

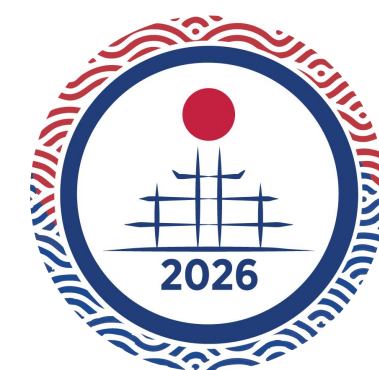


Association of Preoperative Circulating Tumor Cells With Survival in Patients With Resected Non–Small Cell Lung Cancer

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INTRODUCTION

- Although surgery remains the mainstay of curative-intent treatment for NSCLC, 5-year recurrence-free survival varies from 82% in stage I disease to 34% in stage III disease.
- Current risk stratification relies on the ninth edition TNM classification and invasive pathologic features, but recurrence risk remains heterogeneous among patients with similar pathologic profiles.
- Circulating tumor cells (CTCs) has established prognostic value across multiple malignancies, yet their role in resected non–small cell lung cancer (NSCLC) remains uncertain.
- Prior studies are limited by detection methods, including EpCAM-dependent platforms such as CellSearch, which may underdetect EpCAM-low CTCs.

METHODS

- This prospective real-world cohort study was conducted at West China Hospital, Sichuan University. Among 11 621 patients undergoing lung cancer surgery, 2547 were screened for CTC measurement, yielding 1010 eligible participants with resected stage I-III NSCLC.
- Peripheral venous blood samples (6 mL per patient) were collected within 1 month before surgery.
- By targeting folate receptor (FR), FR⁺ CTCs were quantified using a ligand-targeted polymerase chain reaction platform.
- Primary endpoint was disease-free survival (DFS); secondary endpoints included overall survival (OS) and lung cancer–specific survival (LCSS).
- Associations between preoperative FR⁺ CTCs and survival outcomes were analyzed and compared using Kaplan-Meier method, log-rank tests, and Cox proportional hazard models.

DISCUSSION AND CONCLUSION

Actionable Take Away Message

- In our prospective real-world cohort study, preoperative CTCs independently predicted survival and provided incremental prognostic value beyond TNM stage in resected NSCLC, supporting their use to enhance risk stratification.

Future Direction for Research

- Future multicenter studies should standardize assays, validate actionable thresholds, and evaluate perioperative CTC dynamics.
- Interventional trials should then test whether CTC-guided adjuvant therapy and surveillance improve clinical decision-making and patient outcomes.

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Artificial Intelligence (AI) Use Disclaimer

During the preparation of this manuscript, the authors used ChatGPT to assist with language polishing. After using the tool, the authors reviewed and edited the content as necessary and take full responsibility for the content of the publication.

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RESULTS

- Among 1038 patients (median age, 57 years; 56.6% female; median follow-up, 60 months), 217 (20.9%) experienced recurrence or death. At the optimal cutoff of 10.14 FU/3 mL, 452 (43.5%) were classified as high-CTC.
- The high-CTC group had lower 5-year DFS (72.7% vs 84.8%), OS (85.0% vs 91.1%), and LCSS (87.8% vs 93.1%) (all $P < .001$). High CTCs were independently associated with worse DFS (adjusted HR, 1.54; 95% CI, 1.16–2.05; $P = .003$), OS (adjusted HR, 1.45; 95% CI, 1.01–2.08; $P = .046$), and LCSS (adjusted HR, 1.53; 95% CI, 1.01–2.34; $P = .046$). Subgroup analyses demonstrated that the prognostic association of CTCs with survival remained consistent across strata defined by TNM stage, spread through air spaces, lymphovascular invasion, perineural invasion, and histology.
- Incorporating CTCs into the base clinicopathologic model improved the AUC (0.664 to 0.703; $P = .006$) and C-index (0.678 to 0.729; $P < .001$) for predicting 5-year DFS events, with a category-free NRI (0.164; $P = .048$). Concordant results were observed for OS and LCSS.

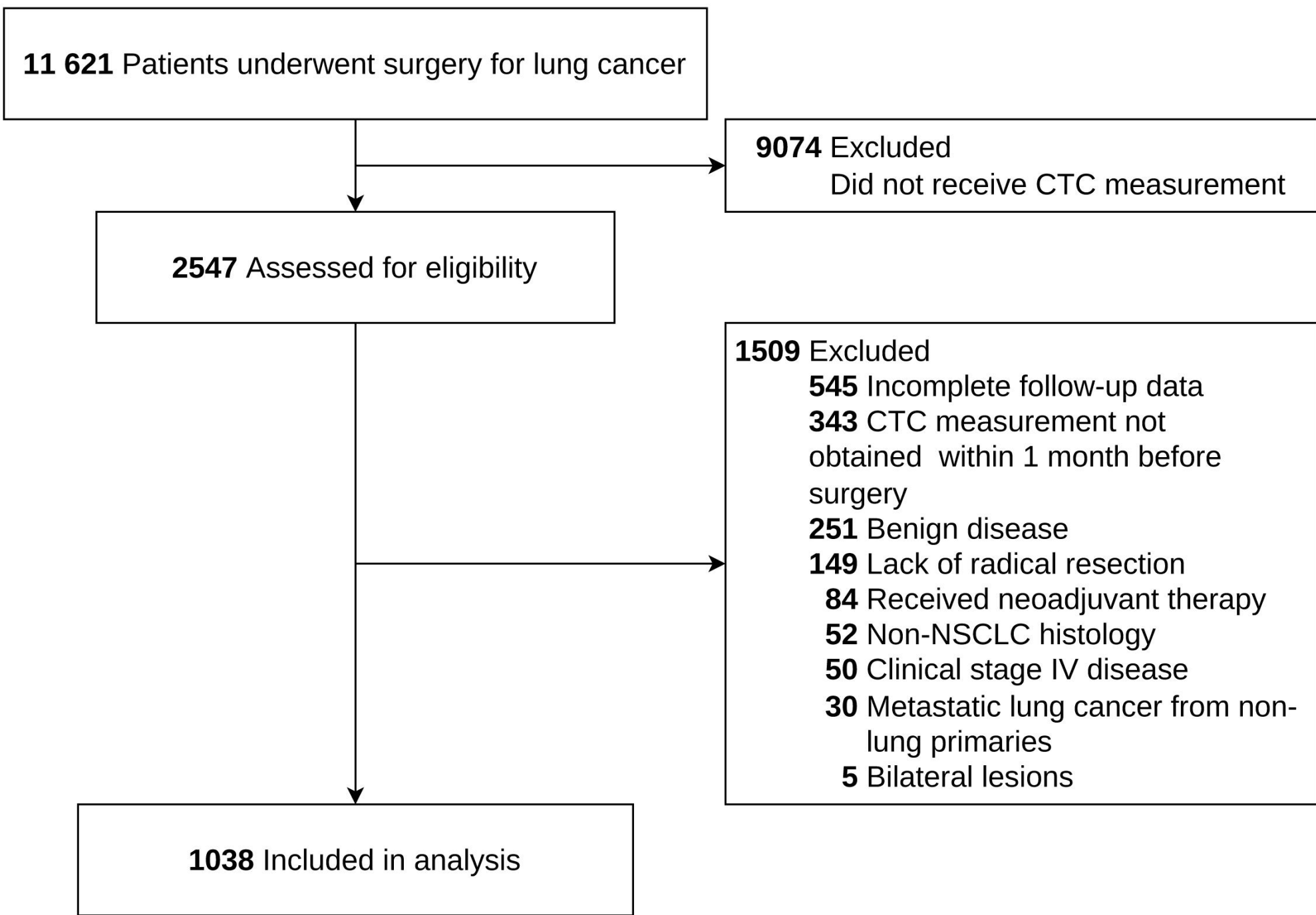


Figure 1. Flow Diagram of Patient Inclusion and Exclusion for This Study

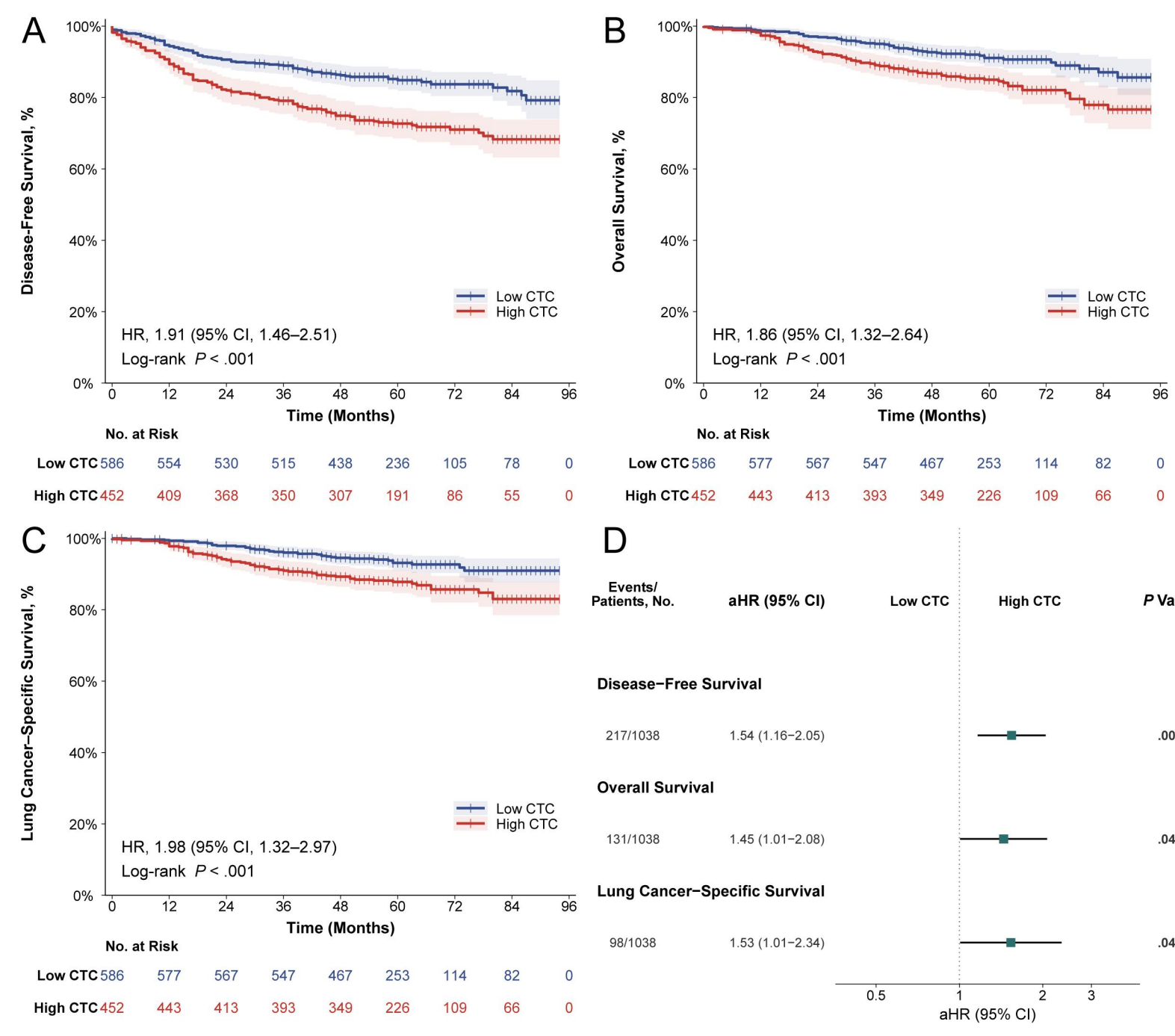


Figure 2. Prognostic Significance of Preoperative Folate Receptor-Positive Circulating Tumor Cells (FR⁺ CTCs) in Resected Non-Small Cell Lung Cancer (A)Kaplan-Meier curves for DFS stratified by preoperative FR⁺ CTCs (low, <10.14 FU/3 mL; high, ≥10.14 FU/3 mL). (B) Kaplan-Meier curves for OS. (C) Kaplan-Meier curves for LCSS. (D) Forest plot of multivariable Cox regression for DFS, OS, and LCSS, with the low-CTC group as the reference. Adjusted HRs were estimated from models adjusted for age, sex, histologic subtype, surgical approach, TNM stage, spread through air spaces, lymphovascular invasion, perineural invasion, and adjuvant therapy.