INPLASY

Predictive role of circulating tumor DNA based molecular residual disease for long-term outcomes in non-small cell lung cancer patients: a meta-analysis

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ADMINISTRATIVE INFORMATION

Support - No.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 19 May 2025 and was last updated on 19 May 2025.

INTRODUCTION

Review question / Objective To identify the predictive role of circulating tumor DNA (ctDNA) based molecular residual disease (MRD) for long-term outcomes in non-small cell lung cancer (NSCLC).

Condition being studied Surgery remains the primary treatment for most non-small cell lung cancers (NSCLC) [1]. However, even when the visible tumor is completely removed, there can still be lesions that are not detectable with the naked eye, leading to a higher risk of postoperative recurrence. Therefore, regular postoperative follow-up is crucial for NSCLC patients. Traditional methods for detecting tumor recurrence after surgery include blood tests for tumor markers and routine pulmonary imaging. However, postoperative inflammation can cause changes such as dense or patchy shadows and fibrous streaks, which may obscure the accurate identification of tumor recurrence on imaging. Additionally, tumor markers can be influenced by other factors, reducing their specificity [2]. Imaging tests also have limited sensitivity, as they can only detect disease recurrence that is visible to the naked eye. Therefore, monitoring the risk of recurrence in NSCLC remains a pressing issue that needs to be addressed in clinical practice.

Liquid biopsy is a new, non-invasive testing method that analyzes tumor-derived substances in blood or any other bodily fluids. Compared to tissue biopsy, liquid biopsy offers the advantages of simplicity and safety. It primarily relies on the analysis of circulating tumor cells (CTCs) or circulating tumor DNA (ctDNA) in blood samples to reflect the tumor mutation burden (TMB) and minimal residual disease (MRD) in cancer patients. MRD, also known as measurable residual disease or molecular residual disease, was initially a concept used in hematologic malignancies, referring to residual tumor cells or molecular remnants remaining in the body after treatment, which are potential sources of tumor recurrence [3, 4]. In recent years, liquid biopsy using ctDNA sequencing to detect MRD has become more widely applied in solid tumors, including NSCLC

[5-8]. Several studies explored the relationship between ctDNA based MRD monitoring and long-term clinical outcomes in NSCLC, but the results have been inconsistent [9-18].
Therefore, this meta-analysis aimed to determine predictive role of ctDNA based MRD for long-term outcomes among NSCLC patients based on available evidence contributing to prognosis assessment and early intervention for high-risk patients.

METHODS

Search strategy We searched PubMed, EMbase, Web of Science and CNKI databases up to August 31, 2024 with following terms: lung, pulmonary, tumor, cancer, neoplasm, carcinoma, minimal residual disease, molecular residual disease, mesurable residual disease, MRD, survival, prognosis and prognostic. Free texts and MeSH terms were applied.

Participant or population Primary NSCLC patients.

Intervention The MRD status was detected and identified after anti-tumor treatment based on the ctDNA.

Comparator Patients were divided into positive or negative MRD group and the clinical outcomes including the progression-free survival (PFS), overall survival (OS) and cancer-specific survival (CSS) were compared.

Study designs to be included Retrospective or prospective cohort studies.

Eligibility criteria Studies meeting following criteria were included: 1) primary NSCLC patients; 2) the MRD status was detected and identified after anti-tumor treatment based on the ctDNA; 3) patients were divided into positive or negative MRD group and the clinical outcomes including the progression-free survival (PFS), overall survival (OS) and cancer-specific survival (CSS) were compared; 4) hazard ratios (HRs) with 95% confidence intervals (CIs) for above endpoints were reported or Kaplan-Meier survival curves were provided; 5) available full texts.

Information sources Following information were extracted from included studies: first author, country, year, sample size, number of patients with positive MRD, tumor stage, treatment, detection time point of MRD, follow-up period, endpoint, HR and 95% CI.

Main outcome(s) Progression-free survival (PFS), overall survival (OS) and cancer-specific survival (CSS).

Quality assessment / Risk of bias analysis All included studies were cohort studies. Therefore, the Newcastle-Ottawa Scale (NOS) scoring tool was used to assess the quality.

Strategy of data synthesis Heterogeneity between studies was assessed by I2 statistics and Q test. If significant heterogeneity was detected ($I^2 > 50\%$ and/or $P < 0.1$), random-effects model was applied; otherwise, fixed-effects model was applied. HRs and 95% CIs were combined. Notably, due to the similarity between PFS and DFS in patients receiving radical surgery, DFS was regarded as PFS during our analysis. Subgroup analyses based on the time point of MRD detection [landmark (within postoperative one month) vs longitudinal] and treatment (surgery vs chemoradiotherapy) were conducted. Sensitivity analysis for PFS was conducted to detect the sources of heterogeneity and assess the stability of the overall results. Begg's funnel plot with Egger's test were performed to detect publication bias, and significant publication bias was defined as $P < 0.05$ [21, 22]. Above analyses were performed using STATA (v. 15.0) software.

Subgroup analysis Subgroup analyses based on the time point of MRD detection [landmark (within postoperative one month) vs longitudinal] and treatment (surgery vs chemoradiotherapy) were conducted.

Sensitivity analysis Sensitivity analysis for PFS was conducted to detect the sources of heterogeneity and assess the stability of the overall results.

Language restriction No.

Country(ies) involved China - The Second Affiliated Hospital Medical School of Nanchang University.

Keywords Molecular residual disease; circulating tumor DNA; survival; non-small cell lung cancer.

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