International Journal of Scientific Research in Dental and Medical Sciences

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Evaluate the Prognostic Value of Non–Small-Cell Lung Cancer Using Blood-Based Circulating Tumor DNA: A Systematic Review and Meta-analysis

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ARTICLE INFO

Article history:
Received 08 February 2024
Received in revised form 10 March 2024
Accepted 14 March 2024
Available online 16 March 2024

Keywords:
Carcinoma
Circulating Tumor DNA
Lung Neoplasms
Treatment Outcome

ABSTRACT

Background and objectives: This research aimed to evaluate the prognostic value(s) of non-small-cell lung cancer (NSCLC) through blood-based circulating tumor DNA (ctDNA).

Material and methods: To achieve the objectives of the study, databases at the international scale, including Web of Science, PubMed, Science Direct, Wiley, Scopus, EBSCO, Web of Knowledge, ISI, Embase, Google Scholar, and Elsevier, were searched according to PRISMA 2020-27-item checklist and respective keywords from 2019 to February 2024. Moreover, the inverse–variance method and the fixed-effect model were applied in the research. In addition, we used STATA/MP v17 for statistical analyses of the data (Sig, < 0.05).

Results: Based on the search, 11 articles were chosen, considering the inclusion criteria intended for the research. The analysis demonstrated that cases suffering from higher levels of ctDNA exhibited greater levels of risk for progression-free survival and overall survival (HR 3.47, 95% CI 2.98-3.97; P-value < 0.001) and (HR 3.16, 95% CI 2.45-3.87, P-value < 0.001) than that of the cases suffering from lower levels of ctDNA.

Conclusions: Positive ctDNA was found to be related to overall survival and progression-free survival individually and collectively in non–small–cell Lung Cancer cases.

1. Introduction

The lung is one of the most important parts of the respiratory system, and one of its most important functions is to separate oxygen from the air and transfer it to the circulatory system.[1] Lung cancer is the most common disease of the pulmonary system. It originates from the uncontrolled growth of cells in this tissue, and the possibility of its spread to other tissues follows.[2] This cancer is divided into two categories: small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC). If lung cancer is not treated, cell growth can spread outside the lung in a process called metastasis and spread to surrounding tissues or other body organs.[3] According to statistics, the incidence of lung cancer is increasing worldwide by 12% per year.[4] This amount is considered a rapid growth for a disease.[5] In order to diagnose lung cancer, things like basic examinations and non-invasive imaging methods such as CT scans and MRIs are used.[6] Identifying prognostic factors for patients with NSCLC is very important.[7]

During the last few years, circulating tumor DNA (ctDNA) has been evaluated as a prognostic indicator of recurrence and mortality in cancers. Studies have shown that circulating tumor DNA (ctDNA) can analyze individual genetic changes by fully identifying target genes. The detection of ctDNA in hematological cancers has been widely investigated and proven; however, its detection in solid tumors is controversial and challenging.[8] The findings of studies have shown that ctDNA can be effective in the prognosis of solid tumors (lung cancer, breast cancer, pancreatic cancer).[9-12] Rapid diagnosis of patients with NSCLC can help identify the higher risk of recurrence and mortality so that doctors can choose more appropriate treatment approaches. However, although ctDNA can predict patient survival, this field has many challenges. Therefore, the present study aimed to evaluate the prognostic value of Non-small-cell lung Cancer Using Blood-Based Circulating Tumor DNA.

2. Material and methods

Search strategy and Information sources

Searching international databases PubMed, Web of Science, Scopus, Science Direct, Web of Knowledge, EBSCO, Wiley, ISI, Elsevier, Embase databases, and Google Scholar search engine based on PRISMA 2020-27-item checklist[13] and keywords Related to the objectives of the study, it was

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https://doi.org/10.30485/IJSRDMS.2024.447142.1566

carried out from 2019 to February 2024. The keywords were standardized in MeSH and used for searching. In addition, the reference list of the selected articles was screened to find relevant studies. The search strategy was (((((("Lung Neoplasms"[Mesh]) OR ("Lung Neoplasms/diagnosis"[Mesh] OR "Lung Neoplasms/mortality"[Mesh] OR "Lung Neoplasms/prevention and control"[Mesh] OR "Lung Neoplasms/surgery"[Mesh] OR "Lung Neoplasms/therapy"[Mesh])) OR "Carcinoma, Non-Small-Cell Lung"[Mesh]) OR ("Carcinoma, Non-Small-Cell Lung/diagnosis"[Mesh] OR "Carcinoma, Non-Small-Cell Lung/mortality"[Mesh] OR "Carcinoma, Non-Small-Cell Lung/prevention and control"[Mesh] OR "Carcinoma, Non-Small-Cell Lung/surgery"[Mesh] OR "Carcinoma, Non-Small-Cell Lung/therapy"[Mesh])) AND "Circulating Tumor DNA"[Mesh]) AND ("Survival"[Mesh] OR "Mortality"[Mesh]).

First, a list of titles and abstracts of all articles searched in the databases under review was prepared. This work was done independently by two researchers. The articles with duplicate titles were removed. Next, the abstracts of the articles were checked to find suitable studies. All of the studies that were searched were saved in EndNote. The software performed X8 software and the rest of the steps.

Study selection criteria

The inclusion criteria for the studies were randomized control trial studies, cohort studies, observational studies, cross-sectional studies, NSCLC patients, measurement of ctDNA, and overall survival reports published in English. The exclusion criteria were chosen: irrelevant in terms of study design and research topic, studies that did not contain enough information, low-quality studies, studies with incomplete data, case series studies, Review studies, case reports, letters to the editor, and conferences.

Selection and data collection process

Two researchers independently extracted data from the articles using a standard data collection form prepared in advance to reduce reporting bias and errors in data collection. The study team first designed this form. It included the following items: author name, study title, year of publication, type of study, number of patients, blood samples, and follow-up period.

Article quality assessment

The Newcastle-Ottawa Scale (NOS) evaluates the quality of cohort, observational, and case-control studies.[14] The NOS has a maximum of 9 grades, classified into 3 criteria. Any study with scores equal to or higher than 7 is considered high quality, 2 to 6 is average quality, and equal to and less than 1 is poor quality.

The Cochrane risk-of-bias tool for randomized trials (RoB 2) is recommended for assessing the risk of bias in randomized trials.[15] Bias is assessed as a judgment (high, low, or unclear) for individual elements from five domains (selection, performance, attrition, reporting, and others).

Meta-analysis

The odds and hazard ratios with a 95% confidence interval (CI) were used. The I2 statistic, used to measure inconsistency, was used to analyze the degree of variation across studies (heterogeneity). Low levels of heterogeneity were defined as I^2=25–49%, moderate levels as I^2=50–74%, and high levels as I^2=75–100%.[16] A model with fixed effect and Inverse–variance was used. All statistical analyses are done using STATA/MP software. v17 was done considering the significance of less than 0.05.

3. Results

Study selection

In the first stage of the search, 531 articles were found. After reviewing the titles of the articles, 87 duplicate and overlapping articles were removed. The abstracts of 422 possible related articles were reviewed, and 384 unrelated articles were identified and eliminated. The full text of the remaining 38 articles was reviewed, and finally, eleven suitable articles were selected to enter the meta-analysis stage (Fig. 1).

Study characteristics

1295 NSCLC patients were examined. ctDNA method and other characteristics are reported in Table 1.

Quality assessment

Based on the quality measurement tools, all the selected studies were of high quality; all had 7-8/9 scores (Table 2).

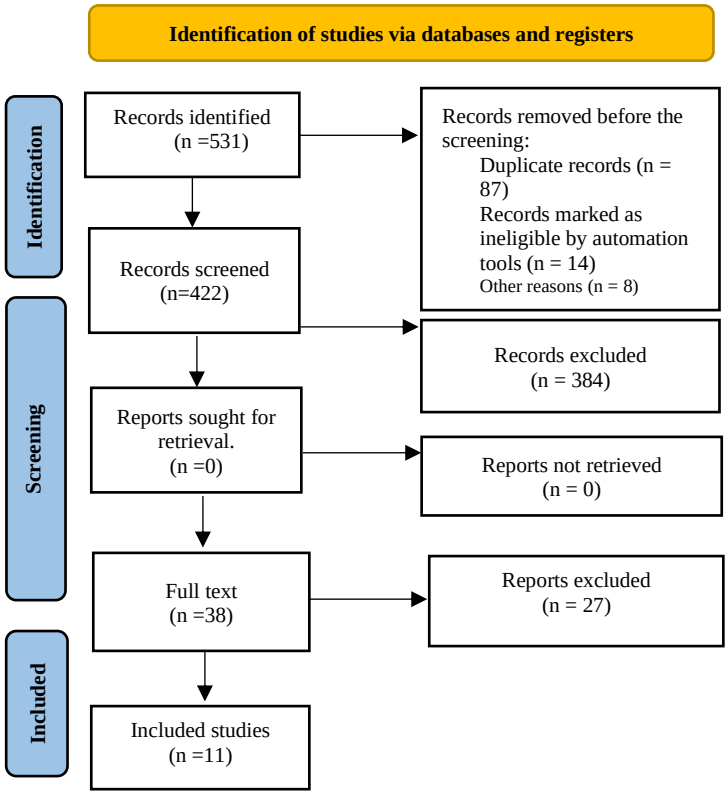

Fig. 1. PRISMA 2020 Checklist.

Table 1. The characteristics of the selected articles according to the purpose of the study.

No.	Study, Years	Number of NSCLC patients	Number of blood samples	Follow-up (years)	ctDNA method	Outcome
1	Wang et al., 2024[17]	269	269	---	NGS	Patient progression-free survival, overall survival
2	Pan et al., 2023[18]	139	761	24	NGS	Patient progression-free survival
3	Peng et al., 2023[19]	160	160	---	NGS	Patient progression-free survival
4	Zhang et al., 2022[20]	261	913	1.7	NGS	Patient progression-free survival
5	Chen et al., 2022[21]	81	---	5	NGS	Patient progression-free survival, overall survival
6	Provencio et al., 2022[22]	41	41	3.1	NGS	Patient progression-free survival, overall survival
7	Yue et al., 2022[23]	22	22	1.4	NGS	Patient progression-free survival
8	Li et al., 2022[24]	119	119	2.5	NGS	Patient progression-free survival, overall survival
9	Gale et al., 2022[25]	69	69	1.5	NGS	Patient progression-free survival, overall survival
10	Tan et al., 2021[26]	57	57	2.7	NGS, multiplex-PCR	Patient progression-free survival
11	Peng et al., 2020[27]	77	77	3.6	NGS, multiplex-PCR	Overall survival

Table 2. Risk assessment of bias in cohort studies.

Study, years	Selection			Comparability		Outcome			score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at the start of the study	Comparability of cohorts based on the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow-up of cohorts	
Wang et al., 2024[17]	1	1	1	1	1	1	1	1	8
Pan et al., 2023[18]	1	1	1	1	1	1	1	1	8
Peng et al., 2023[19]	1	1	1	1	1	1	1	1	8
Zhang et al., 2022[20]	1	1	1	0	1	1	1	1	7
Chen et al., 2022[21]	1	1	1	1	1	1	1	1	8
Provencio et al., 2022[22]	1	1	1	1	1	1	1	1	8
Yue et al., 2022[23]	1	1	1	1	1	1	1	1	8
Li et al., 2022[24]	1	1	1	1	1	1	1	1	8
Gale et al., 2022[25]	0	1	1	1	1	1	1	1	7
Tan et al., 2021[26]	1	1	1	1	1	1	1	1	8
Peng et al., 2020[27]	1	1	1	1	1	1	1	1	8

Compared with patients with low-level ctDNA, those with high-level ctDNA had a higher risk for overall survival (HR 3.16, 95% CI 2.45-3.87; P-value < 0.001) (Fig. 2). The heterogeneity test showed that Q = 17.78, p-value<0.01, I^2 = 77.5%, which denotes a high heterogeneity among studies.

Compared with patients with low-level ctDNA, those with high-level ctDNA had a higher risk for progression-free survival (HR 3.47, 95% CI 2.98-3.97; P-value < 0.001) (Fig. 3). The heterogeneity test showed that Q = 19.60, p-value=0.02, I^2 = 54.08%, which denotes a moderate heterogeneity among studies.

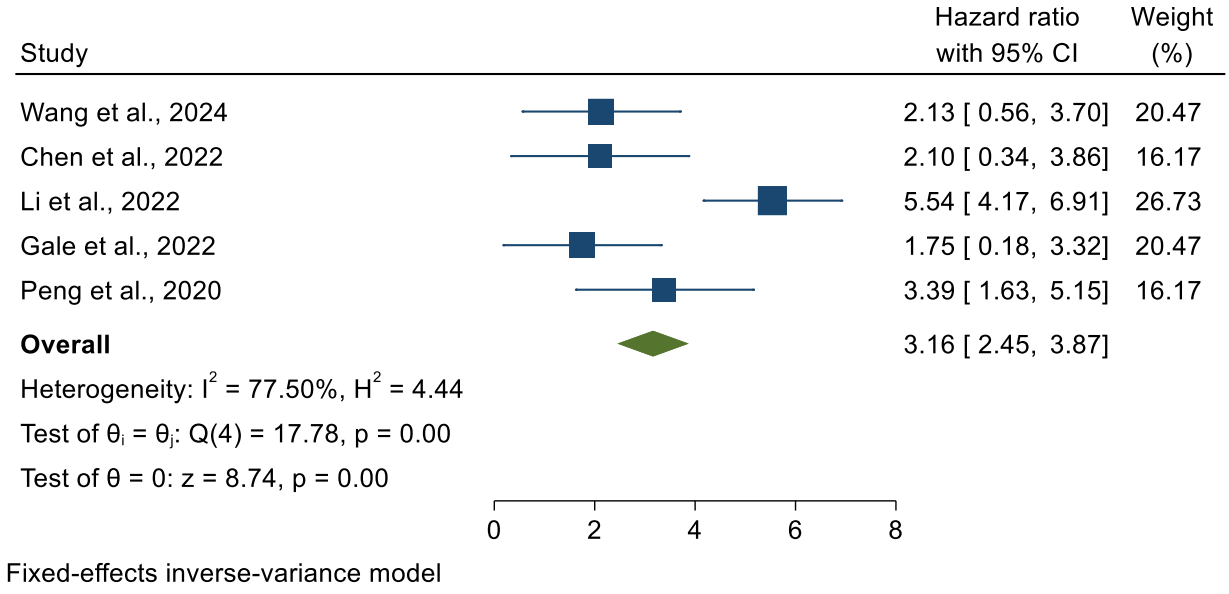

Fig. 2. The forest plot showed ctDNA level with patient overall survival.

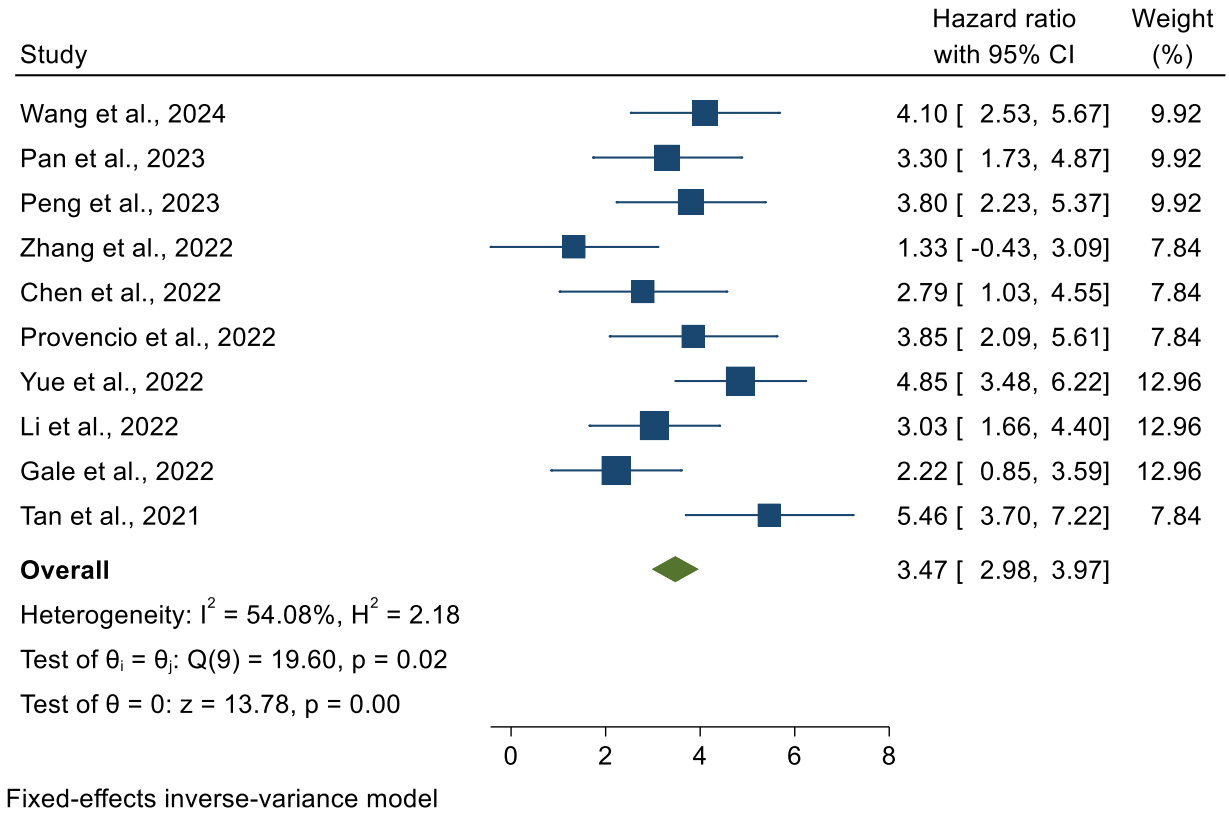

Fig. 3. The forest plot showed ctDNA level with patient progression-free survival.

4. Discussion

Studies have shown that high levels of ctDNA can be considered an important indicator in identifying cancer recurrence and mortality.[28] However, evidence has shown that the ctDNA status is not positive after surgery in some patients, which can reduce the detection rate of ctDNA after surgery. Therefore, the sensitivity of ctDNA before surgery can be higher than ctDNA after surgery.[29] It has also been shown that preoperative ctDNA in patients with NSCLC leads to better results than postoperative ctDNA.[24] According to the present meta-analysis, preoperative ctDNA detection directly correlates with the risk of recurrence and survival in patients with NSCLC. A study showed that monitoring ctDNA changes before treatment in advanced NSCLC patients undergoing treatment accurately predicts tumor response and progression-free survival.[21] Therefore, all this evidence shows the importance of comprehensively identifying independent prognostic factors and individually assessing patients' prognoses for each physician. The association between increased ctDNA levels and death rate may be related to tumor burden or comorbidities. This study had limitations: firstly, very few studies with a small sample size met the inclusion criteria and were selected. Secondly, the period of the studies was different; thirdly, high and moderate heterogeneity was observed, which should be interpreted with caution. Be interpreted, and the reason can be the variety of ctDNA analysis methods used in the studies.

5. Conclusion

The present meta-analysis showed that high levels of ctDNA are directly related to progression-free survival and death in patients with NSCLC. Elevating ctDNA levels in NSCLC patients can be used as a diagnostic method, along with other methods, such as imaging, to evaluate efficacy.

Conflict of Interest

The authors declared that there is no conflict of interest.

Acknowledgments

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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How to Cite this Article: Eghbalifard N, Rabiee F, Yasaman Shariati Y. Evaluate the Prognostic Value of Non–Small-Cell Lung Cancer Using Blood-Based Circulating Tumor DNA: A Systematic Review and Meta-analysis. International Journal of Scientific Research in Dental and Medical Sciences. 2024;6(1):34-39. https://doi.org/10.30485/IJSRDMS.2024.447142.1566.