirtley S, Waffenschmidt S, et al. PRISMA-S: an extension to the PRISMA statement for reporting literature searches in systematic reviews. *Syst Rev*. 2021;10(1):39. doi:10.1186/s13643-020-01542-z
18. Li F, Zheng L, Xu X, Jin J, Li X, Zhou L. The impact of chronic obstructive pulmonary disease on the risk of immune-related pneumonitis in lung cancer patients undergoing immunotherapy: a systematic review and meta-analysis. *BMC Pulm Med*. 2024;24(1):393. doi:10.1186/s12890-024-03180-w
19. Zhou J, Chao Y, Yao D, et al. Impact of chronic obstructive pulmonary disease on immune checkpoint inhibitor efficacy in advanced lung cancer and the potential prognostic factors. *Transl Lung Cancer Res*. 2021;10(5):2148–2162. doi:10.21037/tlcr-21-214
20. Suzuki Y, Inui N, Karayama M, et al. Effect of PD-1 inhibitor on exhaled nitric oxide and pulmonary function in non-small cell lung cancer patients with and without COPD. *Int J Chron Obstruct Pulmon Dis*. 2019;14:1867–1877. doi:10.2147/copd.S214610
21. Wang X, She X, Gao W, Liu X, Shi B. Correlation between the Treg/Thl7 Index and the Efficacy of PD-1 monoclonal antibody in patients with advanced non-small-cell lung cancer complicated with chronic obstructive pulmonary disease. *Comput Math Methods Med*. 2022;2022:2923998. doi:10.1155/2022/2923998
22. Yin Y, Zeng A, Abuduwayiti A, et al. MAIT cells are associated with responsiveness to neoadjuvant immunotherapy in COPD-associated NSCLC. *Cancer Med*. 2024;13(6):e7112. doi:10.1002/cam4.7112
23. Mazzaschi G, Facchinetti F, Missale G, et al. The circulating pool of functionally competent NK and CD8+ cells predicts the outcome of anti-PD1 treatment in advanced NSCLC. *Lung Cancer*. 2019;127:153–163. doi:10.1016/j.lungcan.2018.11.038
24. Liu CH, Chen Z, Chen K, et al. Lipopolysaccharide-mediated chronic inflammation promotes tobacco carcinogen-induced lung cancer and determines the efficacy of immunotherapy. *Cancer Res*. 2021;81(1):144–157. doi:10.1158/0008-5472.Can-20-1994
25. Zeng A, Yin Y, Xu Z, et al. Down-regulated HHLA2 enhances neoadjuvant immunotherapy efficacy in patients with non-small cell lung cancer (NSCLC) with chronic obstructive pulmonary disease (COPD). *BMC Cancer*. 2024;24(1):396. doi:10.1186/s12885-024-12137-5
26. Mark NM, Kargl J, Busch SE, et al. Chronic obstructive pulmonary disease alters immune cell composition and immune checkpoint inhibitor efficacy in non-small cell lung cancer. *Am J Respir Crit Care Med*. 2018;197(3):325–336. doi:10.1164/rccm.201704-0795OC
27. Biton J, Ouakrim H, Dechartres A, et al. Impaired tumor-infiltrating T cells in patients with chronic obstructive pulmonary disease impact lung cancer response to PD-1 blockade. *Am J Respir Crit Care Med*. 2018;198(7):928–940. doi:10.1164/rccm.201706-1110OC
28. Suzuki Y, Karayama M, Uto T, et al. Assessment of immune-related interstitial lung disease in patients with NSCLC treated with immune checkpoint inhibitors: a multicenter prospective study. *J Thoracic Oncol*. 2020;15(8):1317–1327. doi:10.1016/j.jtho.2020.04.002
29. Zhang K, Zhou C, Gao J, et al. Treatment response and safety of immunotherapy for advanced non-small cell lung cancer with comorbid chronic obstructive pulmonary disease: a retrospective cohort study. *Transl Lung Cancer Res*. 2022;11(11):2306–2317. doi:10.21037/tlcr-22-667
30. Akkad N, Thomas TS, Luo S, Knoche E, Sanfilippo KM, Keller JW. A real-world study of pneumonitis in non-small cell lung cancer patients receiving durvalumab following concurrent chemoradiation. *J Thorac Dis*. 2023;15(12):6427–6435. doi:10.21037/jtd-22-1604
31. Chao Y, Zhou J, Hsu S, et al. Risk factors for immune checkpoint inhibitor-related pneumonitis in non-small cell lung cancer. *Transl Lung Cancer Res*. 2022;11(2):295–306. doi:10.21037/tlcr-22-72
32. Yamaguchi T, Shimizu J, Hasegawa T, et al. Pre-existing pulmonary fibrosis is a risk factor for anti-PD-1-related pneumonitis in patients with non-small cell lung cancer: a retrospective analysis. *Lung Cancer*. 2018;125:212–217. doi:10.1016/j.lungcan.2018.10.001
33. Zeng Z, Qu J, Yao Y, et al. Clinical outcomes and risk factor of immune checkpoint inhibitors-related pneumonitis in non-small cell lung cancer patients with chronic obstructive pulmonary disease. *BMC Pulm Med*. 2022;22(1):458. doi:10.1186/s12890-022-02190-w
34. Wei Y, Yang L, Wang Q. Analysis of clinical characteristics and prognosis of lung cancer patients with CPFE or COPD: a retrospective study. *BMC Pulm Med*. 2024;24(1):274. doi:10.1186/s12890-024-03088-5
35. LeClair JN, Merl MY, Cohenuram M, Luon D. Real-world incidence of pneumonitis in patients receiving durvalumab. *Clin Lung Cancer*. 2022;23(1):34–42. doi:10.1016/j.cllc.2021.08.006
36. Reuss JE, Brigham E, Psoter KJ, et al. Pretreatment lung function and checkpoint inhibitor pneumonitis in NSCLC. *JTO Clin Res Rep*. 2021;2(10):100220.
37. Morimoto M, Nishino K, Wada K, et al. Elective nodal irradiation for non-small cell lung cancer complicated with chronic obstructive pulmonary disease affects immunotherapy after definitive chemoradiotherapy. *Anticancer Res*. 2020;40(12):6957–6970. doi:10.21873/anticanres.14720
38. Kesireddy M, Marr A, Schissel M, Ganti AK. A retrospective analysis of immune checkpoint inhibitors in patients with preexisting organ dysfunction. *Cancer*. 2023;129(22):3603–3619. doi:10.1002/cncr.34958
39. Zarogoulidis P, Oikonomidou R, Petridis D, et al. Chronic obstructive pulmonary disease and non-small cell lung cancer an association. *J Cancer*. 2024;15(3):603–609. doi:10.7150/jca.90594
40. Nair VS, Eaton K, McGarry Houghton A. A case series of morbid COPD exacerbations during immune checkpoint inhibitor therapy in cancer patients. *Respir Med Case Rep*. 2021;34:101541. doi:10.1016/j.rmcr.2021.101541
41. Kawakami N, Saito H, Takahashi S, et al. Airway disorders associated with immune checkpoint inhibitor therapy: two case reports and a systematic review. *Semin Oncol*. 2022;49(6):439–455. doi:10.1053/j.seminoncol.2023.01.003
42. Elkrief A, Montesion M, Sivakumar S, et al. Intratumoral Escherichia is associated with improved survival to single-agent immune checkpoint inhibition in patients with advanced non-small-cell lung cancer. *J Clin Oncol*. 2024;42(28):3339–3349. doi:10.1200/jco.23.01488

43. Guo MZ, Balaji A, Murray JC, et al. Infectious complications in patients with non-small cell lung cancer treated with immune checkpoint inhibitors. *Clin Lung Cancer*. 2023. doi:10.1016/j.cllc.2023.06.011
44. He X, Wei SN, Qin WW, et al. Evaluating the effect of immune checkpoint inhibitors on venous thromboembolism in non-small cell lung cancer patients. *Expert Rev Hematol*. 2023;16(12):1135–1142. doi:10.1080/17474086.2023.2276209
45. Chua KJ, Kronstedt S, Kaldany A, et al. Comparing the rate of immunotherapy treatment change due to toxicity by sex. *Cancer Rep*. 2024;7(2): e1932. doi:10.1002/cnr2.1932
46. Shin SH, Park HY, Im Y, et al. Improved treatment outcome of pembrolizumab in patients with nonsmall cell lung cancer and chronic obstructive pulmonary disease. *Int J Cancer*. 2019;145(9):2433–2439. doi:10.1002/ijc.32235
47. Dong W, Yin Y, Yang S, et al. Impact of chronic obstructive pulmonary disease on the efficacy and safety of neoadjuvant immune checkpoint inhibitors combined with chemotherapy for resectable non-small cell lung cancer: a retrospective cohort study. *BMC Cancer*. 2024;24(1):153. doi:10.1186/s12885-024-11902-w
48. Zhou YM, Shin J, Jelinek M, et al. Four-phase, definitive chemoradiation for a real-world (Poor Risk and/or Elderly) patient population with locally advanced non-small cell lung cancer. *Cureus*. 2022;14(9):e29423. doi:10.7759/cureus.29423
49. Wehlte L, Walter J, Daisenberger L, et al. The association between the body mass index, chronic obstructive pulmonary disease and SUV of the non-tumorous lung in the pretreatment [(18)F]FDG-PET/CT of Patients with Lung Cancer. *Diagnostics*. 2024;14(11). doi:10.3390/diagnostics14111139
50. Takamori S, Takada K, Shimokawa M, et al. Prognostic impact of primary cancer adjoining emphysematous bullae in non-small cell lung cancer patients treated with immune checkpoint inhibitors. *Cancer Immunol Immunother*. 2021;70(6):1745–1753. doi:10.1007/s00262-020-02783-6
51. Takayama Y, Nakamura T, Fukushiro Y, Mishima S, Masuda K, Shoda H. Coexistence of emphysema with non-small-cell lung cancer predicts the therapeutic efficacy of immune checkpoint inhibitors. *Vivo*. 2021;35(1):467–474. doi:10.21873/invivo.12280
52. Flakus MJ, Kent SP, Wallat EM, et al. Metrics of dose to highly ventilated lung are predictive of radiation-induced pneumonitis in lung cancer patients. *Radiother Oncol*. 2023;182:109553. doi:10.1016/j.radonc.2023.109553
53. Noda Y, Shiroyama T, Masuhiro K, et al. Quantitative evaluation of emphysema for predicting immunotherapy response in patients with advanced non-small-cell lung cancer. *Sci Rep*. 2022;12(1):8881. doi:10.1038/s41598-022-13131-2
54. Thomas HMT, Hippe DS, Forouzannezhad P, et al. Radiation and immune checkpoint inhibitor-mediated pneumonitis risk stratification in patients with locally advanced non-small cell lung cancer: role of functional lung radiomics? *Discov Oncol*. 2022;13(1):85. doi:10.1007/s12672-022-00548-4
55. Zhang Q, Feng X, Hu W, et al. Chronic obstructive pulmonary disease alters the genetic landscape and tumor immune microenvironment in lung cancer patients. *Front Oncol*. 2023;13:1169874. doi:10.3389/fonc.2023.1169874
56. Feng Z, Yin Y, Liu B, et al. ZNF143 expression is associated with COPD and tumor microenvironment in non-small cell lung cancer. *Int J Chron Obstruct Pulmon Dis*. 2022;17:685–700. doi:10.2147/copd.S352392
57. Ma H, Zhang Q, Zhao Y, et al. Molecular and clinicopathological characteristics of lung cancer concomitant chronic obstructive pulmonary disease (COPD). *Int J Chron Obstruct Pulmon Dis*. 2022;17:1601–1612. doi:10.2147/copd.S363482
58. Tiu BC, Zubiri L, Iheke J, et al. Real-world incidence and impact of pneumonitis in patients with lung cancer treated with immune checkpoint inhibitors: a multi-institutional cohort study. *J ImmunoTherapy Cancer*. 2022;10(6). doi:10.1136/jitc-2022-004670
59. Zeneyedpour L, Dekker LJM, van Sten-van THJJM, Burgers PC, Ten Hacken NHT, Luider TM. Neoantigens in chronic obstructive pulmonary disease and lung cancer: a point of view. *Proteomics Clin Appl*. 2019;13(2):e1800093. doi:10.1002/prca.201800093
60. Bu T, Wang LF, Yin YQ. How do innate immune cells contribute to airway remodeling in COPD progression? *Int J Chron Obstruct Pulmon Dis*. 2020;15:107–116. doi:10.2147/copd.S235054
61. Faget J, Peters S, Quantin X, Meylan E, Bonnefoy N. Neutrophils in the era of immune checkpoint blockade. *J ImmunoTherapy Cancer*. 2021;9 (7). doi:10.1136/jitc-2020-002242
62. Huber ME, Larson E, Lust TN, Heisler CM, Harriff MJ. Chronic obstructive pulmonary disease and cigarette smoke lead to dysregulated mucosal-associated invariant T-cell activation. *Am J Respir Cell Mol Biol*. 2023;68(1):90–102. doi:10.1165/rcmb.2022-0131OC
63. Qi C, Sun SW, Xiong XZ. From COPD to lung cancer: mechanisms linking, diagnosis, treatment, and prognosis. *Int J Chron Obstruct Pulmon Dis*. 2022;17:2603–2621. doi:10.2147/copd.S380732
64. Hirano T, Matsunaga K, Sugiura H, et al. Relationship between alveolar nitric oxide concentration in exhaled air and small airway function in COPD. *J Breath Res*. 2013;7(4):046002. doi:10.1088/1752-7155/7/4/046002
65. Hogg JC, Chu F, Utokaparch S, et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. *New Engl J Med*. 2004;350(26):2645–2653. doi:10.1056/NEJMoa032158
66. McKendry RT, Spalluto CM, Burke H, et al. Dysregulation of antiviral function of CD8(+) T cells in the chronic obstructive pulmonary disease lung. role of the PD-1-PD-L1 Axis. *Am J Respir Crit Care Med*. 2016;193(6):642–651. doi:10.1164/rccm.201504-0782OC
67. Parris BA, O'Farrell HE, Fong KM, Yang IA. Chronic obstructive pulmonary disease (COPD) and lung cancer: common pathways for pathogenesis. *J Thorac Dis*. 2019;11(Suppl 17):S2155–s2172. doi:10.21037/jtd.2019.10.54
68. Kim TK, Vandsemb EN, Herbst RS, Chen L. Adaptive immune resistance at the tumour site: mechanisms and therapeutic opportunities. *Nature Reviews Drug Discovery*. 2022;21(7):529–540. doi:10.1038/s41573-022-00493-5
69. Trudzinski FC, Seiler F, Wilkens H, et al. Microbiological airway colonization in COPD patients with severe emphysema undergoing endoscopic lung volume reduction. *Int J Chron Obstruct Pulmon Dis*. 2018;13:29–35. doi:10.2147/copd.S150705
70. Karakasidis E, Kotsiou OS, Gourgoulianis KI. Lung and Gut Microbiome in COPD. *J Pers Med*. 2023;13(5). doi:10.3390/jpm13050804
71. Liu Y, O'Brien JL, Ajami NJ, et al. Lung tissue microbial profile in lung cancer is distinct from emphysema. *Am J Cancer Res*. 2018;8 (9):1775–1787.
72. Laroumagne S, Lepage B, Hermant C, et al. Bronchial colonisation in patients with lung cancer: a prospective study. *Europ resp J*. 2013;42 (1):220–229. doi:10.1183/09031936.00062212
73. Eklöf J, Sørensen R, Ingebrigtsen TS, et al. Pseudomonas aeruginosa and risk of death and exacerbations in patients with chronic obstructive pulmonary disease: an observational cohort study of 22 053 patients. *Clin Microbiol Infect*. 2020;26(2):227–234. doi:10.1016/j.cmi.2019.06.011

74. Martinez-García MA, Rigau D, Barrecheguren M, et al. Long-term risk of mortality associated with isolation of pseudomonas aeruginosa in COPD: a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis*. 2022;17:371–382. doi:10.2147/copd.S346294
75. Newsome BR, McDonnell K, Hucks J, Dawson Estrada R. Chronic obstructive pulmonary disease: clinical implications for patients with lung cancer. *Clin J Oncol Nurs*. 2018;22(2):184–192. doi:10.1188/18.cjon.184-192
76. Sul J, Blumenthal GM, Jiang X, He K, Keegan P, Pazdur R. FDA approval summary: pembrolizumab for the treatment of patients with metastatic non-small cell lung cancer whose tumors express programmed death-ligand 1. *Oncologist*. 2016;21(5):643–650. doi:10.1634/theoncologist.2015-0498
77. Atchley WT, Alvarez C, Saxena-Beem S, et al. Immune checkpoint inhibitor-related pneumonitis in lung cancer: real-world incidence, risk factors, and management practices across six health care centers in North Carolina. *Chest*. 2021;160(2):731–742. doi:10.1016/j.chest.2021.02.032
78. Venkatesan P. GOLD COPD report: 2023 update. *Lancet Respir Med*. 2023;11(1):18. doi:10.1016/s2213-2600(22)00494-5
79. Kim S, Lim JU. Immune checkpoint inhibitor-related interstitial lung disease in patients with advanced non-small cell lung cancer: systematic review of characteristics, incidence, risk factors, and management. *J Thorac Dis*. 2022;14(5):1684–1695. doi:10.21037/jtd-22-93
80. Lee TS, Jin KN, Lee HW, et al. Interstitial lung abnormalities and the clinical course in patients with COPD. *Chest*. 2021;159(1):128–137. doi:10.1016/j.chest.2020.08.017
81. Lynch DA, Moore CM, Wilson C, et al. CT-based visual classification of emphysema: association with mortality in the COPDGene study. *Radiology*. 2018;288(3):859–866. doi:10.1148/radiol.2018172294
82. Cottin V, Nunes H, Brillet PY, et al. Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity. *Europ resp J*. 2005;26(4):586–593. doi:10.1183/09031936.05.00021005
83. Zhou C, Qin Y, Zhao W, et al. International expert consensus on diagnosis and treatment of lung cancer complicated by chronic obstructive pulmonary disease. *Transl Lung Cancer Res*. 2023;12(8):1661–1701. doi:10.21037/tlcr-23-339
84. Liu H, Luo SX, Jie J, Peng L, Wang S, Song L. Immune checkpoint inhibitors related respiratory disorders in patients with lung cancer: a meta-analysis of randomized controlled trials. *Front Immunol*. 2023;14:1115305. doi:10.3389/fimmu.2023.1115305
85. Dong W, Yin Y, Liu B, et al. Efficacy and safety of pembrolizumab as first-line treatment for advanced non-small cell lung cancer complicated with chronic obstructive pulmonary disease: protocol for a prospective, single-arm, single-center, Phase II clinical trial. *Front Oncol*. 2024;14:1179232. doi:10.3389/fonc.2024.1179232
86. Jeon D, Hill E, Moseman JE, McNeel DG. Combining toll-like receptor agonists with immune checkpoint blockade affects antitumor vaccine efficacy. *J ImmunoTherapy Cancer*. 2024;12(5). doi:10.1136/jitc-2024-008799
87. Ichikawa T, Sugiura H, Koarai A, et al. TLR3 activation augments matrix metalloproteinase production through reactive nitrogen species generation in human lung fibroblasts. *J Immunol*. 2014;192(11):4977–4988. doi:10.4049/jimmunol.1302919
88. Liu D, Chen Q, Zhu H, et al. Association of respiratory syncytial virus toll-like receptor 3-mediated immune response with COPD exacerbation frequency. *Inflammation*. 2018;41(2):654–666. doi:10.1007/s10753-017-0720-4
89. Tian J, Liu C, Wang X, et al. Comparative analysis of clinical features of lower respiratory tract infection with respiratory syncytial virus and influenza virus in adults: a retrospective study. *BMC Pulm Med*. 2023;23(1):350. doi:10.1186/s12890-023-02648-5
90. Couturaud F, Bertoletti L, Pastre J, et al. Prevalence of pulmonary embolism among patients with COPD hospitalized with acutely worsening respiratory symptoms. *JAMA*. 2021;325(1):59–68. doi:10.1001/jama.2020.23567
91. Jiménez D, Agustí A, Tabernero E, et al. Effect of a pulmonary embolism diagnostic strategy on clinical outcomes in patients hospitalized for COPD exacerbation: a randomized clinical trial. *JAMA*. 2021;326(13):1277–1285. doi:10.1001/jama.2021.14846
92. Kalathil SG, Lugade AA, Pradhan V, et al. T-regulatory cells and programmed death 1+ T cells contribute to effector T-cell dysfunction in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2014;190(1):40–50. doi:10.1164/rccm.201312-2293OC
93. Bhat TA, Panzica L, Kalathil SG, Thanavala Y. Immune dysfunction in patients with chronic obstructive pulmonary disease. *Ann Am Thorac Soc*. 2015;12(Suppl 2):S169–75. doi:10.1513/AnnalsATS.201503-126AW
94. Hamashima R, Uchino J, Morimoto Y, et al. Association of immune checkpoint inhibitors with respiratory infections: a review. *Cancer Treat Rev*. 2020;90:102109. doi:10.1016/j.ctrv.2020.102109
95. Chalela R, Gea J, Barreiro E. Immune phenotypes in lung cancer patients with COPD: potential implications for immunotherapy. *J Thorac Dis*. 2018;10(Suppl 18):S2186–s2189. doi:10.21037/jtd.2018.06.143
96. Riondino S, Rosenfeld R, Formica V, et al. Effectiveness of immunotherapy in non-small cell lung cancer patients with a diagnosis of COPD: is this a hidden prognosticator for survival and a risk factor for immune-related adverse events? *Cancers*. 2024;16(7). doi:10.3390/cancers16071251
97. Iwama E, Okamoto I, Yabuuchi H, et al. Characteristics of smoking patients with lung cancer with emphysematous bullae. *J Thoracic Oncol*. 2016;11(9):1586–1590. doi:10.1016/j.jtho.2016.04.024
98. Huang CY, Jiang N, Shen M, et al. Oncogene-driven non-small cell lung cancers in patients with a history of smoking lack smoking-induced mutations. *Cancer Res*. 2024;84(12):2009–2020. doi:10.1158/0008-5472.Can-23-2551
99. Caramori G, Ruggeri P, Mumby S, et al. Molecular links between COPD and lung cancer: new targets for drug discovery? *Expert Opin Ther Targets*. 2019;23(6):539–553. doi:10.1080/14728222.2019.1615884
100. Ying H, Xu J, Zhang X, Liang T, Bai X. Human endogenous retrovirus-H long terminal repeat-associating 2: the next immune checkpoint for antitumour therapy. *EBioMedicine*. 2022;79:103987. doi:10.1016/j.ebiom.2022.103987
101. Ritzmann F, Jungnickel C, Vella G, et al. IL-17C-mediated innate inflammation decreases the response to PD-1 blockade in a model of Kras-driven lung cancer. *Sci Rep*. 2019;9(1):10353. doi:10.1038/s41598-019-46759-8
102. Sudduth ER, Trautmann-Rodriguez M, Gill N, Bomb K, Fromen CA. Aerosol pulmonary immune engineering. *Adv Drug Deliv Rev*. 2023;199:114831. doi:10.1016/j.addr.2023.114831
103. Jin Q, Zhu W, Zhu J, et al. Nanoparticle-mediated delivery of inhaled immunotherapeutics for treating lung metastasis. *Adv Mater*. 2021;33(7):e2007557. doi:10.1002/adma.202007557
104. Le Naour J, Galluzzi L, Zitvogel L, Kroemer G, Vacchelli E. Trial watch: TLR3 agonists in cancer therapy. *Oncoimmunology*. 2020;9(1):1771143. doi:10.1080/2162402x.2020.1771143

105. Meier P, Legrand AJ, Adam D, Silke J. Immunogenic cell death in cancer: targeting necroptosis to induce antitumour immunity. *Nat Rev Cancer*. 2024;24(5):299–315. doi:10.1038/s41568-024-00674-x
106. Dubinett SM, Spira AE. Impact of chronic obstructive pulmonary disease on immune-based treatment for lung cancer. moving toward disease interception. *Am J Respir Crit Care Med*. 2018;197(3):278–280. doi:10.1164/rccm.201710-2065ED
107. Metwally EM, Lund JL, Drummond MB, Peacock Hinton S, Poole C, Thompson CA. COPD with lung cancer among older United States adults: prevalence, diagnostic timeliness, and association with earlier stage tumors. *Chronic Obstr Pulm Dis*. 2024. doi:10.15326/jcopdf.2024.0489
108. Girard N, Bar J, Garrido P, et al. Treatment characteristics and real-world progression-free survival in patients with unresectable stage III NSCLC who received durvalumab after chemoradiotherapy: findings from the PACIFIC-R study. *J Thoracic Oncol*. 2023;18(2):181–193. doi:10.1016/j.jtho.2022.10.003
109. Putman RK, Hatabu H, Araki T, et al. Association between interstitial lung abnormalities and all-cause mortality. *JAMA*. 2016;315(7):672–681. doi:10.1001/jama.2016.0518
110. Nemoto M, Koo CW, Scanlon PD, Ryu JH. Combined pulmonary fibrosis and emphysema: a narrative review. *Mayo Clin Proc*. 2023;98(11):1685–1696. doi:10.1016/j.mayocp.2023.05.002
111. Liu Y, Carlson SA, Watson KB, Xu F, Greenlund KJ. Trends in the prevalence of chronic obstructive pulmonary disease among adults aged ≥18 Years - United States, 2011-2021. *MMWR Morb Mortal Wkly Rep*. 2023;72(46):1250–1256. doi:10.15585/mmwr.mm7246a1
112. Olson E, Faucheux A, Liang J, et al. 656 Time to diagnostic clarity for suspected checkpoint-inhibitor pneumonitis in patients with lung cancer. *BMJ Spec J*. 2020.
113. Bhatt SP, Rabe KF, Hanania NA, et al. Dupilumab for COPD with Type 2 inflammation indicated by eosinophil counts. *New Engl J Med*. 2023;389(3):205–214. doi:10.1056/NEJMoa2303951