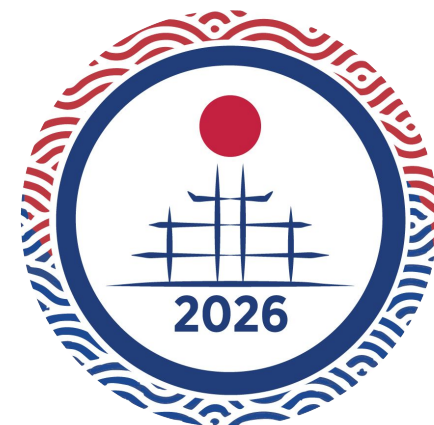


Real-World Comparative Effectiveness of Neoadjuvant Immunochemotherapy versus Chemotherapy in Resectable Stage II–III NSCLC
A Systematic Review and Meta-Analysis of 17 Real-World Studies and 6,088 Patients

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INTRODUCTION

NSCLC remains a leading cause of cancer death worldwide, and relapse after curative-intent surgery for stage II–III disease is common.

Trials changed practice: phase 3 studies (CheckMate 816, KEYNOTE-671, RATIONALE-315) showed higher pathological response and longer event-free survival with chemo-immunotherapy (CT-IO); NCCN now designates it the preferred perioperative strategy for immunotherapy-eligible, driver-negative disease.

The gap: trial populations are younger and fitter, with uniform staging and biomarker testing; in routine care allocation is shaped by comorbidity, access to immunotherapy and institutional expertise.

Prior syntheses pooled mainly randomized data or mixed neoadjuvant with perioperative designs, leaving real-world effectiveness unresolved.

Objective: to quantify the real-world comparative effectiveness and safety of neoadjuvant CT-IO versus chemotherapy alone (CT) in adults with resectable stage II–III NSCLC undergoing resection.

METHODS

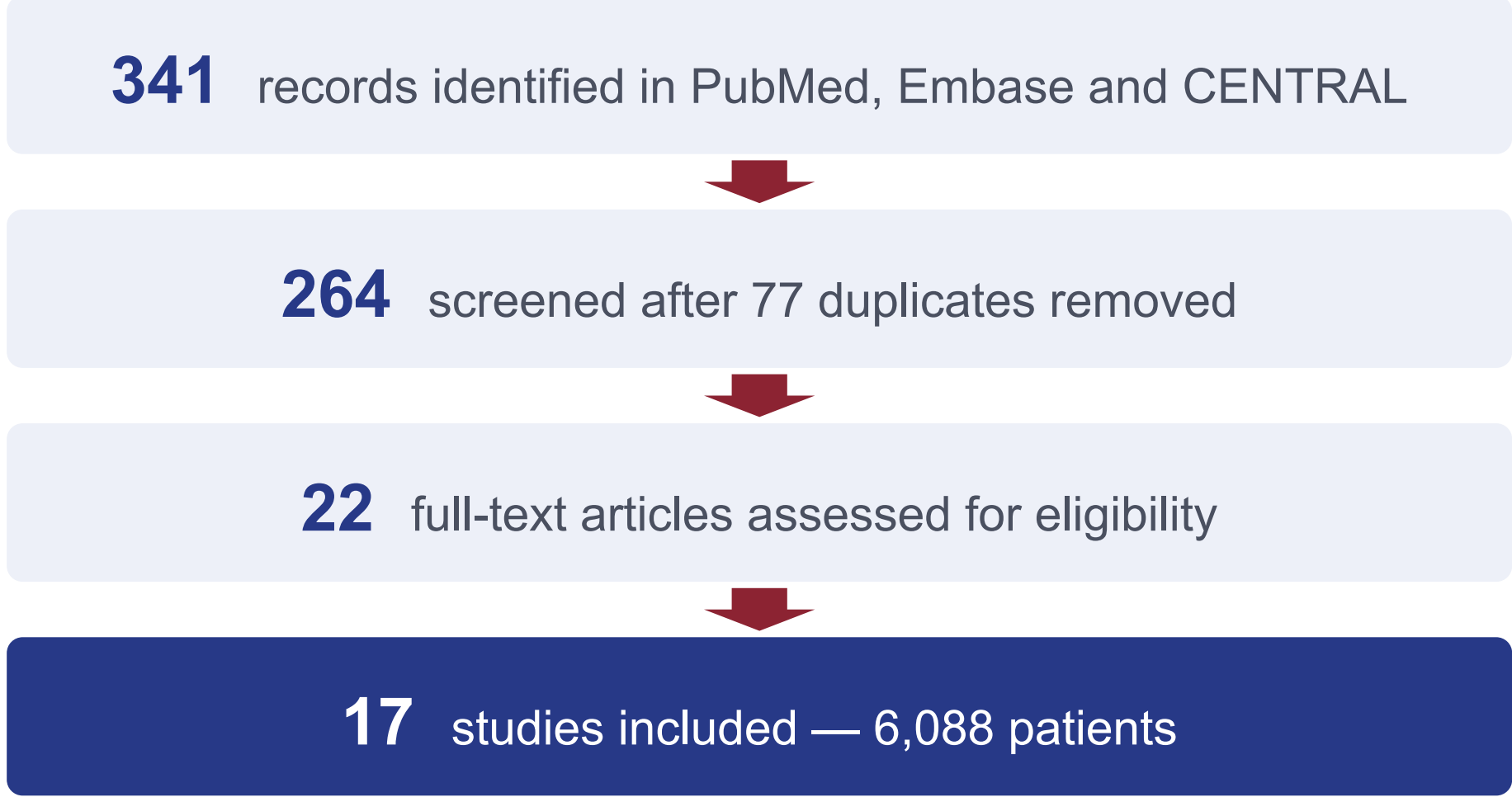
Design: systematic review and meta-analysis of comparative observational studies, reported per PRISMA 2020 and the Cochrane Handbook (PROSPERO CRD420261362760).

Eligibility: adults with resectable stage II–III NSCLC receiving neoadjuvant CT-IO versus CT alone before resection, reporting ≥ 1 outcome of interest. Excluded: metastatic or unresectable disease, immunotherapy without chemotherapy, no comparator arm, abstracts without extractable data.

Search: PubMed, Embase and CENTRAL from inception to 7 March 2026, plus reference snowballing; duplicate screening (Rayyan) and independent extraction, disagreements resolved by consensus.

Endpoints: primary — overall survival. Secondary — event-free and disease-free survival, pCR, MPR, R0 resection, nodal downstaging and treatment-related adverse events (any grade and grade ≥ 3).

Analysis: random-effects models (REML); generic inverse-variance for hazard ratios and Mantel–Haenszel for risk ratios; heterogeneity by Cochran’s Q and I²; leave-one-out sensitivity analyses for pCR and MPR; funnel plots and Egger’s test when ≥ 10 studies. R version 4.5.2.



Study selection (PRISMA 2020)

DISCUSSION AND CONCLUSION

Actionable take-away message

- In 6,088 patients treated outside trials, neoadjuvant CT-IO was associated with better overall, event-free and disease-free survival, roughly fivefold higher pCR and fourfold higher MPR, and more frequent nodal downstaging.
- R0 resection and treatment-related adverse events were comparable, so the deeper regression did not come at a surgical or safety cost.

Interpretation

- Effect sizes exceeded those of the pivotal trials (overall survival HR 0.71 in CheckMate 816 and 0.72 in KEYNOTE-671). Confounding by indication is the most plausible explanation: fitter patients with better performance status are preferentially selected for CT-IO.
- Direction of benefit is nevertheless consistent and biologically coherent — no heterogeneity for overall or event-free survival, and concordant gains in pathological response and nodal downstaging.

Limitations

- All 17 studies were non-randomized; 14 were at serious and 3 at critical overall risk of bias (ROBINS-I), with serious confounding in every study.
- Predominantly Asian, largely single-region cohorts; heterogeneous outcome definitions without central pathology review; immature follow-up; no sex-disaggregated outcome data.

Future direction for research

- Prospective, biomarker-driven studies with standardized protocols, Western and community cohorts, and sex-disaggregated reporting are needed to refine patient selection and define long-term impact.

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RESULTS

17 comparative studies (16 Chinese cohorts and 1 large US multicentre cohort), all retrospective, contributed **6,088 patients**. Adenocarcinoma predominated, more than 70% of patients were male, and reported mean or median age ranged from 56 to 66 years.

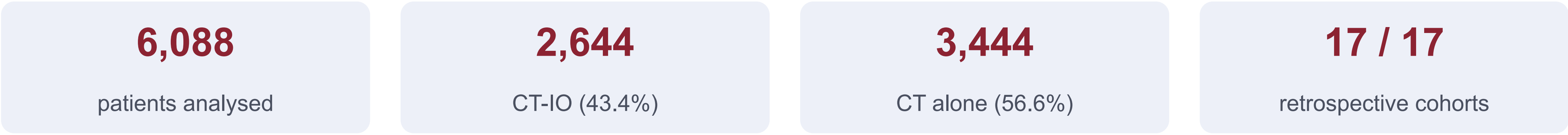
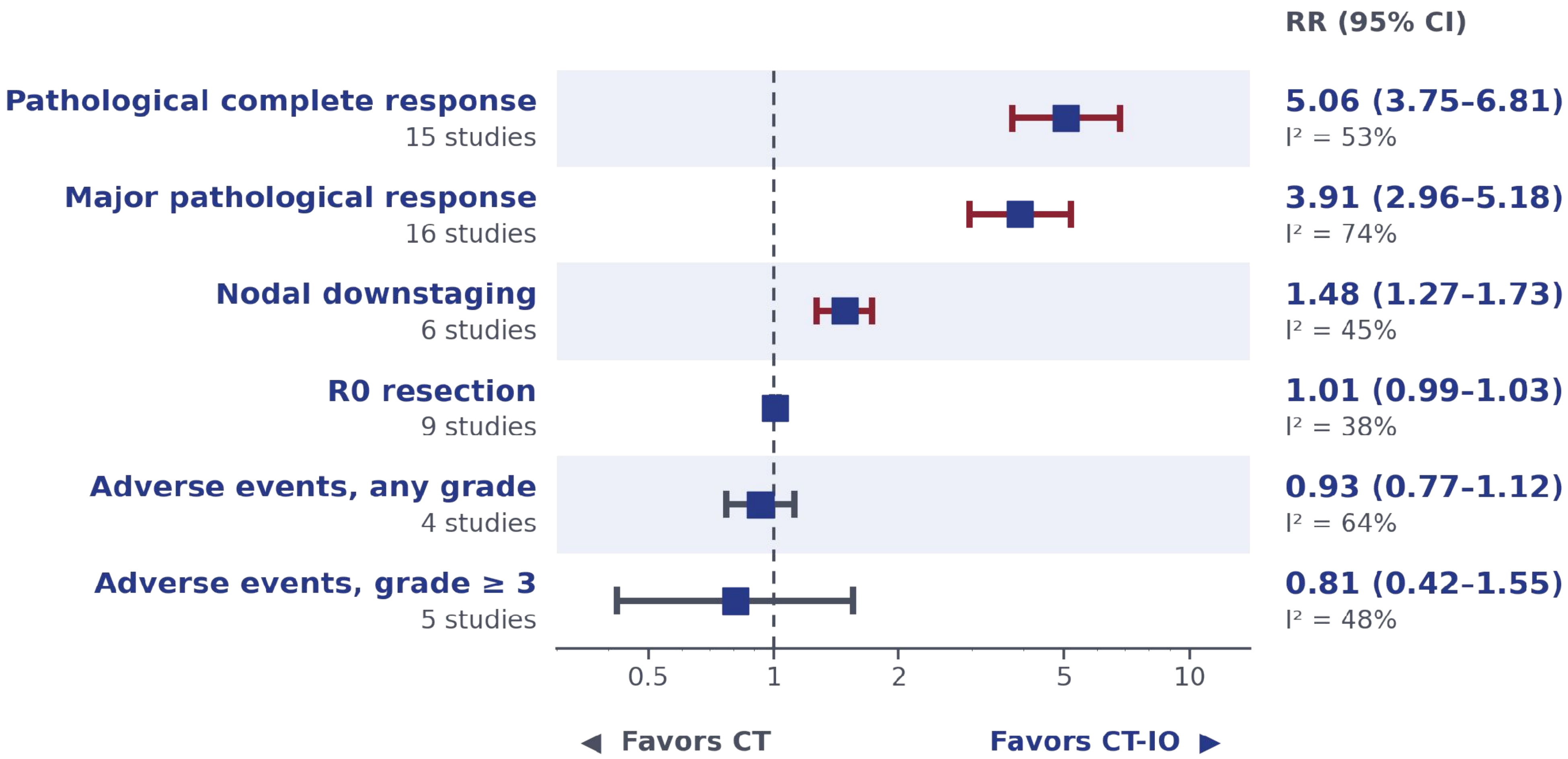


Figure 1. Survival outcomes — CT-IO versus CT alone (hazard ratios, random-effects inverse-variance).



Figure 2. Pathological, surgical and safety outcomes (risk ratios, Mantel–Haenszel random-effects).



Leave-one-out analyses for pCR and MPR did not materially change the pooled estimates. CT-IO, immunochemotherapy; CT, chemotherapy; pCR, pathological complete response; MPR, major pathological response.