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META-ANALYSIS

Zhu and Wang: COPD and ICIs in NSCLC

The role of COPD in survival of NSCLC patients receiving immune checkpoint inhibitors: A meta-analysis

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ABSTRACT

The impact of chronic obstructive pulmonary disease (COPD) on the survival of patients with non-small cell lung cancer (NSCLC) receiving immune checkpoint inhibitors (ICIs) remains unclear. Given the growing use of ICIs in NSCLC treatment and the high prevalence of COPD among these patients, understanding this relationship is essential. This meta-analysis aims to evaluate the association between COPD and survival outcomes in NSCLC patients treated with ICIs. A systematic search was conducted in PubMed, Embase, and Web of Science from inception to February 10, 2025. Observational studies reporting survival outcomes in NSCLC patients with and without COPD undergoing ICI therapy were included. Hazard ratios (HRs) with 95% confidence intervals (CIs) were pooled using a random-effects model to account for heterogeneity. Thirteen retrospective cohort studies involving 5,564 patients were included. COPD was associated with improved progression-free survival (PFS) (HR: 0.68, 95% CI: 0.54–0.85, $p < 0.001$) and overall survival (OS) (HR: 0.80, 95% CI: 0.68–0.95, $p = 0.01$) in NSCLC patients receiving ICIs. Heterogeneity was moderate ($I^2 = 46\%$ for PFS, $I^2 = 43\%$ for OS). Subgroup analyses indicated that the association between COPD and survival outcomes was consistent across study regions (Asian vs. Western countries), patient age, sex distribution, COPD diagnostic criteria (spirometry, clinical diagnosis, or CT-diagnosed emphysema), follow-up duration, analytic models (univariate vs. multivariate), and study quality scores (p for subgroup differences > 0.05). Furthermore, univariate meta-regression analysis showed no significant modification of results by sample size, mean age, sex distribution, follow-up duration, or study quality scores (all $p > 0.05$).

Keywords: Non-small cell lung cancer; NSCLC; chronic obstructive pulmonary disease; COPD; immune checkpoint inhibitors; ICIs; survival; meta-analysis.

INTRODUCTION

Lung cancer remains the leading cause of cancer-related mortality worldwide, with non-small cell lung cancer (NSCLC) accounting for approximately 85% of all cases (1, 2). Despite advancements in diagnostic techniques and treatment modalities, the prognosis for NSCLC remains poor, particularly in patients with advanced-stage disease (3). Historically, chemotherapy and targeted therapies have been the mainstay of treatment, but in recent years, immune checkpoint inhibitors (ICIs) have revolutionized the therapeutic landscape (4, 5). By targeting programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), ICIs restore antitumor immune responses (6), leading to significant improvements in survival outcomes for selected patients with NSCLC (7). However, the response to ICIs varies considerably among individuals, necessitating the identification of predictive factors that can help refine patient selection and optimize therapeutic efficacy (8).

Chronic obstructive pulmonary disease (COPD), a progressive inflammatory lung condition characterized by persistent airflow limitation, is highly prevalent among patients with NSCLC, with reported rates ranging from 40% to 70% (9, 10). Shared risk factors, particularly cigarette smoking, contribute to this strong association (11). COPD has traditionally been considered a poor prognostic factor in NSCLC, as it is linked to increased perioperative complications, a higher risk of pulmonary infections, and reduced tolerance to chemotherapy and radiotherapy (12). Several observational studies (13, 14) and a meta-analysis (15) have suggested that COPD may be associated with inferior survival in NSCLC. However, most of these studies have focused on patients receiving conventional treatments, while those undergoing ICI therapy were largely underrepresented (15). This gap in knowledge has led to uncertainties regarding the impact of COPD on ICI efficacy in NSCLC.

Emerging evidence suggests that COPD may not uniformly exert a detrimental effect on NSCLC outcomes, particularly in the context of ICI treatment (16). Recent studies indicate that COPD-related immune dysregulation may paradoxically enhance the effectiveness of ICIs in lung cancer (17). COPD is associated with chronic inflammation and alterations in the tumor microenvironment, which may modulate immune responses (18). Specifically, patients with COPD have been found to exhibit

increased PD-L1 expression on tumor cells and elevated tumor mutational burden (TMB), both of which are established biomarkers of ICI response (17, 19). Moreover, COPD has been linked to alterations in immune cell composition, including an increased infiltration of CD8+ T cells and heightened immune activation, which could potentiate the antitumor effects of ICIs (17, 19). Emerging clinical studies have also reported improved survival outcomes in NSCLC patients with coexisting COPD treated with ICIs (20-29), though not all findings reached statistical significance. These findings have challenged the conventional belief that COPD universally worsens lung cancer prognosis. However, the available evidence remains inconsistent (30-32), and no comprehensive meta-analysis has systematically evaluated the influence of COPD on ICI efficacy in NSCLC. Given these uncertainties, this meta-analysis aims to provide a comprehensive evaluation of the impact of COPD on survival outcomes in patients with NSCLC receiving ICIs, including progression-free survival (PFS) and overall survival (OS).

MATERIALS AND METHODS

The study adhered to PRISMA 2020 (33, 34) and the Cochrane Handbook for Systematic Reviews and Meta-analyses (35) guidelines for conducting this meta-analysis, including for the study protocol design, data extraction, statistical analysis, and results presentation. The protocol of the meta-analysis has been registered at the International Prospective Register of Systematic Reviews (PROSPERO) with the identifier CRD420251006457.

Literature search

To identify studies pertinent to this meta-analysis, we searched PubMed, Embase, and Web of Science databases using an extensive array of search terms, which included: (1) chronic obstructive pulmonary disease" OR "COPD" OR "chronic obstructive lung disease" OR "chronic obstructive airway disease" OR "emphysema" OR "chronic airflow limitation" OR "chronic airway obstruction"; (2) Non-Small Cell Lung Cancer" OR "Non-Small Cell Carcinoma" OR "NSCLC" OR "Lung Adenocarcinoma" OR "Lung Squamous Cell Carcinoma" OR "Lung Neoplasms"; and (3) "Immune Checkpoint Inhibitors" OR "ICI" OR "Programmed Cell Death Protein 1" OR "PD-1" OR "PD-L1" OR "Cytotoxic T-Lymphocyte-Associated Protein 4" OR

"CTLA-4" OR "Pembrolizumab" OR "Nivolumab" OR "Atezolizumab" OR "Durvalumab" OR "Cemiplimab" OR "Avelumab" OR "Ipilimumab" OR "Tremelimumab". The search was restricted to studies conducted on human subjects and included only full-length articles published in English in peer-reviewed journals. Additionally, the references of relevant original and review articles were manually screened to identify any additional eligible studies. The literature search covered the period from the inception of the databases to February 10, 2025. The detailed search strategy for each database is shown in Supplemental File 1.

Inclusion and exclusion criteria

The inclusion criteria for potential studies were defined according to the PICOS framework:

P (patients): Adult patients (aged 18 years or older) with confirmed diagnosis of NSCLC receiving ICIs, regardless of the cancer histology, stage, or previous anticancer treatments.

I (exposure): Patients with COPD. The methods for the validation of COPD were consistent with those used in the original studies.

C (comparison): Patients without COPD.

O (outcome): Survival outcomes, including OS and PFS, compared between patients with and without COPD. In general, PFS is defined as the time from ICIs treatment initiation to disease progression or death, whichever occurs first, while OS is defined as the time from ICIs treatment initiation to death from any cause.

S (study design): Observational studies with longitudinal follow-up, such as cohort studies, nested case-control studies, or post-hoc analyses of clinical trials;

Studies were excluded if they were reviews, editorials, meta-analyses, or preclinical research, or if they did not exclusively include patients with NSCLC, did not receive ICIs, lacked COPD as an exposure, or did not report the survival outcomes of interest. For studies with overlapping populations, the one with the largest sample size was included in the meta-analysis.

Study quality assessment and data extraction

The literature search, study selection, quality assessment, and data extraction were independently performed by two authors, with discrepancies resolved through discussion and consensus between the two authors. Study quality was assessed using the Newcastle–Ottawa Scale (NOS) (36), which evaluates selection, control of confounding factors, and outcome measurement and analysis, with scores ranging from 1 to 9, where a score of 9 indicates the highest quality. Studies with the NOS scores of 7 or above were generally considered as high-quality studies (36). Data extracted for analysis included study characteristics (author, year, country, and design), participant details (number of patients, mean age, sex, cancer stage, and ICIs used), methods for the diagnosis of COPD and the number of patients with COPD in each study, median follow-up durations, and variables adjsuted when the associations between COPD and survival outcomes of patients with NSCLC receiving ICIs were reported.

Statistical analysis

The associations between COPD and PFS/OS of patients with NSCLC receiving ICIs were summarized as hazard ratios (HRs) and corresponding 95% confidence intervals (CIs), compared between patients with and without COPD. The HRs and their standard errors were derived from 95% CIs or p-values and subsequently log-transformed to stabilize variance and achieve a normalized distribution (35). To assess heterogeneity, we used the Cochrane Q test and I^2 statistics (37), with I^2 < 25%, 25~75%, and > 75% indicating low, moderate, and high heterogeneity. A random-effects model was applied to integrate the results, accounting for study variability (35). Via excluding individual studies sequentially, a sensitivity analysis was performed to evaluate the robustness of the findings. In addition, subgroup analyses were performed to evaluate study characteristics on the outcomes, such as study country (Asian versus Western countries), mean ages of the patients, proportions of men, diagnostic methods for COPD, median follow-up durations, analytic models (univariate or multivariate), and NOS scores. The medians of continuous variables were used as cutoff points to define subgroups. In addition, the univariate meta-regression analysis was performed to evaluated if the association between COPD and survival outcomes could be significantly modified by characteristics such as sample

size, mean age, proportion of men, follow-up duration, and NOS scores (35). Publication bias was evaluated using funnel plots and visual inspection for asymmetry, supplemented by Egger's regression test (38). Analyses were performed using RevMan (Version 5.1; Cochrane Collaboration, Oxford, UK) and Stata software (version 12.0; Stata Corporation, College Station, TX, USA).

RESULTS

Study identification

The study selection process is summarized in Figure 1. A total of 569 potentially relevant records were initially identified from the three databases searched and screening of citations of related articles, with 159 duplicates removed. Screening of titles and abstracts resulted in the exclusion of 386 articles that did not meet the objectives of the meta-analysis. The full texts of the remaining 24 articles were independently reviewed by two authors, leading to the exclusion of 11 studies for various reasons detailed in Figure 1. Ultimately, 13 studies were included in the quantitative analysis (20-32).

Overview of the study characteristics

Table 1 shows the summarized characteristics of the available studies included in the meta-analysis. Overall, 13 retrospective cohorts, published between 2018 and 2025, and performed in France, the United States, Korea, Japan, China, Australia, and Canada, were involved in the meta-analysis (20-32). A total of 5,564 patients with NSCLC were included in these studies. The mean ages of the patients varied from 60.6 to 73.0 years, and the proportion of men varied from 35.7 to 95.1%. As for the cancer stage, 10 studies included patients with advanced NSCLC with stage III to IV (20-26, 29, 30, 32), while the other three studies included patients with stage I-III (27, 31) and stage I-IV NSCLC (28), respectively. All of the included patients received ICIs. The diagnosis of COPD was evidenced by the forced expiratory volume in one second/forced vital capacity (FEV1/FVC) ratio < 0.7 in five studies (20, 22, 27, 30, 31), via clinical diagnosis in medical chart in five studies (21, 26, 28, 29, 32), and by CT diagnosed pulmonary emphysema (PE) in three studies (23-25). Accordingly, 2,945 (52.9%) of the included patients were with COPD at the initiation of ICIs treatment. The median follow-up durations were 10 to 42 months among the included

studies. The outcome of PFS was reported in 11 studies (20-22, 24-27, 29-32), while the outcome of OS was reported in 10 studies (20-26, 28, 31, 32). As shown in Table 1, survival outcomes were derived from either univariate or multivariate Cox proportional hazards regression analyses. For data synthesis, we extracted the most adequately adjusted HRs and corresponding 95% CIs available from each study. Univariate analyses were performed in five studies when the associations between COPD and survival outcomes were reported (20, 23, 26, 30, 31), while multivariate analyses with adjustments of age, sex, tumor stage, and histology etc. were conducted in the other eight studies (21, 22, 24, 25, 27-29, 32). The included studies achieved NOS scores ranging from five to nine, reflecting a generally moderate to high quality of methodology and reporting (Table 2).

Association between COPD and PFS

Overall, 11 studies (20-22, 24-27, 29-32) reported the association between COPD and PFS of patients with NSCLC receiving ICIs. A moderate heterogeneity was observed among these studies (p for Cochrane Q test = 0.05; I^2 = 46%). The pooled results showed that overall, COPD was associated with better PFS of these patients (HR: 0.68, 95% CI: 0.54 to 0.85, p < 0.001; Figure 2A). Sensitivity analyses by excluding one study at a time showed similar results (HR: 0.64 to 0.72, p all < 0.05). Moreover, subgroup analyses showed that the association between COPD and PFS of NSCLC patients on ICIs was not significantly affected by study country, mean ages of the patients, proportions of men, the diagnosis of COPD, follow-up durations, the analytic model, or NOS scores of the included studies (p for subgroup difference all > 0.05; Table 3).

Association between COPD and OS

The pooled results of 10 studies (20-26, 28, 31, 32) showed that COPD also was associated with better OS in patients with NSCLC on ICIs (HR: 0.80, 95% CI: 0.68 to 0.95, p = 0. 01; Figure 2B) with moderate heterogeneity (p for Cochrane Q test = 0.07; I^2 = 43%). Further sensitivity analysis by excluding one study at a time did not significantly change the results (HR: 0.75 to 0.89, p all < 0.05). Similar to the findings for OS, subgroup analyses according to study country, mean ages, proportions of men, COPD diagnosis, follow-up durations, the analytic model, or NOS scores did not significantly modify the results (p for subgroup difference all > 0.05; Table 3). In

addition, results of the univariate meta-regression analysis did not suggest that the results could be significantly modified by characteristics such as sample size, mean age, proportion of men, follow-up duration, or study quality scores (p all > 0.05; Table 4).

Publication bias

The funnel plots for the meta-analyses assessing the associations between COPD and PFS/OS of patients with NSCLC on ICIs are shown in **Figure 3A and 3B**. Visual inspection of the plots reveals symmetry, indicating a low risk of publication bias. These findings are further supported by Egger's regression analyses (for PFS: p = 0.47; for OS: p = 0.42).

DISCUSSION

Our meta-analysis provides comprehensive evidence on the influence of COPD on the survival of patients with NSCLC treated with ICIs. The pooled results from 13 retrospective cohort studies, including 5,564 patients, indicate that COPD is associated with improved PFS and OS in patients receiving ICIs. These findings challenge the conventional notion that COPD universally worsens lung cancer outcomes and suggest that COPD may confer a survival advantage in NSCLC patients undergoing ICI therapy.

The potential mechanisms underlying the observed association between COPD and improved ICI efficacy remain an area of active investigation (17, 19). Several studies have proposed that COPD-related immune dysregulation may enhance the therapeutic effects of ICIs (17). Patients with COPD exhibit chronic inflammation and immune alterations that may increase tumor immunogenicity (39). Notably, COPD is associated with increased infiltration of CD8+ tumor-infiltrating lymphocytes (TILs), which play a crucial role in anti-tumor immunity (40). A study by Biton et al. demonstrated that COPD patients with NSCLC exhibited a higher level of PD-1/TIM-3 coexpression in CD8+ T cells, suggesting increased T-cell exhaustion and a potential for greater responsiveness to PD-1 blockade (20). In addition, Th1 cell populations were observed to be expanded in both lung and tumor microenvironments in patients with COPD and NSCLC, which may also be associated with better responsiveness to ICIs (21). Furthermore, PD-L1 expression, a key biomarker for ICI

efficacy, appears to be upregulated in COPD-associated NSCLC, which may partly explain the improved ICI response observed in our meta-analysis (41, 42). Increased TMB has also been reported in COPD-associated lung cancer (41), which is another well-recognized predictor of better ICI efficacy. Collectively, these findings suggest that the inflammatory milieu of COPD may foster an immune microenvironment that is more susceptible to ICI therapy. Consistently, a recent study (43) also found better PFS with chemotherapy in NSCLC patients with COPD, which is possibly related to the reduced systemic inflammation and enhanced immune activation. These mechanisms may likewise contribute to improved ICI efficacy in patients with NSCLC and COPD.

Subgroup analyses in our study revealed that the association between COPD and improved survival was consistent across various study characteristics, including geographic region, patient age, sex distribution, COPD diagnostic criteria (spirometry vs. clinical diagnosis vs. CT-diagnosed emphysema), and follow-up duration. Notably, the survival benefit was more pronounced in studies that reported multivariate-adjusted hazard ratios, suggesting that confounding factors such as smoking history, tumor histology, and comorbidities did not fully account for the observed association. This reinforces the hypothesis that COPD itself, rather than associated lifestyle factors, contributes to enhanced ICI efficacy. In addition, results of the univariate meta-regression analysis did not support that the results could be significantly modified by characteristics such as sample size, mean age, proportion of men, follow-up duration, or NOS scores, which also validated the robustness of the findings.

Beyond survival outcomes, the interaction between ICIs and COPD itself is of particular interest. Recent evidence suggests that PD-1 blockade may modulate lung inflammation and pulmonary function in COPD patients (44, 45). A prospective study by Suzuki et al. demonstrated that COPD patients treated with nivolumab exhibited significant increases in FVC and FEV1, suggesting a potential beneficial effect of PD-1 inhibition on pulmonary function (44). Furthermore, while fractioned exhaled nitric oxide (FeNO) levels were significantly elevated in COPD patients after ICI therapy—indicating increased airway inflammation—no significant worsening of dyspnea or COPD exacerbations was observed (44). Notably, the study also found a numerically higher tumor response rate in COPD patients, reinforcing the hypothesis that immune

changes associated with COPD may enhance ICI efficacy (44). However, while this study suggested that ICIs appear to improve NSCLC survival and may not worsen COPD symptoms (44), a recent study reported an increased risk of COPD exacerbations following ICI therapy (45). In a large retrospective cohort from the United States, COPD patients treated with ICIs had higher rates of COPD exacerbations and respiratory-related hospitalizations, likely due to immune-related inflammation (45). The discrepancy between these findings highlights the complexity of ICI effects on COPD and the need for further research to optimize patient management.

Clinically, our findings suggest that COPD should not be considered a contraindication to ICI therapy in NSCLC. Instead, the presence of COPD may serve as a potential biomarker for enhanced ICI efficacy. However, given the possibility of COPD exacerbation following ICI treatment, close monitoring and proactive management of COPD symptoms are essential to ensure optimal patient outcomes. Future research should focus on prospective studies to validate our findings and elucidate the precise mechanisms by which COPD modulates the tumor immune microenvironment. Additionally, investigations into the role of COPD treatments, such as inhaled corticosteroids and bronchodilators, on ICI efficacy are warranted, as these therapies may influence immune responses.

Our meta-analysis has several strengths. It represents the most up-to-date and comprehensive synthesis of data on this topic, incorporating an extensive literature search across multiple databases. The inclusion of cohort studies with longitudinal follow-up enhances the reliability of our findings, as these studies provide robust estimates of real-world survival outcomes. Additionally, multiple sensitivity, subgroup, and meta-regression analyses were performed to validate the robustness of the findings, minimizing the potential impact of bias and confounding. However, our study also has limitations. First, all included studies were retrospective in nature, which introduces inherent risks of recall bias and selection bias (46). Second, the potential impact of COPD-specific treatments, including inhaled corticosteroids and bronchodilators, on survival outcomes could not be evaluated due to lack of detailed treatment data in most studies. These medications may influence systemic inflammation or immune responses and could confound the observed associations (47, 48) could have influenced survival outcomes. Moreover, due to the observational

design of the included studies, causality cannot be established, and residual confounding remains a possibility. Third, we were unable to assess the impact of certain patient and study characteristics, such as concurrent medications, tumor histology, and the presence of immune-related adverse events, as individual patient data were not accessible. These factors may have modulated the relationship between COPD and ICI response. Additionally, some included studies enrolled patients with early-stage NSCLC (stage I–II) who received ICIs in the neoadjuvant or adjuvant setting (27, 28, 31), where survival outcomes may be more strongly influenced by surgical success and perioperative factors rather than systemic therapy alone. Although the majority of studies included patients with unresectable stage III–IV disease, we were unable to perform subgroup analyses by cancer stage due to the lack of individual patient data. This limitation should be considered when interpreting the pooled results. Moreover, the impact of ICI therapy on COPD progression was not evaluated in our included studies, though recent evidence suggests that COPD symptoms may worsen following treatment. Future research should explore strategies to mitigate ICI-associated COPD exacerbations while maintaining treatment efficacy. Furthermore, not all included studies used spirometry to define COPD; some relied on clinical diagnosis or CT evidence of emphysema, which may not fully meet standardized diagnostic criteria. This heterogeneity in exposure definition may introduce misclassification bias and affect the interpretation of pooled results. Finally, the interpretation of funnel plots and Egger's test should be made with caution due to the limited number of included studies. A nonsignificant Egger's test does not preclude the possibility of publication bias due to the limited studies included.

CONCLUSION

In conclusion, this meta-analysis demonstrates that COPD is associated with improved survival in NSCLC patients treated with ICIs. The underlying mechanisms may involve enhanced tumor immunogenicity, increased PD-L1 expression, and higher TMB in COPD-associated lung cancer. However, recent evidence indicates that ICI therapy may exacerbate COPD symptoms, necessitating careful patient monitoring. These findings provide novel insights into the interaction between COPD and immunotherapy response, warranting further prospective validation and mechanistic studies.

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Data availability: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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TABLES AND FIGURES WITH LEGENDS

Table 1. Characteristics of the included cohort studies

Study	Country	Design	No. of patients included	Mean age (years)	Men (%)	Cancer stage	ICIs used	Methods for the diagnosis of COPD	No. of patients with COPD	Median follow-up duration (months)	Outcomes reported	Variables adjusted
Biton 2018	France	RC	39	68.7	61.5	IIIB to IV	Nivolumab	Postbronchodilator FEV1/FVC ratio < 0.7	19	21	PFS and OS	None
Mark 2018	USA	RC	125	66.4	56.8	III to IV	Nivolumab, pembrolizumab, atezolizumab, or avelumab	Clinically diagnosed COPD	60	20	PFS and OS	Age, sex, smoking status, previous history of CAD, previous anticancer treatment, and BMI

Shin 2019	Korea	RC	133	62.9	75.9	IV	Pembrolizumab	Postbronchodilator FEV1/FVC ratio < 0.7	59	12	PFS and OS	Age, sex, smoking, ECOG PS, tumor histology, and previous anticancer treatment
Isono 2020	Japan	RC	180	68.5	77.8	III to IV	Nivolumab, pembrolizumab, or atezolizumab	CT diagnosed pulmonary emphysema	99	10	OS	None
Takayama 2021	Japan	RC	153	68	75.2	III to IV	Nivolumab, pembrolizumab, or atezolizumab	CT diagnosed pulmonary emphysema	71	20	PFS and OS	Age, sex, smoking, ECOG PS, tumor histology, previous anticancer treatment, and PD-L1 expression

												status
Zeng 2022	China	RC	122	66	95.1	IV	Nivolumab, or pembrolizumab	Clinically diagnosed COPD	61	20	PFS and OS	None
Noda 2022	Japan	RC	56	70.8	35.7	IIIB to IV	Nivolumab, pembrolizumab, or atezolizumab	CT diagnosed pulmonary emphysema	41	20	PFS and OS	Age, sex, smoking, ECOG PS, tumor histology, previous anticancer treatment, and PD-L1 expression status
Zhang 2022	China	RC	99	64.9	92.9	IIIB to IV	NR	Postbronchodilator FEV1/FVC ratio < 0.7	80	42	PFS	None
Dong 2024	China	RC	74	63.4	87.8	I-IIIB	Nivolumab, pembrolizumab, atezolizumab,	Postbronchodilator FEV1/FVC ratio < 0.7	30	18	PFS	Age, sex, smoking, ECOG PS, tumor

							tirellizumab, toripalimab, sintilimab, camrelizumab, or durvalumab					histology, tumor stage, and neoadjuvant cycles
Stevens 2024	Australia	RC	152	67	63.2	III	Durvalumab	Clinically diagnosed COPD	50	26.1	PFS and OS	Age, sex, smoking, ECOG PS, CCI, CVD, tumor histology, stage, PD-L1 expression, and previous anticancer treatments
Chang 2024	China	RC	57	60.6	94.7	I-IIIB	NR	Postbronchodilator FEV1/FVC ratio < 0.7	18	18	PFS and OS	None
Hirakawa	Japan	RC	68	73	69.8	III to IV	NR	Clinically	31	11	PFS	Age, sex,

2025								diagnosed COPD				smoking, BMI, PS, histology type, lines of treatment, and PD-L1 expression
Chan 2025	Canada	RC	4306	64.6	51.1	I-IV	Atezolizumab, nivolumab, ipilimumab, or pembrolizumab	Clinically diagnosed COPD	2326	30	OS	Age, sex, ethnicity, tumor stage, SES, and previous anticancer treatments

ICIs, immune checkpoint inhibitors; RC, retrospective cohort; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; PFS, progression-free survival; OS, overall survival; ECOG PS, Eastern Cooperative Oncology Group performance status; CT, computed tomography; PD-L1, programmed death-ligand 1; NR, not reported; CCI, Charlson Comorbidity Index; CVD, cardiovascular disease; SES, socioeconomic status

Table 2. Study quality evaluation via the Newcastle-Ottawa Scale

Study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome not present at baseline	Control for age and sex	Control for other confounding factors	Assessment of outcome	Enough long follow-up duration	Adequacy of follow-up of cohorts	Total
Biton 2018	0	1	1	1	0	0	1	1	1	6
Mark 2018	0	1	1	1	1	1	1	1	1	8
Shin 2019	0	1	1	1	1	1	1	1	1	8
Isono 2020	0	1	1	1	0	0	1	0	1	5
Takayama 2021	0	1	1	1	1	1	1	1	1	8
Zeng 2022	1	1	1	1	0	0	1	1	1	7
Noda 2022	0	1	1	1	1	1	1	1	1	8
Zhang 2022	0	1	1	1	0	0	1	1	1	6
Dong 2024	1	1	1	1	1	1	1	1	1	9

Stevens 2024	0	1	1	1	1	1	1	1	1	8
Chang 2024	0	1	1	1	0	0	1	1	1	6
Hirakawa 2025	0	1	1	1	1	1	1	0	1	7
Chan 2025	0	1	1	1	1	1	1	1	1	8

Table 3. Results of subgroup analysis

	PFS						OS				
Variables	No. of studies	HR (95% CI)	I^2	p for subgroup effects	p for subgroup difference		No. of studies	HR (95% CI)	I^2	p for subgroup effects	p for subgroup difference
Countries											
Asian countries	8	0.66 [0.52, 0.84]	35%	< 0.001			6	0.71 [0.50, 1.00]	56%	0.05	
Western countries	3	0.72 [0.39, 1.34]	72%	0.30	0.80		4	0.93 [0.86, 0.99]	0%	0.03	0.14
Mean ages											
< 65 years	4	0.74 [0.49, 1.12]	42%	0.16			3	0.88 [0.65, 1.19]	56%	0.40	
≥ 65 years	7	0.65 [0.49, 0.86]	53%	0.003	0.62		7	0.75 [0.60, 0.92]	16%	0.007	0.39

Men											
< 75%	5	0.66 [0.42, 1.01]	65%	0.06			5	0.75 [0.57, 0.99]	58%	0.05	
≥ 75%	6	0.69 [0.54, 0.89]	29%	0.004	0.83		5	0.82 [0.62, 1.08]	31%	0.16	0.66
Diagnosis of COPD											
FEV1/FVC ratio < 0.7	5	0.69 [0.47, 1.00]	38%	0.05			3	0.74 [0.44, 1.25]	60%	0.26	
Clinically diagnosed COPD	4	0.79 [0.59, 1.07]	47%	0.13			4	0.93 [0.86, 0.99]	0%	0.03	
CT diagnosed PE	2	0.43 [0.28, 0.67]	0%	< 0.001	0.08		3	0.50 [0.29, 0.86]	16%	0.01	0.06
Mean follow-up duration											
< 20 months	4	0.72 [0.48, 1.08]	38%	0.11			3	0.79 [0.46, 1.37]	55%	0.41	

≥ 20 months	7	0.66 [0.49, 0.88]	55%	0.005	0.74		7	0.80 [0.66, 0.97]	46%	0.02	0.98
Analytic models											
Univariate	4	0.77 [0.59, 1.01]	17%	0.06			4	0.93 [0.75, 1.15]	0%	0.51	
Multivariate	7	0.62 [0.44, 0.86]	56%	0.004	0.30		6	0.69 [0.52, 0.92]	64%	0.01	0.11
NOS											
< 7	3	0.82 [0.51, 1.30]	38%	0.40			3	0.96 [0.68, 1.36]	0%	0.82	
≥ 7	8	0.64 [0.49, 0.83]	50%	< 0.001	0.38		7	0.76 [0.62, 0.94]	57%	0.01	0.26

PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; I^2, heterogeneity index; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; COPD, chronic obstructive pulmonary disease; CT, computed tomography; PE, pulmonary emphysema; NOS, Newcastle-Ottawa Scale;

Table 4. Results of univariate meta-regression analysis

Variables		HR for PFS				HR for OS		
		Coefficient	95% CI	P values		Coefficient	95% CI	P values
Sample size		0.0022	-0.0053 to 0.0096	0.53		0.000054	-0.000066 to 0.000175	0.33
Mean age (years)		-0.030	-0.116 to 0.055	0.44		-0.072	-0.159 to 0.015	0.16
Men (%)		0.0086	-0.0064 to 0.0237	0.23		0.0067	-0.0066 to 0.0199	0.28
Follow-up duration (months)		0.014	-0.021 to 0.048	0.40		0.017	-0.017 to 0.051	0.28
NOS		-0.18	-0.48 to 0.12	0.21		-0.11	-0.38 to 0.15	0.35

HR, hazard ratio; PFS, progression-free survival; OS, overall survival; CI, confidence interval; NOS, Newcastle-Ottawa Scale;

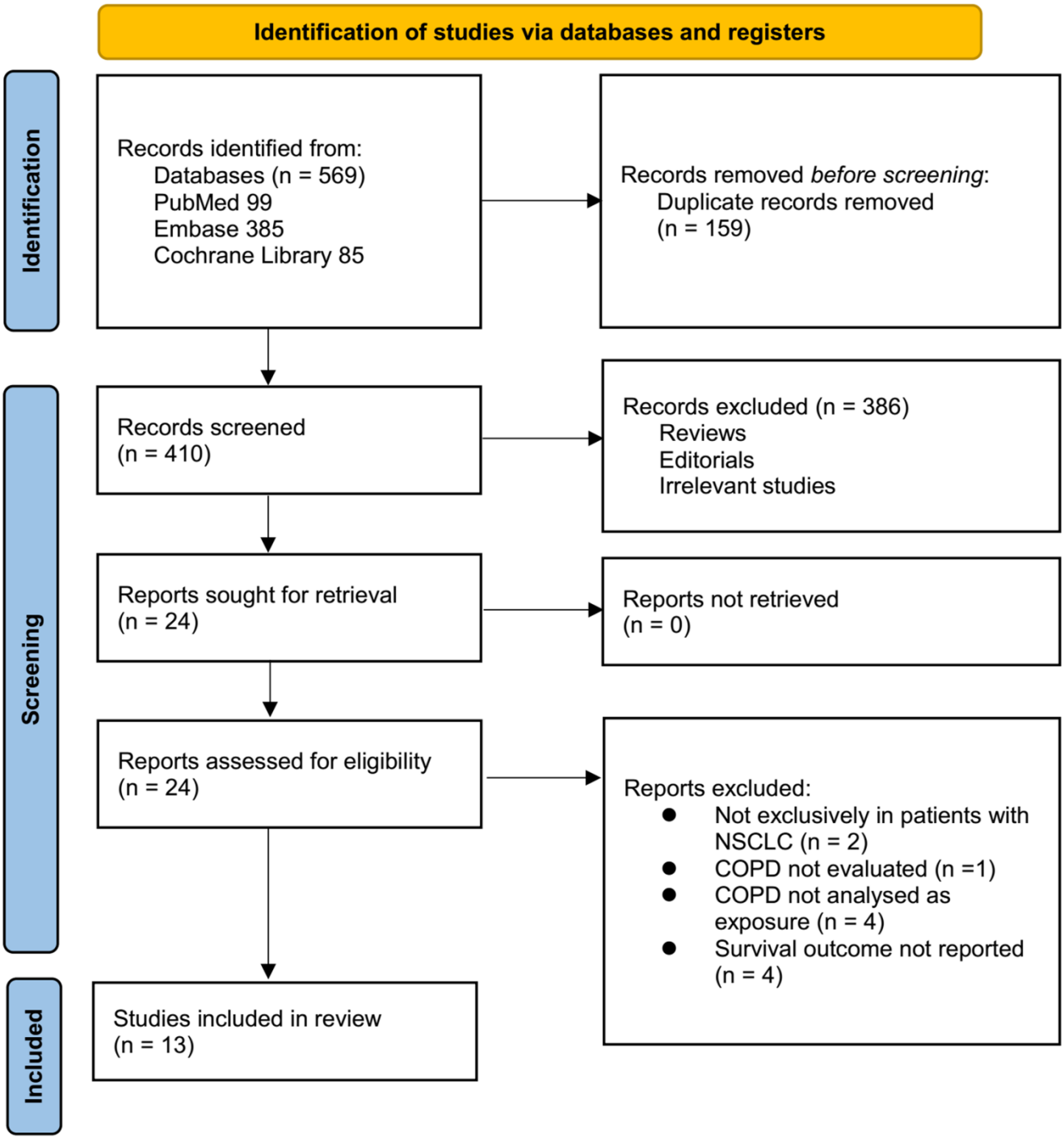

Figure 1. Flowchart of database search and study inclusion

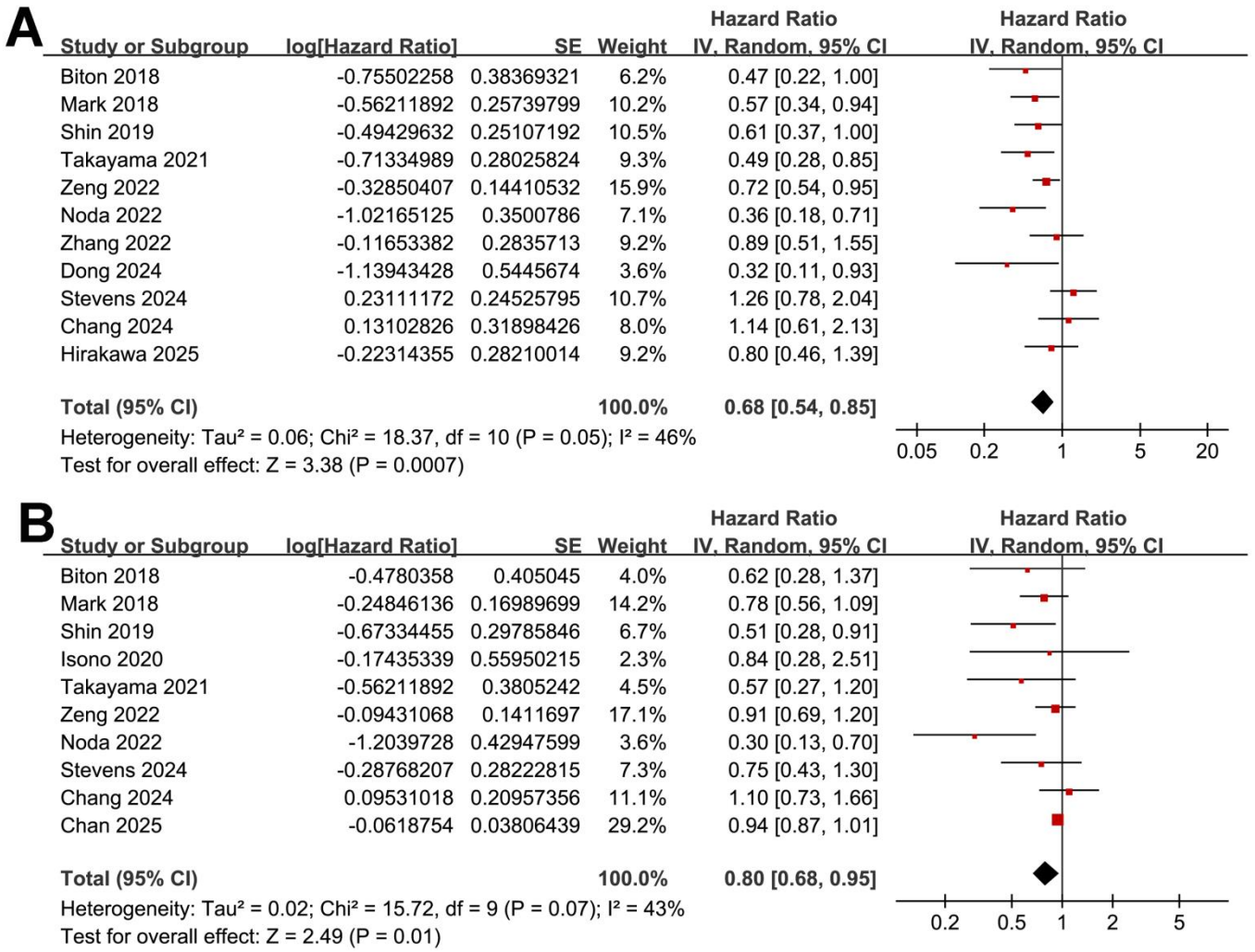

Figure 2. Forest plots for the meta-analyses of the association between COPD and survival outcomes of patients with NSCLC on ICIs. (A) forest plots for the meta-analysis of PFS; and (B) forest plots for the meta-analysis of OS;

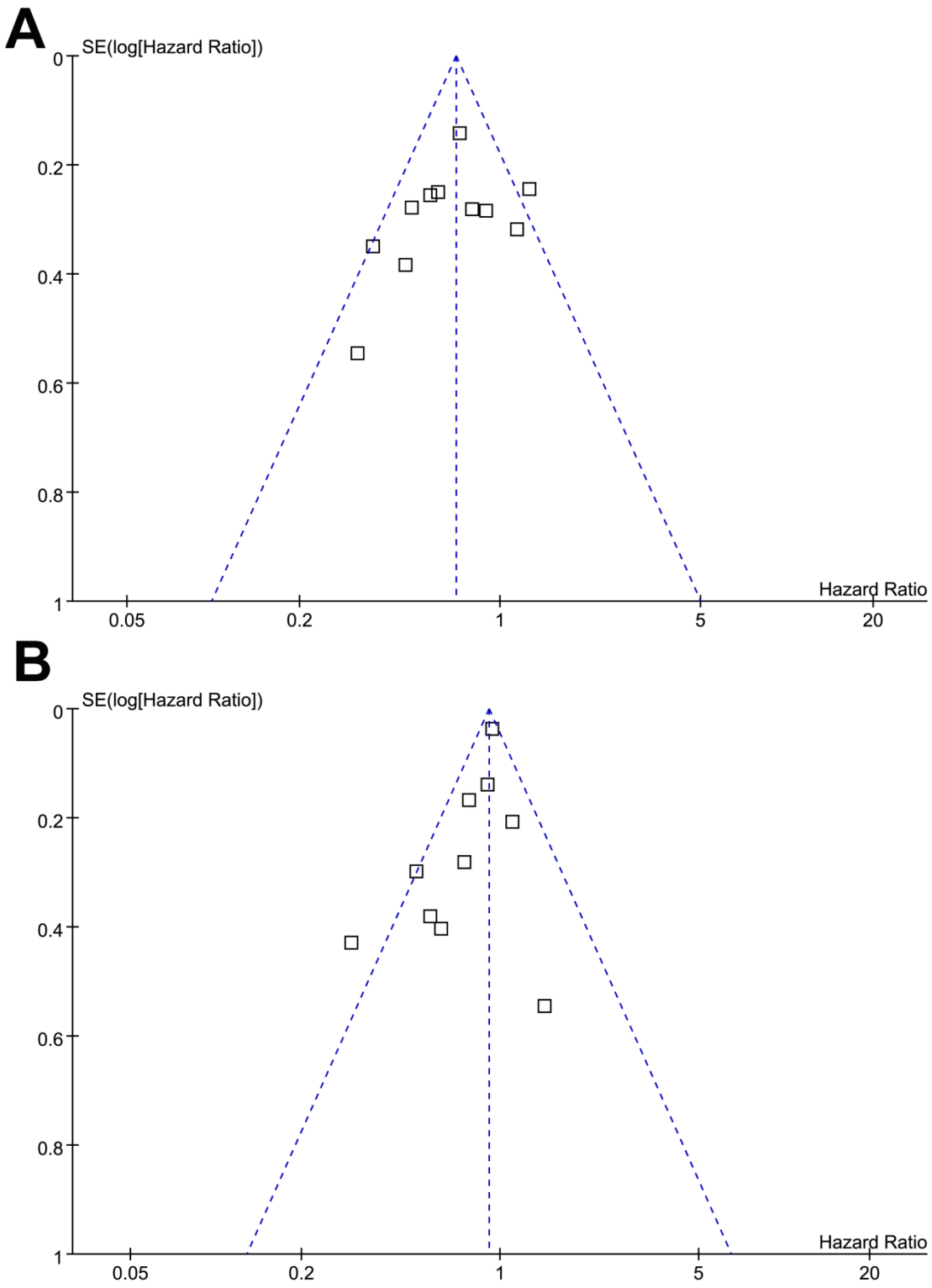

Figure 3. Funnel plots for evaluating the publication bias underlying the meta-analyses. (A) funnel plots for the meta-analysis of the association between COPD and PFS of patients with NSCLC receiving

ICIs; and (B) funnel plots for the meta-analysis of the association between COPD and OS of patients with NSCLC receiving ICIs;

SUPPLEMENTAL DATA

PubMed

((("Pulmonary Disease, Chronic Obstructive"[Mesh]) OR "chronic obstructive pulmonary disease" OR "COPD" OR "chronic obstructive lung disease" OR "chronic obstructive airway disease" OR "emphysema" OR "chronic airflow limitation" OR "chronic airway obstruction")) AND ((("Carcinoma, Non-Small-Cell Lung"[Mesh]) OR "Non-Small Cell Lung Cancer" OR "Non-Small Cell Carcinoma" OR "NSCLC" OR "Lung Adenocarcinoma" OR "Lung Squamous Cell Carcinoma" OR "Lung Neoplasms" OR "Lung Cancer")) AND ((("Immune Checkpoint Inhibitors"[Mesh]) OR "Immune Checkpoint Inhibitors" OR "ICI" OR "Programmed Cell Death Protein 1" OR "PD-1" OR "PD-L1" OR "Cytotoxic T-Lymphocyte-Associated Protein 4" OR "CTLA-4" OR "Pembrolizumab" OR "Nivolumab" OR "Atezolizumab" OR "Durvalumab" OR "Cemiplimab" OR "Avelumab" OR "Ipilimumab" OR "Tremelimumab"))

Embase

('chronic obstructive pulmonary disease'/exp OR 'chronic obstructive pulmonary disease' OR 'COPD' OR 'chronic obstructive lung disease' OR 'chronic obstructive airway disease' OR 'emphysema' OR 'chronic airflow limitation' OR 'chronic airway obstruction') AND ('non small cell lung cancer'/exp OR 'non small cell lung cancer' OR 'non small cell carcinoma' OR 'NSCLC' OR 'lung adenocarcinoma' OR 'lung squamous cell carcinoma' OR 'lung neoplasms' OR 'lung cancer') AND ('immune checkpoint inhibitor'/exp OR 'immune checkpoint inhibitors' OR 'ICI' OR 'programmed cell death protein 1' OR 'PD-1' OR 'PD-L1' OR 'cytotoxic t lymphocyte associated protein 4' OR 'CTLA-4' OR 'pembrolizumab' OR 'nivolumab' OR

'atezolizumab' OR 'durvalumab' OR 'cemiplimab' OR 'avelumab' OR 'ipilimumab' OR 'tremelimumab')

Web of Science

TS=("chronic obstructive pulmonary disease" OR "COPD" OR "chronic obstructive lung disease" OR "chronic obstructive airway disease" OR "emphysema" OR "chronic airflow limitation" OR "chronic airway obstruction") AND TS=("Non-Small Cell Lung Cancer" OR "Non-Small Cell Carcinoma" OR "NSCLC" OR "Lung Adenocarcinoma" OR "Lung Squamous Cell Carcinoma" OR "Lung Neoplasms" OR "Lung Cancer") AND TS=("Immune Checkpoint Inhibitors" OR "ICI" OR "Programmed Cell Death Protein 1" OR "PD-1" OR "PD-L1" OR "Cytotoxic T-Lymphocyte-Associated Protein 4" OR "CTLA-4" OR "Pembrolizumab" OR "Nivolumab" OR "Atezolizumab" OR "Durvalumab" OR "Cemiplimab" OR "Avelumab" OR "Ipilimumab" OR "Tremelimumab")