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Does Smoking Status Predict the Efficacy of Immune Checkpoint Inhibitors in Thoracic Cancers? A Systematic Review and Meta-Analysis

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ADMINISTRATIVE INFORMATION**Support** - National Natural Science Foundation of China.**Review Stage at time of this submission** - Completed but not published.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY2026100062**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 13 October 2026 and was last updated on 13 October 2026.**INTRODUCTION**

Review question / Objective To evaluate whether smoking status predicts the efficacy of immune checkpoint inhibitor (ICI)-based therapy in thoracic cancers, including non-small cell lung cancer (NSCLC), extensive-stage small cell lung cancer (ES-SCLC), and esophageal squamous cell carcinoma (ESCC).

Condition being studied We conducted this systematic review and meta-analysis to clarify whether smoking status predicts survival and pathological responses to ICIs in lung cancer and ESCC. We specifically evaluated advanced NSCLC, resectable NSCLC, ES-SCLC, and advanced ESCC to determine whether the predictive value of smoking status is context-dependent.

METHODS

Search strategy "lung cancer"[Title] OR "esophageal cancer"[Title] AND ("immunotherapy" OR "immune checkpoint inhibitor" OR "CTLA-4" OR "PD-1" OR "PD-L1") AND ("clinical trial"[Publication Type]).

Participant or population Patients with thoracic cancers.

Intervention First-line and/or neoadjuvant immune checkpoint inhibitor-based regimens versus chemotherapy alone.

Comparator Chemotherapy.

Study designs to be included Randomized controlled trials (RCTs) comparing first-line and/or neoadjuvant ICI-based regimens versus chemotherapy alone in thoracic cancers, with predefined subgroup analyses by smoking status.

Eligibility criteria Eligible studies were phase II/III randomized controlled trials (RCTs) that met all of the following criteria: (1) compared first-line or neoadjuvant/perioperative ICI-based regimens (monotherapy or combination) with chemotherapy alone in patients with advanced or resectable NSCLC, ES-SCLC, or advanced ESCC; (2) reported subgroup analyses by smoking status (current/former vs never-smokers), preferably prespecified; (3) reported hazard ratios (HRs) for survival outcomes or event counts by smoking subgroup; and (4) provided sufficient data to calculate effect estimates (HRs or odds ratios [ORs]) with 95% confidence intervals (CIs). Neoadjuvant/perioperative therapy was defined as ICI administered before surgery, with or without adjuvant ICI. Trials of adjuvant-only ICI were excluded.

Information sources PubMed, Embase, Web of Science, Cochrane Library, and ClinicalTrials.gov.

Main outcome(s) Pathological response and survival outcomes were assessed using pooled odds ratios (ORs) and hazard ratios (HRs), both with 95% confidence intervals (CIs). Pathological response and survival outcomes.

Quality assessment / Risk of bias analysis We assessed risk of bias for each outcome using the Cochrane Risk of Bias 2.0 (RoB 2) tool for individually randomized trials. Publication bias was assessed via funnel plot symmetry and Egger's/Begg's tests ($P < 0.10$ indicating significance).

Strategy of data synthesis Dichotomous outcomes (pCR and MPR) are reported as pooled odds ratios (ORs) with 95% CIs, calculated using the Mantel-Haenszel method under a fixed-effects model. Time-to-event outcomes (EFS, PFS, OS) are reported as pooled HRs with 95% CIs using inverse-variance weighting. Heterogeneity was quantified by the I^2 statistic; a random-effects model (DerSimonian-Laird method) was applied if $I^2 > 50\%$, otherwise a fixed-effects model was used.

Subgroup analysis Smoking Status.

Sensitivity analysis Sensitivity analysis employed leave-one-out meta-analysis.

Country(ies) involved China.

Keywords smoking status, lung cancer, esophageal cancer, immunotherapy, meta-analysis.

Contributions of each author

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Author 2 - Li Sun.

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