

Proton pump inhibitor use and the efficacy and safety of immune checkpoint inhibitors in non-small cell lung cancer: a meta-analysis and FAERS pharmacovigilance study

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Abstract

Purpose

Proton pump inhibitors (PPIs), the acid-suppressing agents most widely used in oncology, may impair the efficacy of immune checkpoint inhibitors (ICIs) through gut dysbiosis, but the evidence in non-small cell lung cancer (NSCLC) remains conflicting and safety data are scarce. We assessed the impact of PPI exposure on the efficacy and safety of ICIs in NSCLC.

Methods

We combined a systematic review and meta-analysis of 44 studies comprising more than 58,000 patients with a real-world pharmacovigilance analysis of nearly 18 million deduplicated reports in the FDA Adverse Event Reporting System (FAERS), using four cross-validated signal-detection methods.

Results

PPI exposure was associated with significantly shorter overall survival (35 studies; hazard ratio [HR] 1.33, 95% CI 1.23–1.44) and progression-free survival (23 studies; HR 1.65, 95% CI 1.44–1.89), but not with overall immune-related adverse events (odds ratio 0.98, 95% CI 0.63–1.51) (GRADE certainty: low to very low). The association was independent of treatment regimen and ICI class, strongest for exposure within the window around ICI initiation (HR 1.64; interaction $P = 0.03$), and significantly more pronounced in Asian than in non-Asian studies (HR 1.65 vs. 1.17; interaction $P = 0.0005$). In FAERS, PPI co-medication did not increase fatality or alter the early-onset kinetics of adverse events but shifted their spectrum: 38 four-fold-validated core signals clustered in microbiota–mucosal, infectious, and renal domains.

Conclusion

PPI prescribing in ICI-treated NSCLC warrants rigorous indication review, avoidance of unindicated use around ICI initiation, and vigilant monitoring of infection and renal function.

PROSPERO registration:

CRD420261470983 (meta-analysis) and CRD420261486154 (pharmacovigilance analysis).

1. Introduction

Lung cancer remains the leading cause of cancer incidence and mortality worldwide, accounting for approximately 2.5 million new cases and 1.8 million deaths annually, with non-small cell lung cancer

(NSCLC) representing 85%~90% of all cases [1]. Immune checkpoint inhibitors (ICIs) targeting the programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) axis have fundamentally reshaped the therapeutic landscape of NSCLC and are now established as first-line standard of care across PD-L1 expression strata [2, 3], offering durable benefit exemplified by a 5-year overall survival (OS) rate of 29.3% with pembrolizumab monotherapy in the KEYNOTE-024 trial [4]. Nevertheless, a substantial proportion of patients derive no benefit from ICIs, which has intensified interest in modifiable host-related determinants of response—most notably the gut microbiota and concomitant medications.

Among concomitant medications, proton pump inhibitors (PPIs) warrant particular scrutiny. PPIs are the most widely used acid-suppressing agents in oncology, prescribed for gastroesophageal reflux disease and peptic ulcer as well as for prophylaxis of treatment-related gastrointestinal mucosal injury [5]. Approximately 30% of patients with cancer receive PPIs [6], and baseline PPI use reached 37% in the IMpower150 trial population [7]. Importantly, a considerable share of this use lacks a valid indication or extends far beyond guideline-recommended durations [8], meaning that any deleterious interaction with ICIs would be both clinically consequential and, in part, avoidable.

A coherent biological rationale links PPI exposure to attenuated ICI efficacy. Profound acid suppression elevates intragastric pH and compromises the gastric acid barrier, permitting oralization of the lower gut microbiome and reducing microbial diversity, with depletion of immunologically favorable taxa such as *Akkermansia muciniphila* and *Bifidobacterium spp.* [9, 10]. Because ICI-induced antitumor immunity depends on microbiota-conditioned dendritic-cell antigen presentation and T-cell priming, such dysbiosis may blunt checkpoint blockade. In addition, PPIs exert direct immunomodulatory effects on lymphocytes and polymorphonuclear cells, providing a second, microbiota-independent mechanistic pathway [11].

Clinical evidence, however, remains conflicting. Pooled post hoc analyses of the OAK and POPLAR trials showed that PPI users receiving atezolizumab had a median OS of 9.6 versus 14.5 months in non-users, with no such association in the docetaxel arms, suggesting treatment specificity [12]. Concordant findings emerged from IMpower150 (adjusted hazard ratio [HR] for OS 1.53, 95% CI 1.21 ~ 1.95) [13] and from an individual-participant-data analysis of five randomized trials (n = 4,458), in which the OS benefit of atezolizumab was essentially abolished among PPI users (HR 1.00, 95% CI 0.85 ~ 1.17) yet preserved in non-users (HR 0.76, 95% CI 0.69 ~ 0.83) [7]. Large real-world NSCLC cohorts [14] and pan-cancer meta-analyses [15, 16] point in the same direction. By contrast, several studies found no significant association and attributed earlier positive findings to heterogeneous exposure definitions and residual confounding [17, 18], and a recent post hoc analysis of the PACIFIC trial—reporting differential effects of PPIs and antibiotics on consolidation immunotherapy after chemoradiotherapy—has renewed the debate [19]. Reflecting this uncertainty, current guidelines neither restrict PPI–ICI co-administration nor provide risk-stratified recommendations, advising only symptom-driven use [20, 21], leaving clinicians without actionable guidance.

Three gaps limit the existing evidence base. First, prior meta-analyses pooled biologically heterogeneous tumor types, were published before several recent large real-world studies, and rarely stratified by

exposure timing or duration, ICI class, or treatment regimen—precluding scenario-specific risk estimates for NSCLC. Second, safety has been largely neglected: whether PPI co-medication alters the spectrum of adverse events under ICI therapy, or generates interaction signals beyond the additive class effects of either drug, has never been systematically evaluated. Third, real-world pharmacovigilance evidence is confined to a single pan-cancer analysis restricted to preselected event categories without formal interaction modeling [22]. Established disproportionality methods [23] and the four-arm Omega shrinkage measure for drug–drug interaction surveillance [24] now make a systematic, full-spectrum assessment feasible.

To address these gaps, we conducted a dual-evidence study focused exclusively on NSCLC. A systematic review and meta-analysis was performed to quantify the association between PPI exposure and the efficacy (overall survival, progression-free survival, objective response rate, and disease control rate) and safety (immune-related adverse events) of ICI therapy, with prespecified subgroup analyses to explore potential effect modifiers, including the timing of PPI exposure, ICI class, and treatment regimen. In parallel, a real-world pharmacovigilance analysis of the FDA Adverse Event Reporting System (FAERS) was conducted to characterize the adverse-event spectrum of ICI therapy under PPI co-exposure and to identify potential drug–drug interaction signals beyond the class effects of either agent. Together, these complementary evidence tracks were designed to inform rational acid-suppression management in patients with NSCLC receiving ICIs.

2. Materials and methods

2.1 Study design and registration

This dual-evidence study comprised (i) a systematic review with meta-analysis and (ii) a real-world pharmacovigilance analysis of the FDA Adverse Event Reporting System (FAERS), each prospectively registered on PROSPERO (CRD420261470983 and CRD420261486154). The meta-analysis was conducted and reported in accordance with the PRISMA 2020 statement [25] and its extension for living systematic reviews [26]; the disproportionality analysis was reported following the READUS-PV guideline [27]. Because all analyses were based on published aggregate data and publicly available, anonymized spontaneous reports, ethical approval and informed consent were not required.

2.2 Systematic review and meta-analysis

2.2.1 Eligibility criteria

Because PPI use is a non-randomized, real-world exposure rather than an assigned intervention, eligibility was defined a priori using the PECO-S (Population, Exposure, Comparator, Outcome, Study design) framework. Eligible studies enrolled adults (aged ≥ 18 years) with histologically or cytologically confirmed NSCLC of any stage receiving ICIs as monotherapy or in combination (P); compared patients exposed to PPIs at baseline (typically within ± 30 days of ICI initiation) or during treatment, as defined by the original investigators (E), with patients receiving identical ICI regimens without PPI exposure (C); and

reported at least one extractable efficacy outcome—OS, PFS, objective response rate (ORR), or disease control rate (DCR)—or safety outcome, namely the incidence of overall, grade ≥ 3 , or organ-specific immune-related adverse events (irAEs) (O). Post hoc, subgroup, and individual-participant-data (IPD) analyses of randomized controlled trials (RCTs), prospective and retrospective cohort studies, and case-control studies published in English or Chinese were eligible (S).

We excluded single-arm studies and publications without original comparative data (reviews, meta-analyses, case reports, editorials, letters, and conference abstracts lacking extractable effect estimates); studies of non-NSCLC populations or of patients not receiving ICIs; studies in which the exposure was restricted to non-PPI acid suppressants (histamine-2 receptor antagonists or potassium-competitive acid blockers) or in which PPI-specific effects could not be isolated from pooled acid-suppressant groups; and duplicate or overlapping publications, of which only the largest and most complete dataset was retained. Studies judged at high risk of bias were not excluded a priori; their influence was examined in sensitivity analyses.

2.2.2 Search strategy

We searched PubMed, Embase, Web of Science Core Collection, the Cochrane Library, and three Chinese databases (CNKI, Wanfang, and VIP) from inception to August 2026. Searches combined controlled vocabulary (MeSH or Emtree) with free-text terms across three concept blocks—NSCLC, ICIs, and PPIs—linked by Boolean operators, and were adapted to the syntax of each database. Strategies were drafted independently by two reviewers trained in systematic review methodology and cross-checked following PRESS principles; the full search strings for all seven databases are provided in Supplementary Table S1. Reference lists of included studies and of relevant reviews were hand-searched to identify additional eligible records.

2.2.3 Study selection and data extraction

Records were managed and deduplicated in EndNote X9. Two reviewers independently screened titles and abstracts, then full texts, documenting reasons for exclusion; disagreements were resolved by discussion or adjudication by a third senior reviewer. Using a piloted standardized form, the same reviewers independently extracted study characteristics (first author, year, country or region, design), patient characteristics (sample size, age, sex, ECOG performance status, histology, PD-L1 expression, stage, follow-up), treatment regimens, PPI exposure details (definition, agent, dose, time window, duration, and exposure prevalence), outcomes, and the extent of confounder adjustment (e.g., antibiotics, corticosteroids, ECOG performance status, PD-L1 expression). For OS and PFS, multivariable-adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were extracted preferentially, followed by propensity-matched or weighted estimates; unadjusted HRs were used only when no adjusted estimate was available and were flagged for sensitivity analysis. When HRs were not reported directly, they were estimated from Kaplan–Meier curves or reported summary statistics using the methods of *Tierney et al.* [28]. For ORR, DCR, and irAEs, event counts and group sizes were extracted to compute odds ratios (ORs). Missing key data were requested from corresponding authors.

2.2.4 Risk of bias assessment

The Risk Of Bias in Non-randomized Studies of Exposure (ROBINS-E) tool served as the primary instrument for all included studies, covering confounding, exposure measurement, participant selection, post-exposure intervention, missing data, outcome measurement, and selective reporting [29]. For analyses derived from RCTs, the internal validity of the parent trial was additionally appraised with the Cochrane risk-of-bias tool [30], and retrospective cohort and case-control studies were additionally scored with the Newcastle–Ottawa Scale as a quantitative complement [31]. Assessments were performed independently by two reviewers, with disagreements resolved by consensus or a third reviewer.

2.2.5 Statistical analysis

Time-to-event outcomes were pooled as log-transformed HRs using the generic inverse-variance method; binary outcomes were pooled as ORs. Given the anticipated clinical and methodological heterogeneity of predominantly observational evidence, random-effects models with the DerSimonian–Laird estimator were prespecified for all analyses, irrespective of heterogeneity test results [32]. Heterogeneity was quantified with the χ^2 test and the I^2 statistic. Prespecified subgroup analyses of OS examined treatment regimen (ICI monotherapy vs. combination therapy), timing of PPI exposure (baseline only; peri-initiation, defined as a 21 ~ 42-day window around ICI initiation; or during treatment), ICI class (PD-1 vs. PD-L1 inhibitors, restricted to studies with class-homogeneous cohorts), and study region (Asian vs. non-Asian, excluding multinational studies); between-subgroup differences were tested with the interaction Q test. Sensitivity analyses comprised leave-one-out analysis, exclusion of studies at high risk of bias, and exclusion of studies with estimated or unadjusted HRs. For outcomes with at least ten studies, publication bias was assessed by funnel plots and the Egger regression test, with trim-and-fill adjustment where asymmetry was detected [33, 34]. The certainty of evidence for each outcome was rated with the GRADE approach and presented in a summary-of-findings table [35]. Meta-analyses were performed in RevMan 5.4.1 and R 4.3.3 (package metafor 4.4-0). All tests were two-sided with $\alpha = 0.05$.

2.3 FAERS pharmacovigilance analysis

2.3.1 Data source and processing

Quarterly ASCII files (DEMO, DRUG, REAC, INDI, OUTC, and THER) covering 2011Q1 through 2026Q2 (62 quarters) were downloaded from FAERS. Deduplication proceeded in two stages: for each case identifier, only the most recent report version was retained; cross-case duplicates with identical sex, age, event date, reporting country, and adverse-event term combinations were then removed, with reports missing key fields exempted from the second stage to avoid erroneous deletion. Adverse events and indications were coded at the MedDRA Preferred Term (PT) level using the version current at each quarterly release (v29.0 for the most recent quarter).

2.3.2 Exposure and cohort definitions

ICI exposure was defined as any PD-1, PD-L1, or CTLA-4 inhibitor recorded as the primary or secondary suspect drug; PPI exposure was defined as any of the seven marketed PPIs (omeprazole, esomeprazole, lansoprazole, dexlansoprazole, pantoprazole, rabeprazole, or ilaprazole) in any drug role, with matching of both generic and brand names. Four mutually exclusive groups were constructed: ICI plus PPI (group A), ICI only (group B), PPI only (group C), and neither (group D). The primary population for disproportionality analyses was restricted to reports in which the indication linked to the ICI was coded with NSCLC-specific terms, with broader lung-cancer terms examined in sensitivity analyses. Because interaction analyses require all four groups, they were performed primarily in the full database, with the lung-cancer-indication population analyzed for corroboration.

2.3.3 Disproportionality analysis

For each PT, the reporting odds ratio (ROR) with 95% CI and the Bayesian information component (IC) with 95% credibility interval were computed for group A against group B as the comparator [23, 36], applying the Haldane correction (0.5 added to each cell) when any cell count was zero. A signal required at least three cases in group A together with $ROR_{025} > 1$ or $IC_{025} > 0$. PTs reflecting the underlying disease or medication management were excluded at the interpretation stage.

2.3.4 Drug–drug interaction analysis

Interaction signals exceeding the expected class effects of either drug were assessed with the Ω shrinkage measure based on the four-group design [24]: under the no-interaction assumption, the expected reporting rate in group A was derived from the observed rates in groups B, C, and D, and Ω was computed as the shrinkage-adjusted log2 ratio of observed to expected. A signal required $\Omega_{025} > 0$ with at least three co-exposed cases; additive and multiplicative interaction models were computed as robustness checks. Core signals were defined as PTs that were positive in the NSCLC and pan-cancer disproportionality analyses and in both Ω interaction analyses (four-fold validation).

2.3.5 Time-to-onset and fatal outcomes

Time to onset was calculated as the interval between the adverse-event date and the earliest ICI start date, restricted to reports with complete dates and intervals of 0–3 years, and summarized as median (interquartile range); groups were compared with the Wilcoxon rank-sum test, and Weibull distributions were fitted with the shape parameter β characterizing the onset pattern ($\beta < 1$ indicating early-failure type). Fatal outcomes (outcome code DE) were compared between groups with the χ^2 test. Missing demographic and date fields were not imputed; each analysis used all available data, and resulting differences in denominators are reported as observed. FAERS analyses were conducted in R 4.5.1 (packages `data.table` and `fitdistrplus`).

3. Results

3.1 Study selection and characteristics

Database searches retrieved 2,424 records, and citation tracking identified 8 additional records. After removal of 324 duplicates, 2,100 records were screened by title and abstract, and 101 full texts were assessed for eligibility, of which 57 were excluded (reasons detailed in Fig. 1). Forty-four studies were ultimately included [7, 12–14, 18, 19, 37–74], of which 42 contributed data to quantitative synthesis and 2 were summarized narratively [39, 57] (Fig. 1). Four studies were post hoc or pooled analyses of randomized trials [7, 12, 13, 19]—an individual-participant-data analysis of five atezolizumab trials [13], pooled post hoc analyses of the OAK and POPLAR trials [12], and post hoc analyses of IMpower150 [7] and PACIFIC [19]—and 40 were observational studies [14, 18, 37–74], including real-world analyses of the US Veterans Affairs system, the Korean HIRA database, the TriNetX network, and the French national claims database. Studies originated from Asia ($n = 22$) [14, 41, 42, 44, 45, 48, 51, 53–55, 60, 63–66, 68–74], Europe ($n = 10$) [38, 40, 43, 49, 50, 57–59, 62, 67], North America ($n = 6$) [18, 37, 47, 52, 56, 61], and Australia ($n = 1$) [46], with 5 multinational analyses [7, 12, 13, 19, 39]; publication years spanned 2017 ~ 2026, with 20 studies (45%) published in 2024 or later [19, 37, 39, 43–45, 48–50, 53, 55, 56, 58, 60, 64, 65, 68, 70, 73, 74]. Sample sizes ranged from 63 to 31,257, for a cumulative total of more than 58,000 patients, of whom approximately 25,000 were PPI-exposed. PPI exposure was most commonly defined within ± 30 days of ICI initiation; two studies additionally stratified by cumulative dose or duration of PPI use. OS was available for meta-analysis in 35 studies [7, 14, 18, 19, 37, 38, 40–47, 49, 50, 52–56, 58–64, 66–70, 72, 74], PFS in 23 [7, 18, 19, 38, 40, 42, 43, 46, 48, 50, 51, 53, 59, 60, 62–64, 68–70, 72–74], ORR in 10 [40, 42, 43, 54, 65, 66, 68, 69, 72, 74], DCR in 6 [42, 43, 66, 69, 72, 74], and irAEs in 6 [38, 54, 55, 60, 71, 74]. Characteristics of the included studies are summarized in Supplementary Table S2.

3.2 Risk of bias

Among the 42 studies included in quantitative synthesis, ROBINS-E rated 36 (85.7%) at some risk and 6 (14.3%) [42, 45, 48, 52, 62, 71] at high risk of bias, with none at low risk; the dominant source of bias was confounding by indication, as PPI users typically had poorer performance status, greater comorbidity burden, and more frequent co-medication with corticosteroids or antibiotics. The six high-risk studies [42, 45, 48, 52, 62, 71] reported only unadjusted estimates or estimates derived indirectly from median survival times. The parent trials underlying the four RCT-derived analyses [7, 12, 13, 19] were methodologically robust, with open-label design representing the principal limitation in three [7, 12, 13], whereas the PACIFIC trial was double-blind [19]. On the Newcastle–Ottawa Scale, 26 of 40 observational studies (65%) scored ≥ 7 [14, 18, 37, 40, 43, 44, 49–51, 53–58, 60, 61, 63, 64, 67–70, 72–74], with points most often lost for between-group comparability. Full assessments are provided in Supplementary Figs. S1–S2 and Supplementary Tables S3–S4.

3.3 Efficacy outcomes

OS. Thirty-five studies [7, 14, 18, 19, 37, 38, 40–47, 49, 50, 52–56, 58–64, 66–69] comprising 58,545 patients contributed to the OS analysis. PPI exposure was significantly associated with shorter OS (HR 1.33, 95% CI 1.23 ~ 1.44, $P < 0.001$; $I^2 = 75\%$) (Fig. 2). The direction of effect was highly consistent: 32 of 35 point estimates exceeded 1 (17 statistically significant), and the three studies with point estimates

marginally below 1 (HR 0.96–0.98) were all non-significant. The pooled association was not driven by small studies, as it persisted despite near-null results in several of the largest database analyses.

PFS. Twenty-three studies [7, 18, 19, 38, 40, 42, 43, 46, 48, 50, 51, 53, 59, 60, 62–64, 68–70, 72–74] comprising 9,939 patients contributed to the PFS analysis. PPI exposure was associated with significantly shorter PFS (HR 1.65, 95% CI 1.44 ~ 1.89, $P < 0.001$; $I^2 = 69\%$) (Fig. 3). All 23 point estimates were ≥ 1 , with 13 reaching statistical significance; the three studies carrying the greatest weight [7, 19, 40] all showed significant associations (HR 1.15, 1.32, and 1.57, respectively).

ORR and DCR. Ten studies [40, 42, 43, 54, 65, 66, 68, 69, 72, 74] with PPI exposure (OR 1.21 favoring non-exposure, 95% CI 0.86 ~ 1.70, $P = 0.27$; $I^2 = 60\%$; crude ORR 33.4% vs. 43.1%) (Supplementary Fig. S3). One additional study not poolable for lack of event counts reported a significantly lower ORR in PPI users (41.5% vs. 63.5%). Six studies [42, 43, 66, 69, 72, 74] (764 patients) were pooled for DCR, again showing a non-significant unfavorable trend (OR 1.43, 95% CI 0.84 ~ 2.43, $P = 0.18$; $I^2 = 60\%$; crude DCR 67.8% vs. 75.1%) (Supplementary Fig. S4); a further study reporting only an inverse-probability-weighted estimate found a significant negative association between PPI use and disease control (adjusted OR 0.14, 95% CI 0.05 ~ 0.43) [63]. Overall, effect sizes displayed a gradient across outcomes, with significant associations for survival endpoints and non-significant trends for response endpoints.

3.4 Safety outcomes

Six studies [38, 54, 55, 60, 71, 74] (937 patients) contributed to the analysis of overall irAE incidence, which did not differ significantly by PPI exposure (OR 0.98, 95% CI 0.63 ~ 1.51, $P = 0.91$; $I^2 = 55\%$; crude incidence 43.2% vs. 44.8%) (Supplementary Fig. S5). Heterogeneity reflected two divergent single-study findings: one study reported significantly fewer non-pneumonitis irAEs among PPI users (adjusted OR 0.510, 95% CI 0.274 ~ 0.947) [55], whereas a dedicated study of ICI-associated acute kidney injury reported a higher incidence among PPI users (35.0% vs. 15.9%; univariable OR 2.85, 95% CI 1.12 ~ 7.29), although PPI use was not retained as an independent predictor after multivariable adjustment [71]. Two studies not poolable for lack of event counts likewise reported no significant association with overall adverse-event incidence [47, 70]. No study provided PPI-stratified counts of grade ≥ 3 irAEs; the only comparative dataset showed no difference in grade ≥ 3 checkpoint-inhibitor pneumonitis (4.9% vs. 4.3%, $P = 0.746$) [55]. Organ-specific evidence, each available from a single study [55, 70, 71], is summarized in Supplementary Table S5.

3.5 Subgroup analyses

Prespecified subgroup analyses of OS are shown in Fig. 4 and Supplementary Fig. S6. The association between PPI exposure and shorter OS was consistent between ICI monotherapy (HR 1.41, 95% CI 1.25 ~ 1.59) and combination therapy (HR 1.32, 95% CI 1.17 ~ 1.50; interaction $P = 0.48$), and between PD-1 (HR 1.26) and PD-L1 inhibitors (HR 1.40; interaction $P = 0.52$). By contrast, effect size differed significantly by timing of exposure: the association was strongest for exposure within the peri-initiation window (21 ~ 42 days around ICI start; HR 1.64, 95% CI 1.38 ~ 1.94), compared with baseline-only (HR 1.27) and on-treatment exposure (HR 1.24; interaction $P = 0.03$) (Fig. 4A). Within-study dose–response evidence was

concordant: mortality risk increased with cumulative defined daily doses > 159 (adjusted HR 1.45, 95% CI 1.02 ~ 2.07) in one study, and in another, survival outcomes were unaffected by PPI courses ≤ 7 days but significantly worse with use exceeding 28 days. Effect size also differed by region, with a significantly stronger association in Asian (HR 1.65, 95% CI 1.39 ~ 1.95) than in non-Asian studies (HR 1.17, 95% CI 1.08 ~ 1.28; interaction $P = 0.0005$) (Fig. 4B). No study reported PPI effects stratified by histology; single-study evidence in PD-L1 $\geq 50\%$ populations, consolidation therapy after chemoradiotherapy, and postoperative recurrence settings showed associations in the same direction.

3.6 Sensitivity analyses and publication bias

The OS association was robust across all prespecified sensitivity analyses (Supplementary Fig. S7). Excluding the four high-risk-of-bias studies yielded an HR of 1.31 (95% CI 1.21 ~ 1.42); excluding the three studies with survival-curve-derived, unadjusted estimates yielded an HR of 1.31 (95% CI 1.22 ~ 1.42); and in leave-one-out analyses the pooled HR ranged from 1.31 to 1.38, remaining significant in all 35 iterations. A parallel analysis of PFS excluding high-risk studies gave an HR of 1.67 (95% CI 1.44 ~ 1.94). Funnel plots for OS and PFS were asymmetric, with significant *Egger* tests ($P < 0.001$ and $P = 0.001$, respectively); trim-and-fill imputation of 14 and 7 hypothetical studies attenuated but did not nullify the associations (OS HR 1.15, 95% CI 1.07 ~ 1.24; PFS HR 1.41, 95% CI 1.23 ~ 1.62). No significant asymmetry was detected for ORR (*Egger* $P = 0.189$); publication-bias testing was not performed for outcomes with fewer than ten studies. Funnel plots are shown in Supplementary Fig. S8.

3.7 Certainty of evidence

GRADE assessments are summarized in Table 1 and Supplementary Table S6. Starting from “low” for non-randomized evidence, certainty for OS remained low (downgraded for publication bias; upgraded for a dose–response gradient), whereas certainty for PFS, ORR, DCR, and overall irAEs was very low, reflecting unexplained heterogeneity and, for the response and safety outcomes, imprecision.

Table 1

Summary of pooled results for the association of PPI exposure with efficacy and safety outcomes of ICI therapy in patients with NSCLC.

Outcome	Studies, n (patients)	Pooled effect (95% CI)	P value	I ²	Publication bias (Egger P)	Certainty of evidence (GRADE)
Overall survival	35 (58,545)	HR 1.33 (1.23–1.44)	< 0.001	75%	< 0.001 a	Low
Progression-free survival	23 (9,939)	HR 1.65 (1.44–1.89)	< 0.001	69%	0.001 b	Very low
Objective response rate	10 (2,175)	OR 1.21 (0.86–1.70) c	0.27	60%	0.189	Very low
Disease control rate	6 (764)	OR 1.43 (0.84–2.43) c	0.18	60%	NA d	Very low
Overall immune-related adverse events	6 (937)	OR 0.98 (0.63–1.51) c	0.91	55%	NA d	Very low
Abbreviations: PPI, proton pump inhibitor; ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; HR, hazard ratio; OR, odds ratio; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NA, not assessed.						
All analyses used random-effects models (DerSimonian–Laird). a Trim-and-fill-adjusted HR 1.15 (95% CI 1.07–1.24); direction and significance unchanged. b Trim-and-fill-adjusted HR 1.41 (95% CI 1.23–1.62). c OR expresses the odds in non-exposed relative to PPI-exposed patients; values > 1 indicate less favorable outcomes with PPI exposure. d Fewer than 10 studies; publication-bias testing not performed per Cochrane Handbook guidance. Full GRADE assessments are provided in Supplementary Table S6.						

3.8 FAERS pharmacovigilance analysis

3.8.1 Report characteristics

After two-stage deduplication, 17,958,621 reports submitted between 2011Q1 and 2026Q2 were retained. Of these, 21,272 recorded co-exposure to an ICI (primary/secondary suspect) and a PPI (group A) and 238,766 recorded ICI exposure without a PPI (group B); the PPI co-reporting proportion among ICI reports (8.2%) was well below the approximately 30% PPI-use prevalence in oncology populations, indicating under-reporting of concomitant medication. Restricting to reports with NSCLC-coded ICI indications yielded 5,256 group A and 40,204 group B reports (6,032 and 52,468 with the broader lung-cancer definition). Demographic characteristics were similar between groups, with a higher proportion of healthcare-professional reporters in group A (87.4% vs. 77.9%) (Supplementary Table S7). The proportion of fatal outcomes did not differ significantly between groups (25.9% vs. 24.9%, $P = 0.118$) (Supplementary Table S7).

3.8.2 Disproportionality analysis

In the NSCLC population, 375 of 4,710 screened preferred terms met signal criteria, clustering in infections (57 PTs), gastrointestinal disorders (43 PTs), and renal/electrolyte disorders (26 PTs) (Fig. 5A). The strongest signals were dysbiosis (22 vs. 0 cases; ROR 345.63, 95% CI 20.96 ~ 5698.77) and skin candida infection (24 vs. 1; ROR 184.42, 95% CI 24.94 ~ 1363.52); a renal cluster comprising tubulointerstitial nephritis, acute kidney injury, immune-mediated nephritis, and hypomagnesemia was also disproportionately reported in group A. The pan-cancer analysis (978 signals among 9,161 PTs) produced a highly concordant ranking. The full signal landscape is displayed as a volcano plot (Fig. 5B).

3.8.3 Drug–drug interaction signals and core signal set

Ω shrinkage analysis identified 261 interaction-positive PTs among 23,938 screened in the full database (groups A–D: 21,272; 238,766; 970,949; 16,727,634 reports) and 146 among 6,794 screened in the lung-cancer population, led by skin candida infection ($\Omega_{025} = 4.83$) and dysbiosis ($\Omega_{025} = 4.78$); probiotic therapy, intestinal intraepithelial lymphocytosis, and drug reaction with eosinophilia and systemic symptoms ($\Omega_{025} = 2.87$) were also interaction-positive. Forty-six PTs were positive in all four analyses (four-fold validation) and 106 in three; after exclusion of 8 disease-related or administrative terms, 38 core signals remained, falling into five categories: microbiota–mucosal axis events, infections, renal disorders, hepato-immune disorders, and other events (Fig. 6; Supplementary Tables S8–S9). Triple-validated signals additionally included acute kidney injury, hypomagnesemia, hypokalemia, oral candidiasis, and *Pneumocystis jirovecii* pneumonia.

3.8.4 Time to onset

Among reports with evaluable dates (4,253 in group A; 16,069 in group B), median time to onset was 27 days in both groups (IQR 9 ~ 92 vs. 8 ~ 91; $P = 0.866$), and Weibull shape parameters below 1 in both groups ($\beta = 0.649$ vs. 0.647) indicated an early-failure pattern, with no evidence that PPI co-exposure altered the temporal dynamics of adverse events (Supplementary Fig. S9).

4. Discussion

This dual-evidence study—integrating the largest and most current NSCLC-specific meta-analysis of the PPI–ICI interaction (44 studies, > 58,000 patients) with an interaction-focused pharmacovigilance analysis of nearly 18 million deduplicated FAERS reports—yielded three principal findings. First, PPI exposure was associated with significantly shorter OS (HR 1.33) and PFS (HR 1.65), associations that remained stable across all prespecified sensitivity analyses. Second, response endpoints showed only non-significant unfavorable trends, forming a gradient of impaired survival with attenuated but inconclusive effects on tumor response. Third, PPI co-medication did not increase the overall burden or fatality of adverse events but shifted their spectrum, with 38 four-fold-validated interaction signals concentrated in microbiota–mucosal, infectious, and renal domains. Compared with earlier meta-

analyses, which pooled biologically heterogeneous tumor types [15] or all systemic therapies [16], the present synthesis is restricted to ICI-treated NSCLC, incorporates the roughly twenty studies published since 2024, adds a systematic appraisal of safety outcomes, and identifies two effect modifiers—exposure timing and study region—not previously established. Our findings also accord with umbrella-review evidence ranking PPIs, together with antibiotics, among the concomitant medications most consistently implicated in impaired ICI efficacy [75].

The biological plausibility of this association rests principally on the gut microbiota. ICIs are intravenously administered monoclonal antibodies whose absorption and elimination are independent of gastric pH and cytochrome P450 metabolism [76], excluding a classical pharmacokinetic interaction and pointing to an indirect pathway. Profound acid suppression compromises the gastric barrier, permitting oralization of the lower gut microbiome, reducing microbial α -diversity, and enriching oral taxa such as streptococci, as shown in crossover, population-based, and meta-analytic studies [77–80]; the resulting dysbiosis diminishes short-chain-fatty-acid producers, impairs barrier integrity, and reshapes local immune tone [81]. In parallel, gut microbiome composition has been established as a determinant of checkpoint-blockade efficacy [82, 83], with intestinal *Akkermansia muciniphila* predicting response to PD-1 blockade in NSCLC specifically [84]. Interventional studies close the causal chain: fecal microbiota transplantation (FMT) can overcome anti-PD-1 resistance in melanoma [85, 86], FMT plus first-line anti-PD-1 achieved a 65% response rate in a phase 1 trial [87], and the 2026 phase 2 FMT-LUMINate trial extended feasibility and preliminary efficacy to NSCLC [88]. A medication that durably perturbs this ecosystem would therefore be expected to attenuate ICI benefit.

Several internal observations of the present study cohere with this mechanism. The association was strongest for exposure in the peri-initiation window (HR 1.64), consistent with the decisive role of baseline microbiome state in mounting the antitumor immune response; within-study evidence indicated dose- and duration-dependent gradients, matching the pharmacological expectation that greater acid suppression produces greater dysbiosis; PPI users experienced significantly fewer non-pneumonitis irAEs, suggesting diminished systemic immune activation; and in FAERS, dysbiosis ($\Omega_{025} = 4.78$) and skin candida infection ($\Omega_{025} = 4.83$) remained interaction-positive after subtracting the class effects of either drug, providing independent real-world evidence of microbial disturbance beyond additive expectation. Confounding by indication nevertheless remains a competing explanation, as PPI use partly marks frailty and comorbidity burden. Pure confounding, however, would not readily generate timing- and dose-dependent gradients that persist in analyses restricted to multivariable-adjusted estimates; confounded and causal components are therefore more plausibly coexistent than mutually exclusive.

The gradient across efficacy outcomes deserves comment. Mechanistically, the microbiota is implicated chiefly in sustaining antitumor immunity and immune memory, so PPI-associated dysbiosis may erode the durability rather than the induction of tumor regression—patients may still achieve initial responses whose depth and duration are curtailed, translating into shorter survival. Statistically, the pooled samples for ORR and DCR were an order of magnitude smaller than for survival, underpowered for moderate effects, and both point estimates were directionally concordant with the survival findings; the single

study with rigorous inverse-probability weighting showed a significant negative association with disease control. Measurement error compounds this: response assessment relied on retrospective, non-blinded imaging review, and non-differential misclassification biases estimates toward the null. The null response-endpoint results should therefore not be interpreted as evidence that PPIs spare near-term efficacy.

Subgroup findings offer further insight into effect modification. The predominance of the peri-initiation window is directly actionable, implying that the weeks surrounding ICI initiation constitute the critical period for acid-suppression stewardship. The significantly stronger association in Asian than non-Asian studies (HR 1.65 vs. 1.17; interaction $P = 0.0005$) is biologically credible: CYP2C19 poor-metabolizer genotypes are carried by approximately 13–23% of East Asians versus 2–5% of Caucasians, producing higher plasma PPI exposure and stronger acid suppression at equivalent doses [89], which would amplify dysbiosis and its downstream immunosuppressive effects; dietary patterns and baseline microbiome composition may contribute further. A methodological component cannot be excluded, as Asian studies were predominantly smaller single-center retrospective cohorts, whereas non-Asian evidence derived largely from large databases yielding more conservative estimates. By contrast, neither treatment regimen (interaction $P = 0.48$) nor ICI class (interaction $P = 0.52$) modified the association, supporting an upstream locus of action independent of the specific checkpoint target—concordant with prior observations [75]. Residual heterogeneity for OS ($I^2 = 75\%$) likely reflects the persisting diversity of exposure definitions, dosing and duration reporting, and adjustment sets across studies.

The safety findings delineate the nature, rather than the absence, of harm. PPI co-medication did not increase overall irAE incidence, and FAERS corroborated unchanged fatality and early-onset temporal kinetics—arguing against simple toxicity summation. Because irAE occurrence, particularly non-pneumonitis irAEs, is positively associated with ICI benefit [90, 91], the significant reduction of non-pneumonitis irAEs among PPI users is more plausibly a surrogate of blunted immune activation than a safety advantage. The kidney constitutes the important exception. PPIs are a leading cause of drug-induced acute interstitial nephritis [92], PPI co-medication has repeatedly emerged as an independent risk factor for ICI-associated acute kidney injury [93–95], the dedicated study in our synthesis observed an approximately 2.9-fold risk elevation, and in FAERS both tubulointerstitial nephritis and immune-mediated nephritis survived four-fold validation, with acute kidney injury and hypomagnesemia triple-validated. Literature, pharmacoepidemiological, and spontaneous-report evidence thus converge on additive renal risk, directing monitoring priorities during co-administration toward infection surveillance and renal function rather than generalized irAE apprehension.

These findings carry direct implications for pharmaceutical care in ICI-treated NSCLC. Acid-reducing agents are used by 20–33% of patients in oncology trials [96], often without a persisting indication. Our data support a pharmacist-led pathway: systematic review of PPI indications before ICI initiation, with deprescribing of unindicated empirical use following established frameworks [97]; for patients with compelling indications, continuation at the lowest effective dose for the shortest necessary duration, avoiding new non-essential PPI prescriptions within the peri-initiation window; consideration of

histamine-2 receptor antagonists where on-demand acid suppression suffices, as current NSCLC evidence has not demonstrated a comparable adverse association, albeit with limited data [98] and intensified monitoring of renal function and treatment response in higher-risk groups, particularly Asian patients and CYP2C19 poor metabolizers. Future research should prioritize interaction analyses embedded in prospective cohorts and trials, agent- and dose-stratified exposure–response studies, and microbiota-targeted interventions—an approach supported by early evidence that *Clostridium butyricum* supplementation restored ICI efficacy in PPI-treated lung cancer patients [66] and by the maturing FMT trial program [88].

This study has limitations. PPI exposure was non-randomized in every included study, and residual confounding by indication cannot be eliminated; the observed associations therefore do not establish causality. Heterogeneity in exposure definitions, doses, and durations across studies constrains the precision and generalizability of pooled estimates, and the certainty of evidence was low for OS and very low for the remaining outcomes, with small-study effects evident for the survival endpoints—although trim-and-fill adjustment attenuated without nullifying the associations. The FAERS analysis inherits the constraints of spontaneous reporting: substantial under-recording of co-medication (8.2% PPI co-reporting against an expected ~ 30% prevalence), absence of exposure denominators, and inability to infer causality from disproportionality. Conversely, the inclusion of Chinese-language literature and grey literature reduced language bias, and the influence of the single dissertation was examined in sensitivity analysis. These limitations underscore that our conclusions should inform cautious stewardship rather than strong clinical prohibition, pending prospective confirmation.

5. Conclusions

In patients with NSCLC receiving ICIs, PPI exposure was associated with significantly shorter OS and PFS—independent of treatment regimen and ICI class, strongest for exposure around ICI initiation, dose- and duration-dependent, and more pronounced in Asian populations—without an increase in overall irAE burden, indicating that the clinical impact of PPIs is dominated by efficacy attenuation rather than toxicity summation. Real-world pharmacovigilance corroborated this profile, identifying a shifted adverse-event spectrum concentrated in microbiota–mucosal, infectious, and renal domains. Pending prospective validation, PPI prescribing in this population warrants rigorous indication review, avoidance of unindicated empirical use—particularly within the window surrounding ICI initiation—use of the lowest effective dose for the shortest necessary duration, and vigilant monitoring of infection and renal function during co-administration.

Declarations

Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Ethics approval

Ethical approval was not required for this study. The systematic review and meta-analysis was based exclusively on previously published studies, and the pharmacovigilance analysis used publicly available, de-identified reports from the FDA Adverse Event Reporting System (FAERS).

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Author Contribution

Z.X. conceived and designed the study, performed the literature search, data extraction, statistical analyses, and pharmacovigilance analyses, prepared all figures and tables, and wrote the main manuscript text. X.W. and M.L. performed independent study screening, data extraction and validation. L.Y. conceived the study, supervised the project, and administered the work. All authors critically reviewed and approved the final manuscript.

Data availability

All data supporting the findings of the systematic review and meta-analysis are available within the article and its supplementary materials. The FAERS quarterly data files analyzed in this study are publicly available from the FDA website (<https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html>). The R code used for the pharmacovigilance analysis is available from the corresponding author upon reasonable request.

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Figures

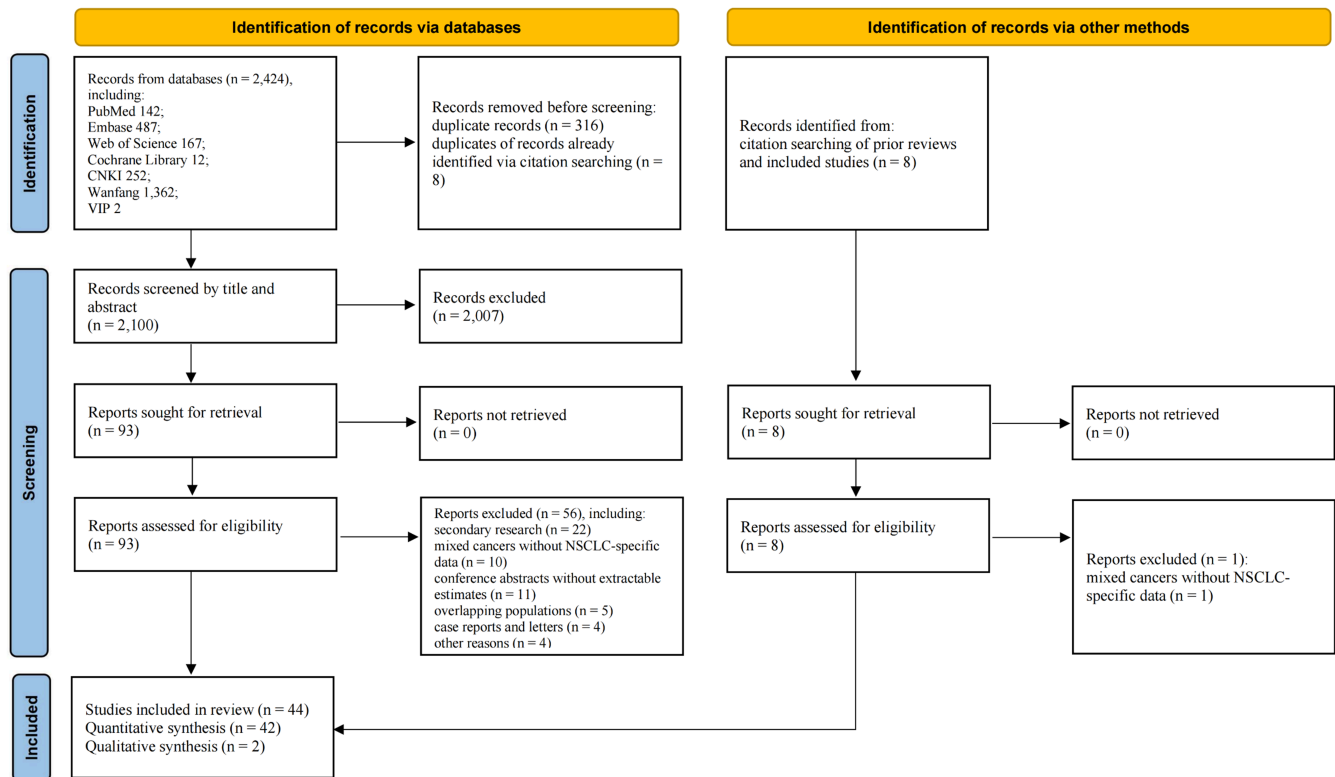


Figure 1

PRISMA 2020 flow diagram of study selection

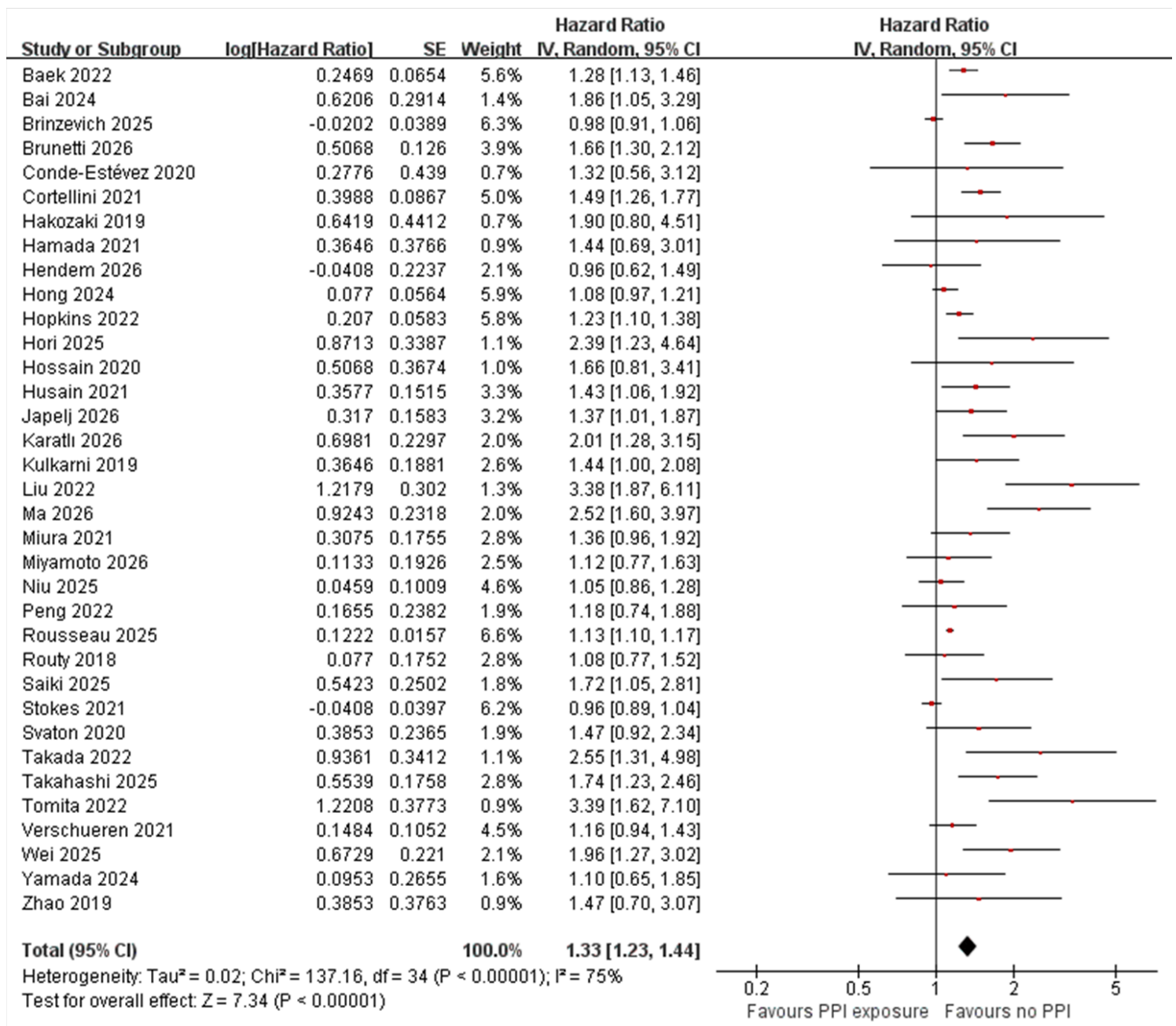


Figure 2

Forest plot of the association between PPI exposure and overall survival in patients with NSCLC receiving ICIs. Hazard ratios (HR) express the risk of death in PPI-exposed relative to non-exposed patients; multivariable-adjusted estimates were used where available and pooled with a random-effects model (DerSimonian–Laird). Two RCT-derived analyses reporting OS (Chalabi 2020; Hopkins 2022a) were excluded from pooling because their populations are contained within the five-trial pooled analysis (Hopkins 2022b)

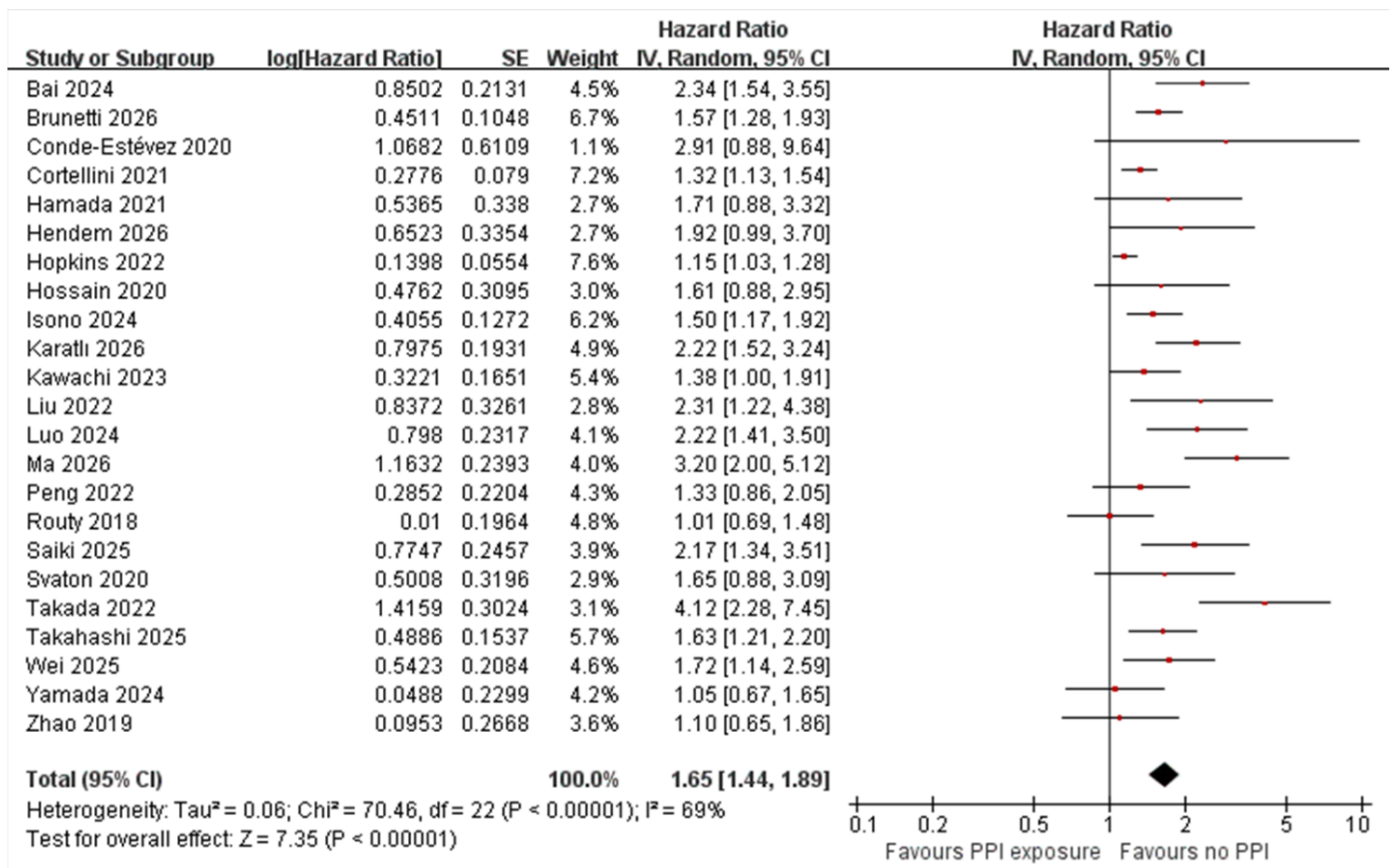


Figure 3

Forest plot of the association between PPI exposure and progression-free survival in patients with NSCLC receiving ICIs. Hazard ratios (HR) express the risk of progression or death in PPI-exposed relative to non-exposed patients; multivariable-adjusted estimates were used where available and pooled with a random-effects model (DerSimonian–Laird)

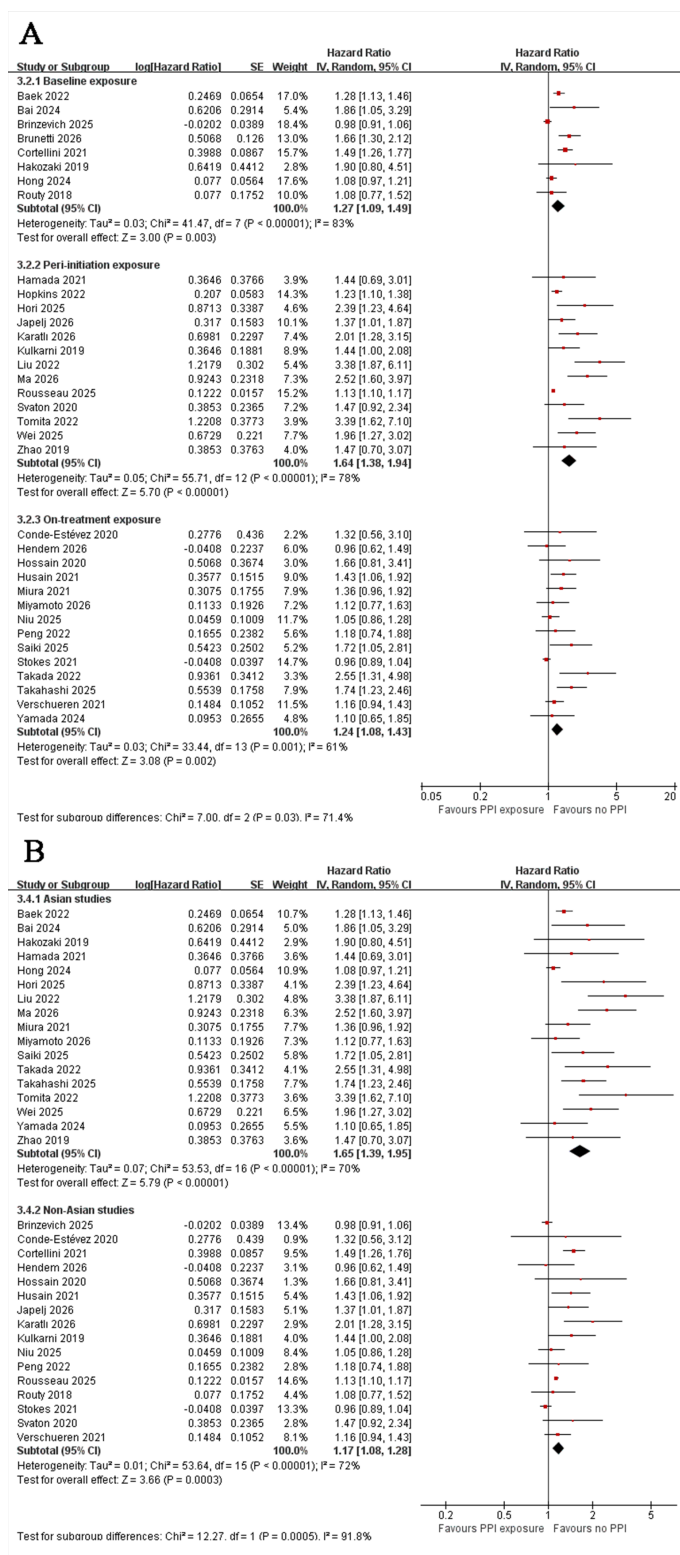


Figure 4

Subgroup analyses of overall survival by (A) timing of PPI exposure and (B) study region. Hazard ratios express the risk of death in PPI-exposed relative to non-exposed patients, pooled with random-effects models. The association was strongest for exposure within the peri-initiation window (21~42 days around ICI initiation; interaction $P = 0.03$) and was significantly more pronounced in Asian than in non-Asian studies (interaction $P = 0.0005$). Multinational studies were excluded from the regional analysis

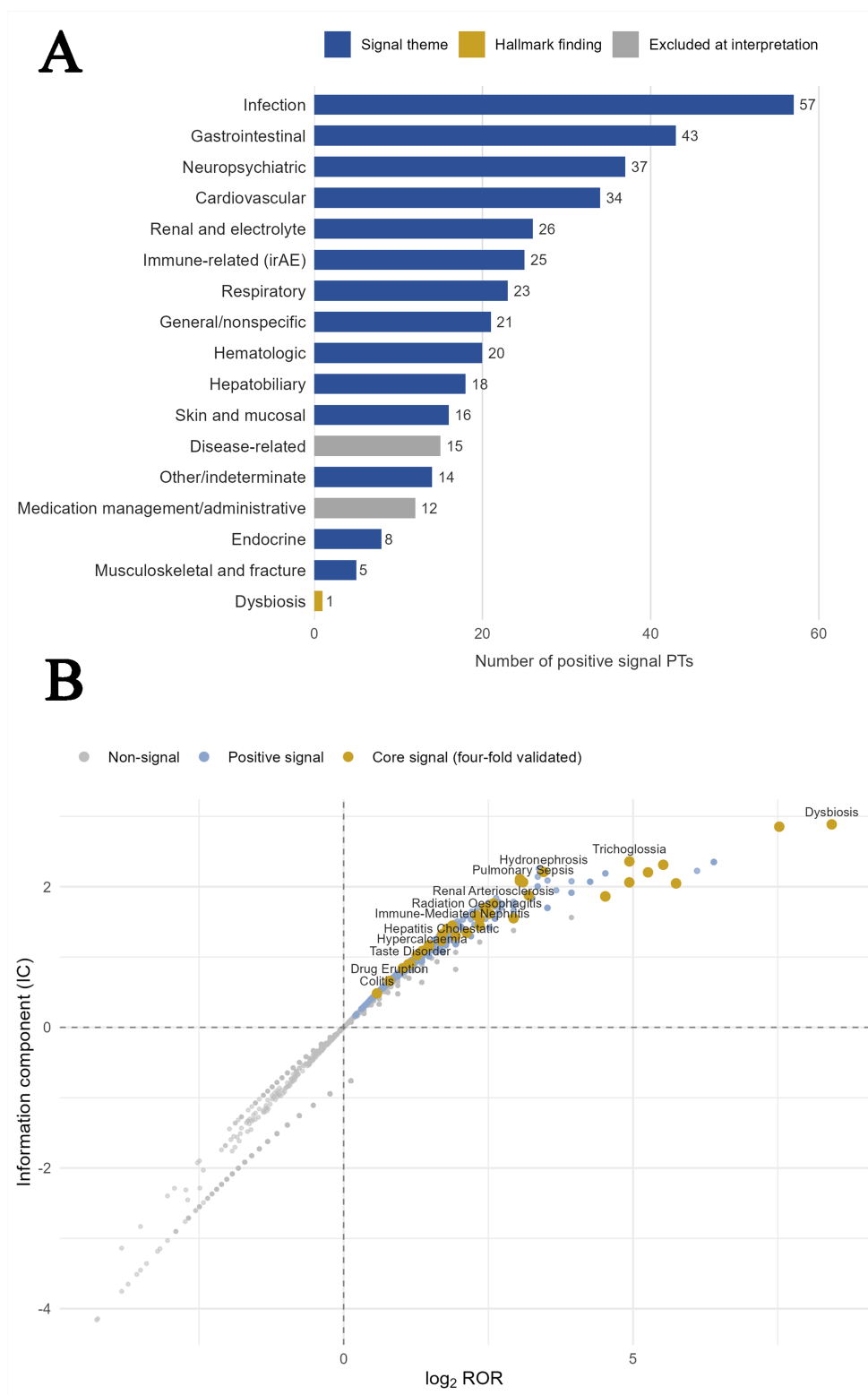


Figure 5

Disproportionality signals of ICI therapy under PPI co-exposure in the NSCLC population of FAERS. (A) Thematic distribution of the 375 positive signals (ICI + PPI vs. ICI only). Disease-related and medication-management terms (grey) were excluded at the interpretation stage; dysbiosis (gold) is shown separately as the hallmark finding. (B) Volcano plot of all screened preferred terms, plotting the information component (IC) against log₂ ROR. Grey, non-signal terms; blue, positive signals (≥ 3 cases

with $ROR_{0.25} > 1$ or $IC_{0.25} > 0$); gold, the 38 core signals positive in all four validation analyses (labels shown for core signals with ≥ 8 cases). ROR, reporting odds ratio; IC, information component; dashed lines indicate the null thresholds ($\log_2 ROR = 0$ and $IC = 0$)

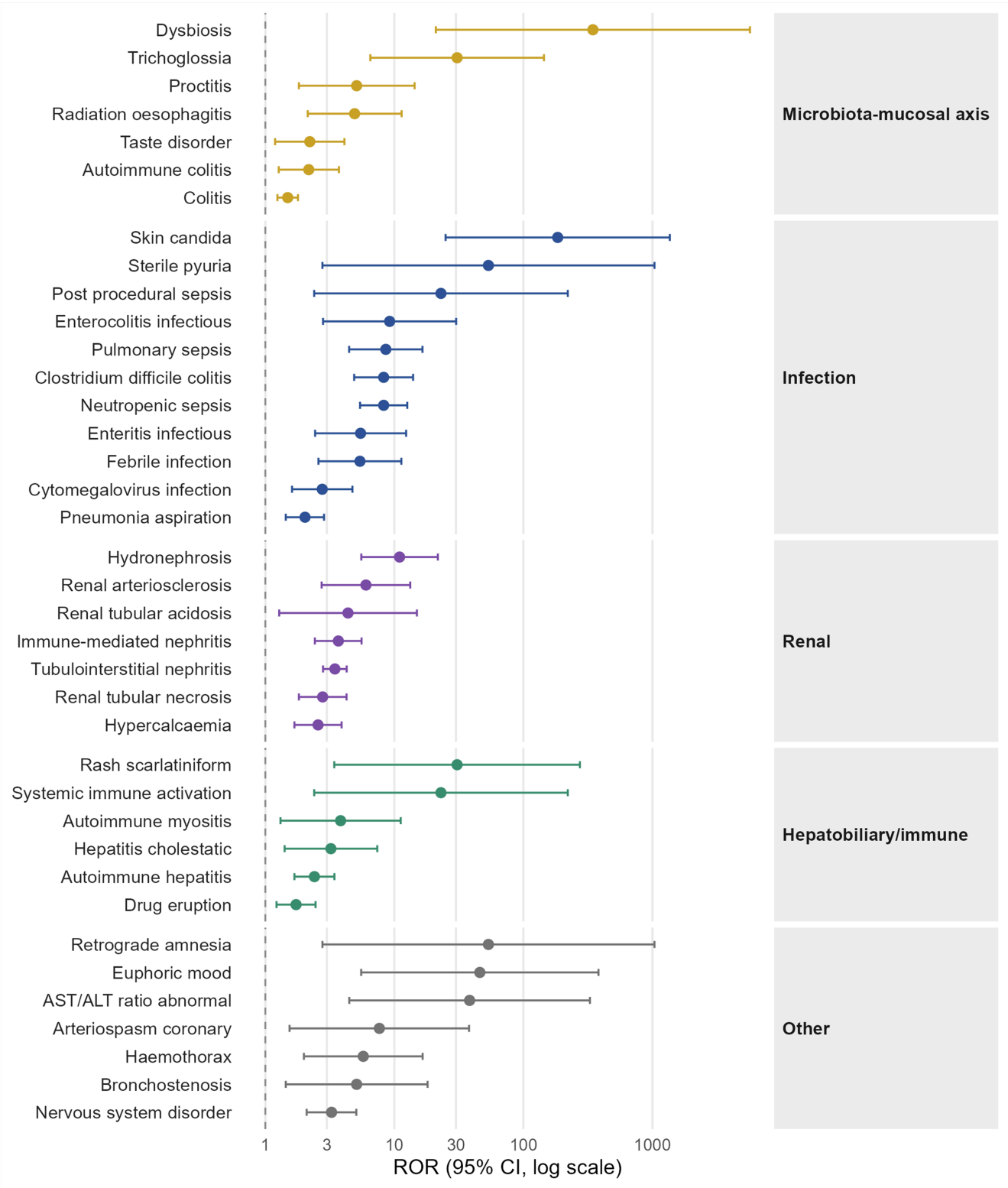


Figure 6

Forest plot of the 38 core adverse-event signals positive in all four validation analyses. Reporting odds ratios (ROR) with 95% confidence intervals are from the NSCLC-restricted disproportionality analysis (ICI + PPI vs. ICI only), grouped by signal category and plotted on a logarithmic scale; the dashed line indicates ROR = 1. Full numerical results, including information components and Ω interaction estimates, are provided in Supplementary Table S9

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