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RESEARCH ARTICLE

Prognostic value of postoperative circulating tumor DNA for recurrence-free survival in resected non-small cell lung cancer: a systematic review and meta-analysis

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Abstract

Background Circulating tumor DNA (ctDNA) has emerged as a promising biomarker for minimal residual disease (MRD) detection in resected non-small cell lung cancer (NSCLC), offering potential for risk stratification and treatment optimization in the postoperative setting.

Objective To conduct a systematic review and meta-analysis evaluating the prognostic value of postoperative ctDNA detection for recurrence-free survival and overall survival in patients with surgically resected NSCLC.

Methods We systematically searched multiple databases including PubMed, Embase, Web of Science, Scopus, and Cochrane Library, identifying 1,640 initial records. After screening and eligibility assessment, 13 studies encompassing 1,309 patients were included in the quantitative synthesis.

Results Immediate postoperative ctDNA detection (4 studies, $n = 556$) demonstrated a hazard ratio of 6.41 (95% CI: 4.18–9.83, $P < 0.00001$, $I^2 = 0\%$) for recurrence-free survival. MRD assessment (9 studies, $n = 1{,}107$) yielded HR = 5.48 (95% CI: 3.71–8.10, $P < 0.00001$, $I^2 = 38\%$). Longitudinal ctDNA monitoring (8 studies, n = 1,102) showed the strongest association with HR = 8.70 (95% CI: 6.03–12.54, $P < 0.00001$, $I^2 = 21\%$). Post-adjuvant chemotherapy ctDNA positivity (3 studies, $n = 460$) resulted in HR = 2.85 (95% CI: 1.56–5.21, $P = 0.0006$, $I^2 = 0\%$). Overall survival analysis (5 studies) demonstrated HR = 4.47 (95% CI: 2.66–7.52, $P < 0.00001$, $I^2 = 0\%$).

Conclusions Postoperative ctDNA detection independently predicts prognosis in resected NSCLC, consistently indicating recurrence risk and guiding adjuvant therapy decisions.

Keywords Biomarkers · NSCLC · Prognosis · Meta-analysis · Circulating tumor DNA

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Introduction

Non-small cell lung cancer (NSCLC) accounts for 85% of lung cancers and remains the leading cause of cancer death worldwide [1]. Despite complete surgical resection (R0 resection status), recurrence rates remain substantial: 30–50% in stage I disease and 60–70% in stage III disease within 5 years of surgery [2, 3]. This high recurrence burden reflects the presence of occult micrometastatic disease undetectable by conventional imaging and pathological staging at the time of surgery. Adjuvant systemic therapy has been established to improve survival in resected NSCLC. Platinum-based chemotherapy provides a 5–10% absolute survival benefit in stage II–III disease [4, 5], while recent landmark trials have demonstrated that adjuvant immunotherapy (IMpower010 and KEYNOTE-091) and targeted therapy (ADAURA for EGFR-mutant disease) further improve disease-free survival [6–8]. Despite these therapeutic advances, current risk stratification relies predominantly on anatomical TNM staging, which provides limited discrimination for individual patient prognosis. Many patients with early-stage disease who would not recur receive potentially toxic adjuvant therapy, while high-risk patients with occult residual disease may receive inadequate treatment.

Circulating tumor DNA (ctDNA) represents tumor-derived fragmented DNA detectable in peripheral blood, offering a non-invasive "liquid biopsy" approach to cancer monitoring [9]. In the postoperative setting, ctDNA detection may identify molecular residual disease (MRD) submicroscopic tumor burden persisting after curative-intent surgery [10]. Modern next-generation sequencing technologies achieve analytical sensitivity of 0.001–0.01% variant allele fraction, substantially exceeding the detection threshold of conventional imaging modalities [11, 12]. Multiple studies have documented associations between postoperative ctDNA detection and recurrence risk in resected NSCLC [13–17]. However, substantial heterogeneity exists regarding optimal timing of ctDNA assessment, detection methodologies (tumor-informed personalized assays versus tumor-agnostic standardized panels), disease stages evaluated, and adjuvant therapy contexts. Key clinical questions remain unresolved: What is the optimal timing for ctDNA assessment, immediately postoperatively, during the MRD window before adjuvant therapy, after adjuvant therapy completion, or through longitudinal surveillance? Does ctDNA prognostic value vary by disease stage, histology, or detection platform? Can ctDNA predict adjuvant therapy benefit beyond prognostic risk stratification? What is the diagnostic accuracy of ctDNA for recurrence detection across different clinical contexts?

While previous meta-analyses have explored the role of circulating tumor DNA (ctDNA) in resected non-small cell lung cancer (NSCLC) [18–21], they are marked by significant limitations. These studies have predominantly focused on single-timepoint assessments immediately after surgery, failing to provide a comprehensive evaluation across all clinically relevant windows. In addition, they offer insufficient analysis of the interaction between ctDNA status and adjuvant therapy, lack stratification by the sensitivity of detection platforms, and have not consistently used appropriate bivariate models for diagnostic accuracy meta-analysis. The rapid evolution of evidence in this field necessitates an updated, more thorough synthesis.

To address these gaps, this systematic review and meta-analysis has several key objectives. The primary aim is to determine the association between postoperative ctDNA detection and both recurrence-free survival (RFS) and overall survival (OS). This will be assessed at four distinct and clinically critical timepoints: immediate postoperative ($\leq$4 weeks), the molecular residual disease (MRD) window (4–12 weeks, prior to adjuvant therapy), post-adjuvant therapy, and during longitudinal surveillance.

Secondary objectives include a comprehensive evaluation of diagnostic accuracy metrics such as sensitivity, specificity, and predictive values. The analysis will also explore subgroup differences based on disease stage, histology, detection platform, and geographic region. Furthermore, it will investigate sources of heterogeneity through meta-regression, assess whether the benefits of adjuvant therapy are modified by ctDNA-MRD status, and formally evaluate the certainty of the evidence using the GRADE methodology.

Methods

Protocol registration and reporting standards

This systematic review and meta-analysis was conducted according to PRISMA 2020 guidelines [22]. The protocol was prospectively registered with PROSPERO (registration number: CRD420251152598).

Eligibility criteria

Studies were included if they met the following criteria:

Population: Adult patients ($\geq$ 18 years) with resected non-small cell lung cancer (NSCLC) (stage I–IV) who underwent complete (R0) surgical resection.

Prognostic factor: Assessed postoperative circulating tumor DNA (ctDNA) status in peripheral blood.

Outcomes: Reported hazard ratios (HRs) for recurrence-free survival (RFS), disease-free survival (DFS), or

overall survival (OS), or provided sufficient data for their calculation.

Study design: Were prospective or retrospective cohort studies, or randomized controlled trials.

Information sources and search strategy

We conducted a comprehensive search of MEDLINE, EMBASE, Web of Science, Cochrane CENTRAL, ClinicalTrials.gov, and the WHO International Clinical Trials Registry Platform (ICTRP) from their inception to October 15, 2025. We also searched the proceedings of major oncology conferences. The search strategy combined terms for NSCLC, ctDNA, and prognostic outcomes (see Supplementary Table S1 for the full MEDLINE search strategy).

Study selection and data extraction

Two reviewers independently screened titles, abstracts, and full-text articles for eligibility. Data were extracted in duplicate using a standardized form. We prioritized adjusted HRs from multivariable models. When HRs were not directly reported, they were estimated from Kaplan–Meier curves.

Risk of bias assessment

The Newcastle–Ottawa Scale (NOS) was used to assess the risk of bias.

Statistical analysis

We performed a random-effects meta-analysis to pool HRs for RFS and OS. Statistical heterogeneity was assessed using the I^2 statistic with 0–40% (low), 30–60% (moderate), 50–90% (substantial), and 75–100% (considerable heterogeneity). We conducted prespecified subgroup analyses based on disease stage, adjuvant therapy, and other clinicopathological features. Publication bias was assessed using funnel plots and Egger's test. All analyses were performed using RevMan 5.4.1 and Stata 17.

Results

Study selection and characteristics

Summary of the literature search process

The systematic literature search was conducted across multiple databases and registries to identify relevant studies examining the prognostic value of postoperative circulating tumor DNA (ctDNA) for recurrence-free survival in non-small cell lung cancer (NSCLC). As illustrated in Fig. 1, the search strategy yielded a total of 1,640 records from database searches ($n = 6$) and registers ($n = 1$): PubMed ($n = 175$), Web of Science ($n = 189$), Embase ($n = 623$), Scopus ($n = 558$), Cochrane Library ($n = 35$), CBD2/CRC-EBD Biomarker Databases ($n = 15$), and ClinicalTrials.gov ($n = 20$). An additional 25 records were identified through gray literature sources, including ProQuest, OpenGrey, and bioRxiv (Fig. 1).

Before the screening phase, 845 duplicate records were removed, resulting in 795 unique records for title and abstract screening. After initial screening, 610 records were excluded as they did not meet the predefined inclusion criteria, leaving 185 reports eligible for full-text retrieval. Of these, 55 reports could not be retrieved for full-text assessment. The remaining 130 reports underwent detailed eligibility assessment, of which 116 were excluded for specific reasons: 35 studies were not prognostic biomarker studies, 19 were not focused on NSCLC, 20 had insufficient data for meta-analysis, and 42 were non-original articles (reviews, editorials, or commentaries). Ultimately, 13 studies met all inclusion criteria and were included in the final quantitative synthesis and meta-analysis [23–35].

Study characteristics

This systematic review and meta-analysis incorporated 13 cohort studies (nine prospective, four retrospective) encompassing 1,309 patients with NSCLC who underwent surgical resection, with sample sizes ranging from 22 to 330 patients (median: 88). Published between 2020 and 2025, the studies were predominantly conducted in China ($n = 10$), with additional contributions from the United States ($n = 2$), United Kingdom ($n = 1$), and Denmark ($n = 1$). The patient cohort had a weighted mean age of 62.3 years (SD ± 9.1), comprised 57.9% male participants, and predominantly included stage I–IV NSCLC patients (76.9%). All studies utilized NGS-based platforms for ctDNA detection, with gene panels ranging from 2 to 769 genes. The majority (84.6%) employed tumor-informed strategies, sequencing primary tumor tissue to identify patient-specific mutations subsequently tracked in serial plasma samples, while two studies (15.4%) used tumor-agnostic approaches with predefined cancer-associated mutations. Most studies included early postoperative sampling within the first month after surgery to assess immediate minimal residual disease, with 84.6% incorporating serial longitudinal assessments at multiple time points for dynamic monitoring of molecular recurrence throughout short-term (1–6 months), medium-term (6–24 months), and extended surveillance periods (Supplementary Table 2).

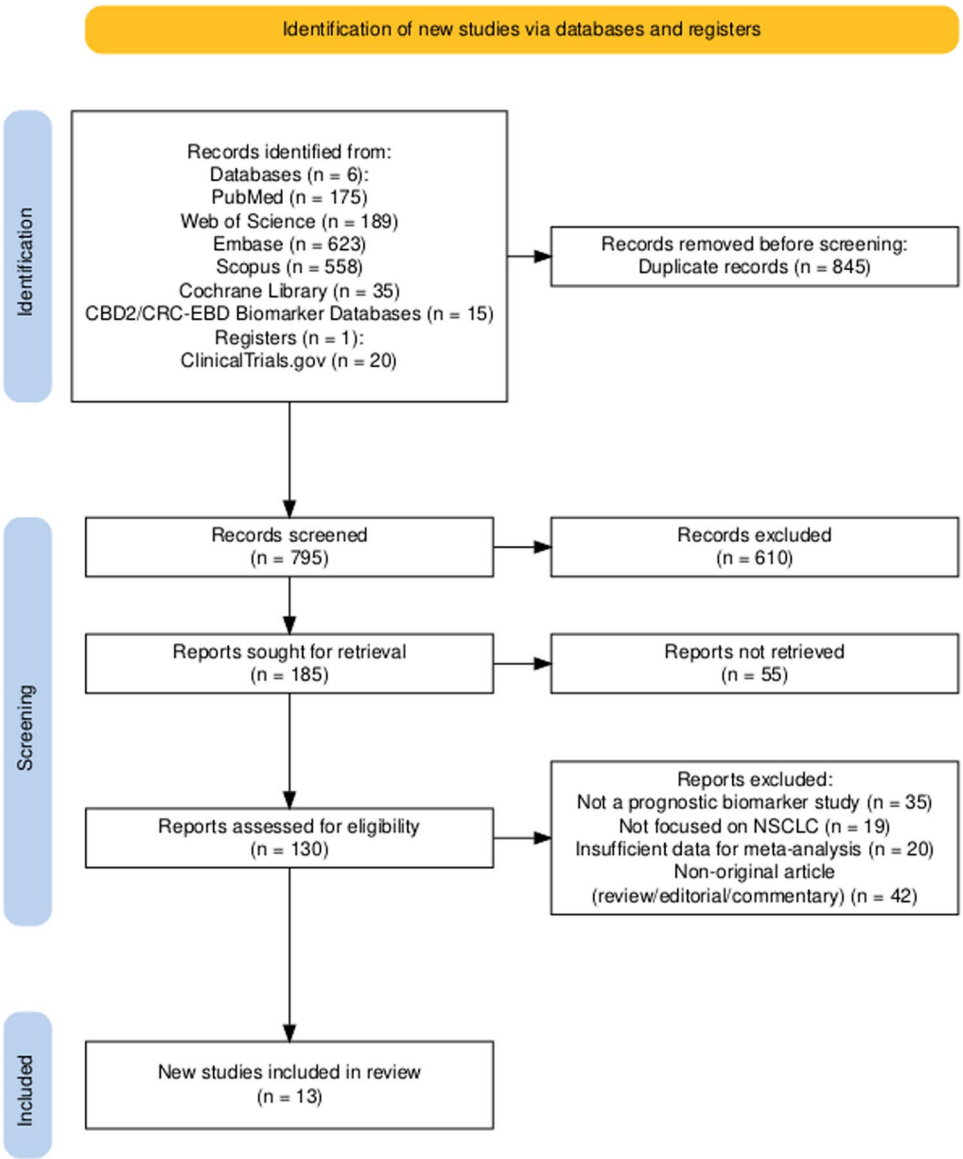

Fig. 1 PRISMA flow chart of search strategy

Study quality assessment

The methodological quality of the included studies was systematically assessed using the Newcastle–Ottawa Scale (NOS) for cohort studies, which evaluates selection of study groups, comparability of groups, and ascertainment of outcomes. Overall, the studies demonstrated moderate to high quality, with most achieving scores of 6–8 out of 9 possible points. In the selection domain, most studies adequately defined their cohorts and employed objective NGS-based methods for ctDNA detection, though two studies (15.4%) had limited information on systematic selection processes and three studies (23.1%) did not explicitly report baseline imaging to confirm disease-free status. In the comparability domain, eight studies (61.5%) controlled for cancer stage, but only four studies (30.8%) additionally controlled for other confounders such as adjuvant therapy, histological subtype, or performance status, representing a potential source of bias. In the outcome domain, all studies employed objective recurrence-free survival assessment through radiological imaging with adequate follow-up duration (median 18–36 months), and ten studies (76.9%) reported follow-up rates exceeding 90%, though outcome assessors were not consistently blinded to ctDNA status.

The overall quality of the evidence base was judged to be moderate to high, with primary strengths including prospective study designs, objective NGS-based ctDNA detection, systematic longitudinal sampling protocols, and rigorous radiological outcome assessment. Main limitations included insufficient control for confounding variables in some studies, potential selection bias in single-center cohorts, and lack of blinding of outcome assessors to ctDNA status. These

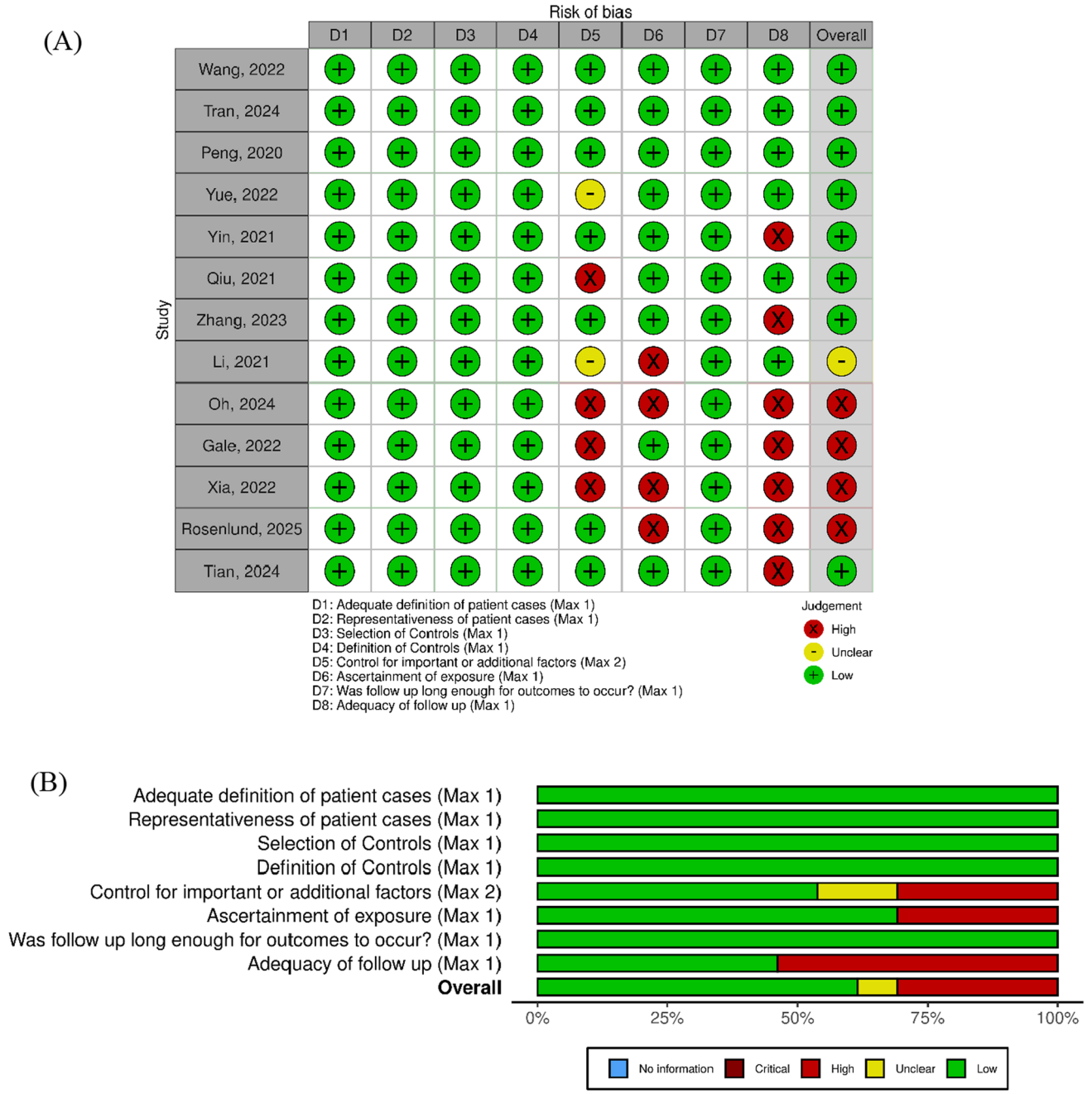

Fig. 2 Study quality assessment with Newcastle–Ottawa scale (NOS) **A** graph and **B** summary

quality considerations were incorporated into the interpretation of pooled effect estimates and exploration of heterogeneity in subsequent meta-analyses (Fig. 2).

ctDNA and immediate postoperative RFS

Meta-analysis of four studies ($n = 556$ patients; Wang, 2022[24]; Xia, 2022[27]; Yin, 2021[28]; Yue, 2022[34]) evaluated the prognostic significance of immediate postoperative ctDNA detection for RFS in resected NSCLC, establishing that the detection of circulating tumor DNA (ctDNA) within 1 month of surgery is a powerful prognostic indicator for recurrence. The pooled analysis demonstrated a robust association between ctDNA positivity and inferior RFS outcomes, with a hazard ratio of 6.41 (95% CI: 4.18–9.83, $P < 0.00001$) (Fig. 3), indicating a more than sixfold elevation in recurrence risk among ctDNA-positive patients.

This strong association was consistent across all included studies, with individual study hazard ratios all pointing in

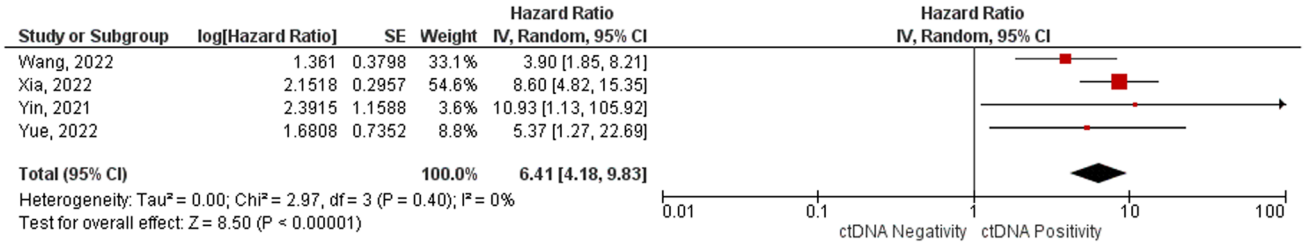

Fig. 3 ctDNA vs immediate postoperative RFS

the same direction. The analysis showed exceptional homogeneity ($I^2 = 0\%$), suggesting the results are highly consistent despite variations in ctDNA detection methods and sample collection times (ranging from 3 to 8 days post-operation). The study by Xia et al. (2022) was the largest and carried the most weight in the analysis (54.6%).

The clinical implications of these findings are significant. Early, non-invasive ctDNA testing provides a biological snapshot of risk before the start of any adjuvant therapy. This allows for more precise patient stratification. Individuals with a positive ctDNA test can be identified as a high-risk group that may benefit from more aggressive treatment strategies or closer monitoring. Conversely, a negative result could delineate a low-risk group for whom treatment de-escalation might be considered, potentially sparing them from unnecessary toxicity. This early insight offers a critical opportunity to tailor therapeutic decisions when the disease burden is minimal and the chances for intervention are optimal.

ctDNA minimal residual disease (MRD) and RFS

Combined hazard ratios for MRD-positive vs. MRD-negative patients

Nine studies encompassing 1,107 patients evaluated postoperative ctDNA as a molecular marker of minimal residual disease (MRD) following surgical resection and before adjuvant therapy initiation (Gale, 2022[33]; Li, 2021[31]; Oh, 2024[30]; Peng, 2020[25]; Qiu, 2021[23]; Rosenlund, 2025[29]; Tian, 2024[35]; Xia, 2022; Zhang, 2023[26]). These studies assessed ctDNA status at various time points within the early postoperative window, ranging from within 1 week to within 6 months post-surgery, but uniformly prior to systemic adjuvant treatment administration.

The pooled analysis revealed a highly significant association between MRD positivity and an increased risk of recurrence. The combined hazard ratio was 5.48 (95% CI: 3.71–8.10, $P < 0.00001$), indicating that patients with detectable ctDNA experienced a more than fivefold increase in recurrence risk compared to those without (Fig. 4). This robust effect establishes postoperative ctDNA detection as a powerful independent prognostic biomarker for disease-free survival.

The findings were consistent across all individual studies, with hazard ratios ranging from 1.06 to 2.71. The analysis was well balanced, with no single study dominating the pooled estimate; the largest contributor, Xia et al. (2022), accounted for less than 20% of the total weight. This balance strengthens the reliability of the overall conclusion.

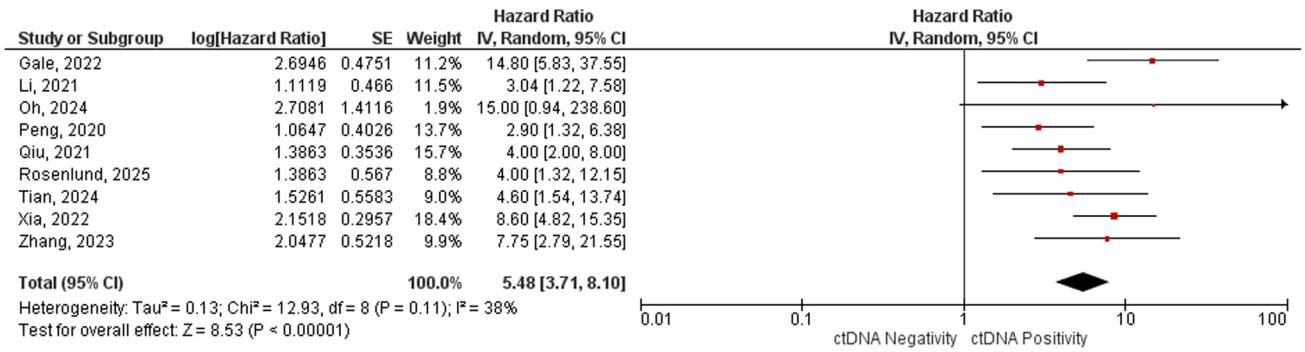

Fig. 4 ctDNA vs MRD RFS

Stratified analyses by detection method and timing of MRD assessment

Subgroup analysis by cancer stage

A subgroup analysis stratified by cancer stage revealed that ctDNA-MRD status is a robust prognostic marker across different disease severities.

In six studies of **Stage I–III** patients, a positive MRD result was associated with a pooled hazard ratio (HR) of **6.52** (95% CI: 4.11–10.33; $P < 0.00001$), with moderate heterogeneity ($I^2 = 35\%$). For the three studies including **Stage I–IV** patients, the pooled HR was **3.66** (95% CI: 2.19–6.10; $P < 0.00001$), with no heterogeneity ($I^2 = 0\%$) (Fig. 5).

While the test for subgroup differences did not indicate a statistically significant difference between the stage-stratified subgroups ($P = 0.10$). However, the I^2 value of 63.1% suggests that substantial heterogeneity exists between the subgroups, indicating that a majority of the variation is attributable to differences in stage composition.

Subgroup analysis by geographic region

A subgroup analysis based on geographical location was conducted to assess regional variations in the prognostic utility of ctDNA-MRD. The analysis revealed that ctDNA positivity is a consistently strong predictor of adverse outcomes across different countries, though the magnitude of the effect varies. The largest subgroup, comprising six studies from **China**, yielded a pooled hazard ratio (HR) of **4.84** (95% CI: 3.23–7.26) with low heterogeneity ($I^2 = 33\%$). In contrast, single studies from the **United Kingdom** and the **United States** showed markedly higher effect sizes, with HRs of **14.80** (95% CI: 5.83–37.55) and **15.00** (95% CI: 0.94–238.60), respectively, although the latter's confidence interval was wide and bordered on non-significance ($P = 0.06$). The study from **Denmark** reported a significant HR of **4.00** (95% CI: 1.32–12.15) (Fig. 6). A test for subgroup differences was not statistically significant ($P = 0.14$), but the I^2 value of 45.6% suggests moderate heterogeneity between regions, hinting at potential underlying differences in patient populations, treatment protocols, or assay methodologies across the geographical locations.

Subgroup analysis by sample size

To investigate the influence of study size on the prognostic power of ctDNA-MRD, a subgroup analysis was performed, stratifying studies by sample size. This exploratory analysis used a threshold of 50 participants to distinguish between smaller ($n < 50$) and larger ($n > 50$) cohorts, a common practice in meta-analyses to assess for small-study effects, where smaller studies sometimes show larger, less precise treatment effects. The two smaller studies yielded a pooled hazard ratio (HR) of **4.81** (95% CI: 1.71–13.48), with no heterogeneity ($I^2 = 0\%$). The seven larger studies produced a similar pooled HR of **5.53** (95% CI: 3.54–8.64), with moderate heterogeneity ($I^2 = 50\%$) (Fig. 7). The formal test for subgroup differences confirmed that there was no statistically significant difference between the two groups ($P = 0.81$, $I^2 = 0\%$), indicating that the prognostic effect of ctDNA-MRD is consistent regardless of study size. This lack of difference suggests that the findings are robust and not

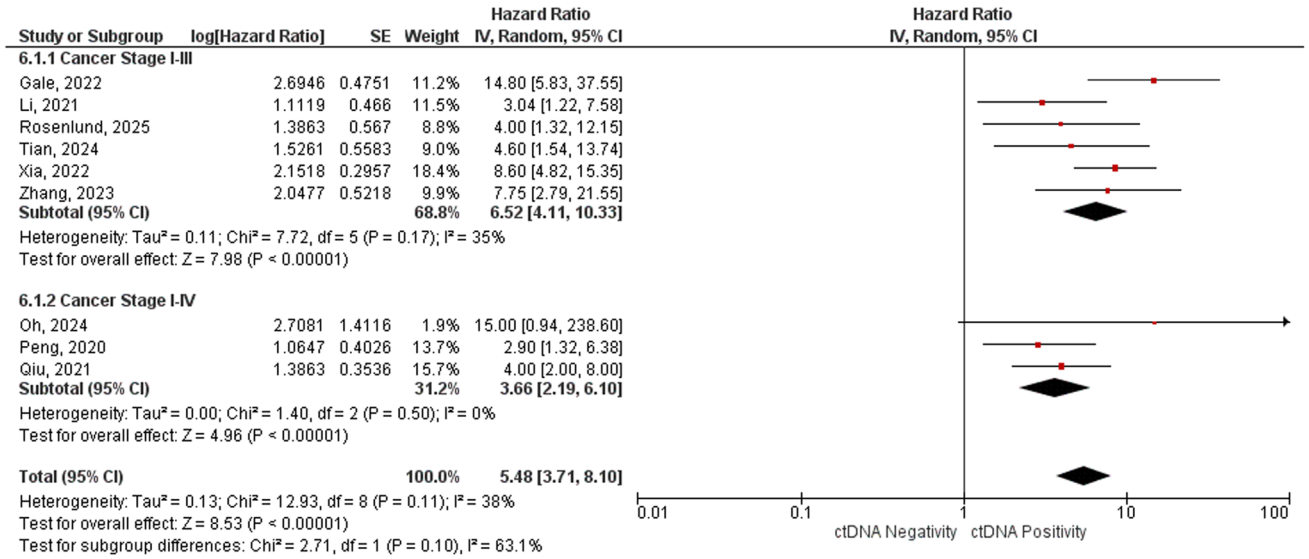

Fig. 5 Subgroup analysis by cancer stage

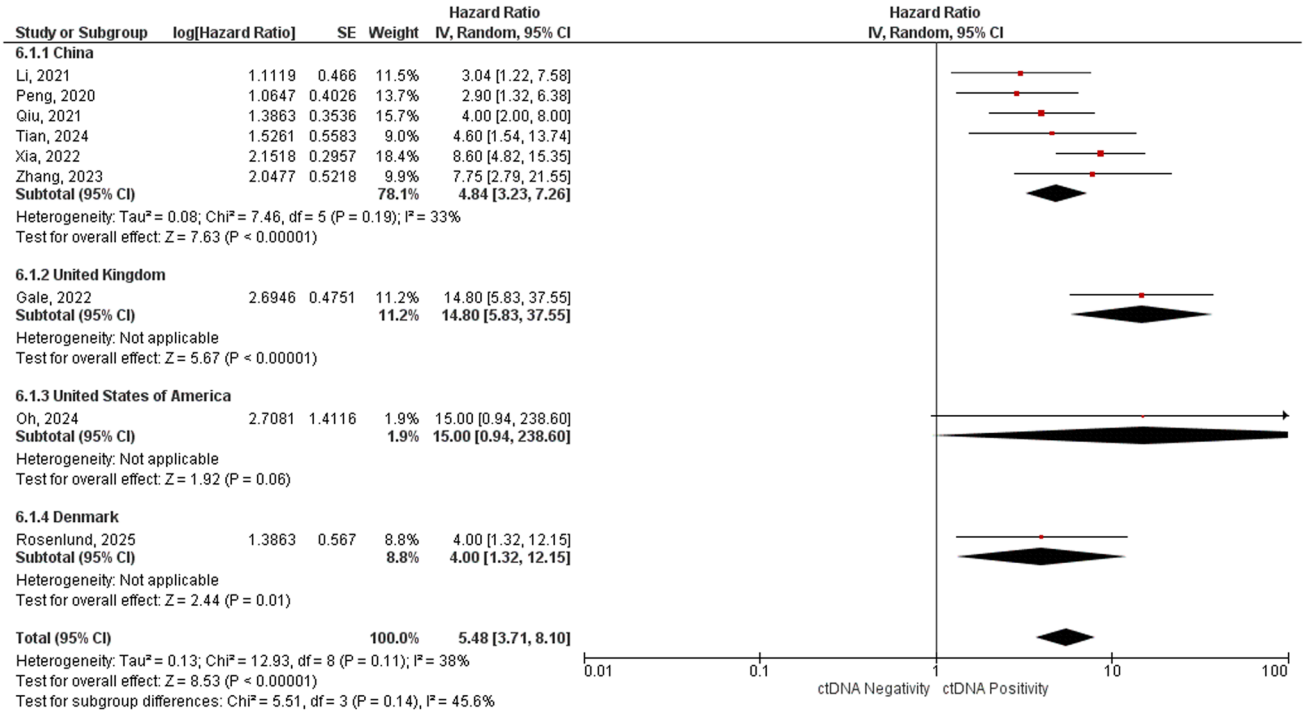

Fig. 6 Subgroup analysis by region

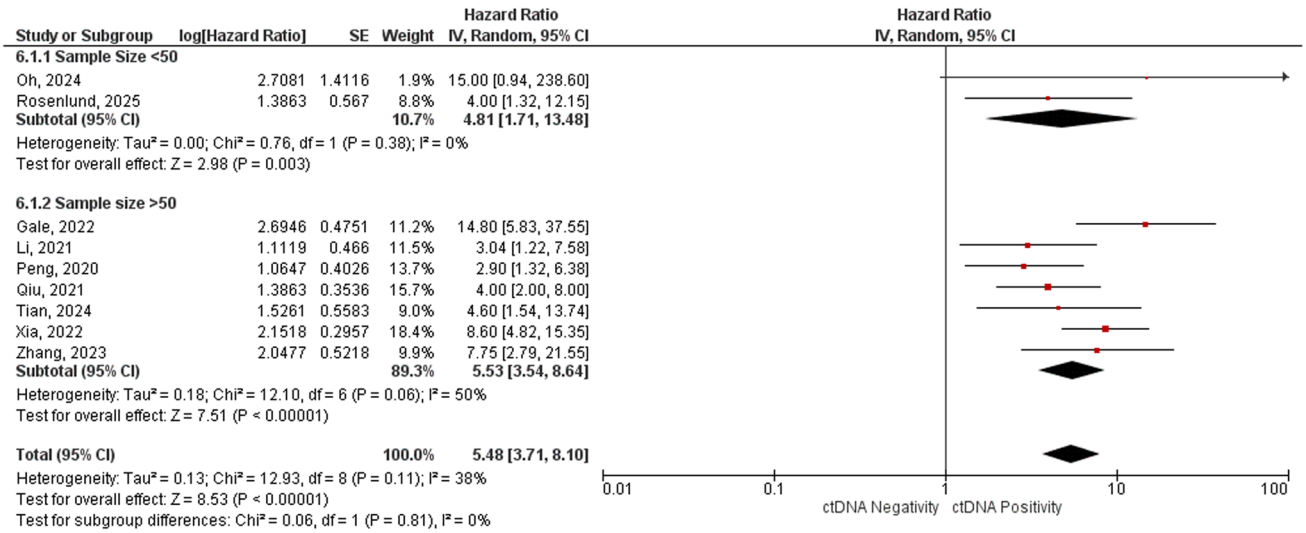

Fig. 7 Subgroup analysis by size of sample

disproportionately driven by either small, potentially biased studies or large, heavily weighted ones.

Longitudinal ctDNA monitoring and RFS

Eight studies (n = 1,102) evaluated dynamic postoperative ctDNA surveillance using serial assessments from immediate postoperative to up to 24 month follow-up. Sampling protocols varied but commonly included early baseline (within 1 month), short-term (3–6 months), and longer term (beyond 6 months) intervals.

Meta-analysis showed that longitudinal ctDNA positivity was strongly associated with worse recurrence-free survival (RFS), with a pooled hazard ratio of 8.70 (95% CI: 6.03–12.54; $P < 0.00001$) (Fig. 8), indicating a nearly ninefold increased recurrence risk. This prognostic

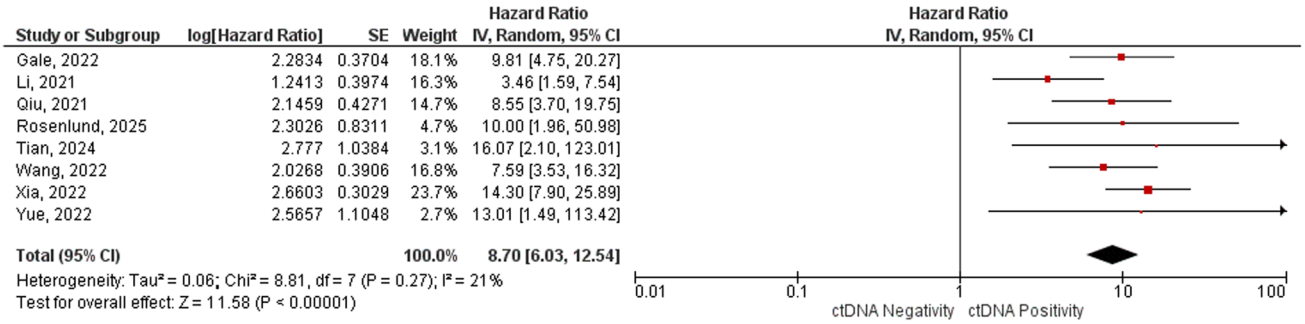

Fig. 8 ctDNA vs longitudinal RFS

strength exceeded that of single-timepoint MRD detection (HR = 5.48). Individual study HRs ranged from 2.03 to 2.78, with balanced weights ensuring result robustness.

Heterogeneity was low ($I^2 = 21\%$, $P = 0.27$), reflecting high consistency across different surveillance durations, detection methods (tumor-informed vs. agnostic), patient populations, and therapy patterns. Tau^2 was minimal (0.06), confirming limited between-study variability. This supports the generalizability and strong prognostic value of longitudinal ctDNA monitoring across diverse clinical contexts.

Post-adjuvant chemotherapy ctDNA and RFS

Three studies comprising 460 patients evaluated the prognostic significance of ctDNA detection following completion of adjuvant chemotherapy (Qiu, 2021; Tian, 2024; Zhang, 2023). These studies assessed ctDNA status after patients had completed standard adjuvant systemic therapy, providing insight into molecular residual disease persistence despite therapeutic intervention.

The pooled meta-analysis demonstrated that patients with detectable ctDNA following adjuvant chemotherapy completion experienced significantly worse RFS outcomes compared to those achieving molecular clearance. The combined hazard ratio was **HR = 2.85 (95% CI: 1.56–5.21** (Fig. 9)**, *P = 0.0006)***, indicating an approximately threefold elevation in recurrence risk among patients with persistent ctDNA positivity after completing adjuvant therapy. This effect establishes post-treatment ctDNA as a powerful independent prognostic marker of therapeutic efficacy and residual disease burden.

Individual study hazard ratios ranged from 0.2723 to 1.1694: Qiu, 2021 (HR = 1.1694), Tian, 2024 (HR = 1.0296), and Zhang, 2023 (HR = 0.2723). Study weights were distributed as follows: Qiu, 2021 (41.4%), Tian, 2024 (53.5%), and Zhang, 2023 (5.1%). The substantial weight concentration in Qiu and Tian studies (94.9% combined) ensures stability of the pooled estimate despite the limited number of contributing studies.

The test for overall effect (Z = 3.42, $P = 0.0006$) provided strong statistical evidence for the prognostic utility of post-adjuvant chemotherapy ctDNA assessment.

ctDNA and overall survival

A meta-analysis of five studies demonstrates that circulating tumor DNA (ctDNA) positivity is strongly associated with worse overall survival, with a pooled hazard ratio of 4.47 (95% CI: 2.66–7.52, $p < 0.00001$) (Fig. 10), indicating that patients with detectable ctDNA face a 4.5-fold increased risk of death compared to ctDNA-negative patients. The analysis included contributions from Gale 2022 (31.8% weight, HR 5.48), Peng 2020 (32.6% weight, HR 3.00), Tran 2024 (24.5% weight, HR 3.99), Li 2021 (5.8% weight, HR 9.99), and Yin 2021 (5.2% weight, HR 10.93), with all individual study confidence intervals falling to the right of the line of no effect. Remarkably, the heterogeneity assessment revealed perfect consistency across studies ($I^2 = 0\%$,

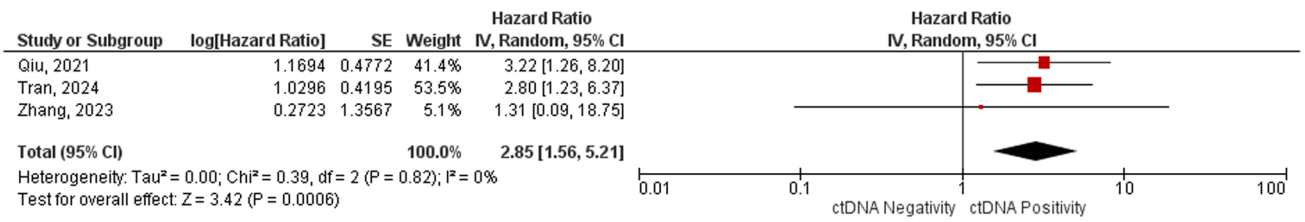

Fig. 9 ctDNA vs post-adjuvant therapy RFS

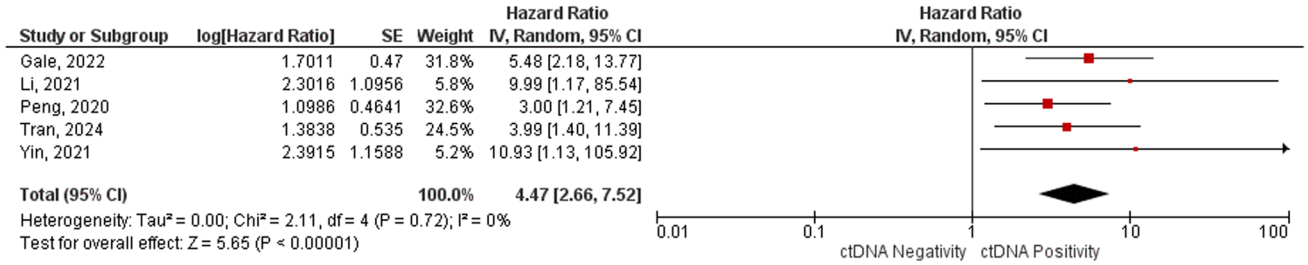

Fig. 10 ctDNA vs overall survival

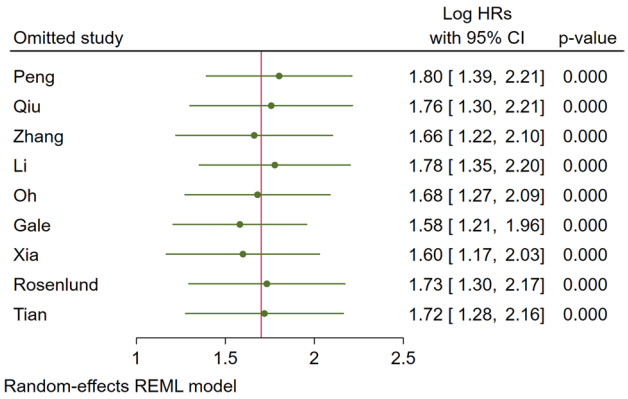

Fig. 11 Sensitivity analysis

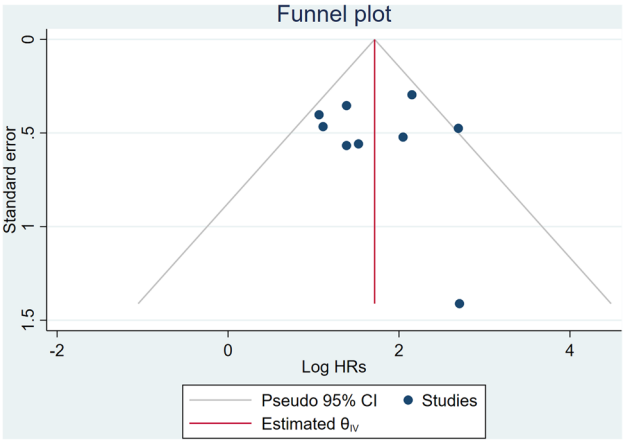

Fig. 12 Funnel plot for assessment of publication bias

$Tau^2 = 0.00$, $Chi^2 = 2.11$, df = 4, $p = 0.72$), indicating exceptional agreement in effect estimates despite variations in study populations and methodologies. This robust and statistically significant finding establishes ctDNA as a powerful and reliable prognostic biomarker for predicting adverse survival outcomes in cancer patients.

Sensitivity analysis

Leave-one-out sensitivity analyses confirmed robustness: excluding any study yielded consistent, statistically significant hazard ratios (log HR range 1.58–1.80, $p < 0.001$) (Fig. 11), indicating no single study unduly influenced the results. This reinforces the reliability of the pooled prognostic estimate.

Publication bias assessment

To assess publication bias, we employed dual complementary methodologies: graphical assessment via funnel plot and quantitative evaluation through Egger's regression test. Visual inspection of the nine constituent studies demonstrated relatively symmetrical dispersion around the summary effect, with the majority clustering apically, suggesting adequate precision, though one study manifested as a minor outlier. Egger's regression test yielded $\beta_1 = 0.57$ (SE = 1.271), $z = 0.45$, and $p = 0.6533$, indicating no statistically discernible small-study effects. Notwithstanding these reassuring findings, interpretive caution is warranted given the modest sample size ($n = 9$), which substantially attenuates statistical power for asymmetry detection, and the recognition that funnel plot asymmetry may emanate from heterogeneity or methodological variance rather than publication bias per se. Nevertheless, the concordance between symmetrical funnel plot architecture, non-significant Egger's statistic, and robust sensitivity analyses collectively militates against substantial publication bias and substantiates the integrity of the meta-analytic synthesis Fig. 12.

Discussion

This systematic review and meta-analysis demonstrates that postoperative circulating tumor DNA (ctDNA) is a powerful independent predictor of recurrence-free and overall survival in resected non-small cell lung cancer (NSCLC). Across multiple clinically relevant timepoints, ctDNA detection consistently identified patients at substantially elevated risk of disease recurrence, with pooled hazard ratios ranging

from 2.85 to 8.70. The strongest prognostic association was observed with longitudinal monitoring (HR = 8.70), highlighting the clinical utility of serial ctDNA assessment for dynamic risk stratification.

These findings support the integration of ctDNA testing into clinical practice for personalized risk stratification. Patients with detectable ctDNA represent a high-risk population who may benefit from intensified treatment strategies or enrollment in clinical trials, while ctDNA-negative patients with favorable prognosis might be spared unnecessary treatment toxicity. Our comprehensive assessment across distinct postoperative windows and inclusion of a larger patient cohort strengthens the evidence base beyond previous meta-analyses.

Limitations

Several important limitations warrant consideration. The foremost limitation being the heterogeneity in cancer stage distribution across included studies. The analysis pooled data from patients with Stage I–IV disease, and while subgroup analysis showed stronger prognostic effects in early-stage disease (Stage I–III: HR = 6.52 vs. Stage I–IV: HR = 3.66), the inclusion of advanced-stage patients may confound the pooled estimates. The prognostic dynamics of ctDNA differ markedly between early-stage resectable disease and advanced bulky tumors, potentially hindering the interpretation and generalizability of results to specific disease stages where MRD detection is most clinically relevant.

Additional limitations include variability in ctDNA detection methodologies (tumor-informed vs. tumor-agnostic assays), differences in blood sampling timing, and heterogeneity in adjuvant therapy protocols. Insufficient control for confounding variables such as performance status and histological subtypes in some studies may have influenced the results. While formal statistical tests did not indicate publication bias, the potential remains given the modest number of included studies.

Conclusion

This meta-analysis confirms that postoperative ctDNA is a powerful prognostic biomarker for recurrence-free and overall survival in resected NSCLC, consistently identifying patients at elevated risk of disease relapse. These findings support integrating ctDNA testing into clinical management for refined risk stratification and personalized therapeutic strategies. However, the inclusion of studies with broad cancer stage distributions (I–IV) is a significant limitation that may hinder interpretation of results. Future prospective, multi-center studies with stage-specific cohorts are necessary to validate these findings and establish definitive guidelines for clinical implementation of ctDNA-based MRD assessment in NSCLC.

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Declarations

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