The value of ctDNA in predicting postoperative recurrence of non-small cell lung cancer: a meta-analysis and systematic review

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Abstract

Objective: Lung cancer is the most common malignant tumor worldwide, and non-small cell lung cancer(NSCLC) accounts for approximately 85% of all lung carcinoma cases. Despite surgical operation is still the primary method for treating early NSCLC, there are still a considerable postoperative recurrence patients even after complete resection. Currently, circulating tumor DNA(ctDNA) is being recognised as a molecular biomarker of minimal residual disease(MRD) in predicting postoperative recurrence of NSCLC in clinical trials and has not been confirmed. The goal of our study is to evaluate the value of ctDNA in predicting postoperative recurrence in NSCLC patients.

Method: A comprehensive systematic literature research was performed for studies exploring the value of ctDNA in predicting postoperative recurrence in NSCLC patients up to February 2022. The eligible studies were collected, and the dependent variable analysis was performed to compare the relative risk (RR) of recurrence in the postoperative ctDNA positive and negative groups. The relative ratio (RR) and 95 % confidence interval (CI) were determined as comparative measures of postoperative recurrence-free survival (RFS). Ten researches comprising 799 patients, published between 2017 and February 2022, were finally enrolled into our meta-analysis.

Result: A total of 10 studies including 799 patients were summarized for meta-analysis of ctDNA in predicting recurrence in NSCLC. The combined RR was 3.75 (95 % CI : 1.98-4.72, P < 0.05), which indicated that patients with postoperative ctDNA positive had a higher postoperative recurrence rate in NSCLC than postoperative ctDNA negative. In addition, Meta-analysis of 4 studies with available data showed that preoperative peripheral blood ctDNA positive showed poor prognosis of RFS with combined HR = 3.40(95%CI: 2.72-4.69, P < 0.05).

Conclusion: For NSCLC patients, ctDNA is a promising biomarker for predicting postoperative recurrence, which can be used as a supplement to the current monitoring of radiation and blood biomarkers to better guide the treatment selection and prognosis of patients after surgery.

Introduction

Lung cancer is one of the most frequent malignant tumor worldwide, as well as the leading cause of cancer-related death, posing a serious threat to human health[1]. Non-Small Cell Lung Cancer (NSCLC) is the most common pathological subtype, accounting for approximately 85% of all lung cancers[2]. According to NCCN guidelines, surgical resection remains the primary treatment for patients with early stage NSCLC. However, even undergoing radical surgery and adjuvant therapy, patients with early stage NSCLC have a substantial chance of recurrence[3]. The monitoring of postoperative recurrence in patients with NSCLC is of critical clinical importance. Early diagnosis and treatment of tumor recurrence may prolong the survival time of patients and improve clinical efficacy. To monitor the recurrence of NSCLC patients after surgery, radiographic modalities like as computed tomography (CT) are commonly utilized. This monitoring method, on the other hand, can only detect lesions visible to the human eyes and is not sensitive to Molecular Residual Disease (MRD).

In recent years, noninvasive liquid biopsy has emerged as a potential method for tracking tumor progression and recurrence in real time[4]. Circulating tumor DNA (ctDNA) is a promising diagnostic method for molecular mapping that is noninvasive. It has been used in solid tumors such as colorectal cancer[5], breast cancer[6], and gastric cancer[7] to detect MRD and track recurrence. ctDNA has been reported to have predictive value in various cancers in several meta-analysis[8–10]. Although significant research has demonstrated that ctDNA may be found in the majority of NSCLC patients, it has yet to be established as an adequate biomarker for monitoring NSCLC patients' postoperative recurrence. There is still controversial on how to make better use of ctDNA in clinical practice.

In order to evaluate the value of ctDNA in predicting postoperative recurrence of NSCLC patients, we systematically collected relevant studies and conducted a comprehensive meta-analysis to evaluate the effect of ctDNA on postoperative recurrence-free survival (RFS) of NSCLC patients.

Table 1
The basic characteristics of enrolled studies

Study	Year	Study region	Median age	Female(%)	Median follow-up	Method	Type	Stage	R/(+)	R/(-)	Ahead of the CT	Blood draw time	HR (95%CI) of RFS
Abbosh et al.[11]	2017	Britain	NA	33.3	25.2m	multiplex-PCR NGS	NSCLC	B- B	13/14	1/10	151d	0 d, once every 3 m to 6m	NA
Chaudhuri et al.[12]	2017	America	66.5	NG	35.1m	CAPP-seq	NSCLC	A- B	13/14	1/15	156d	once every 2 m to 6m	NA
Chen et al.[13]	2019	China	NA	53.6	17.7m	cSMART	NSCLC	-	6/7	5/18	165d	1 d, 3 d and 30 d	NA
Yang et al.[14]	2020	China	55.8	40.2	22.83m	NGS	ADC		3/15	2/67	NA	1 w, once every 3 m to 6m	NA
Peng et al.[15]	2020	China	60.3	27.3	46m	cSMART	NSCLC	-	17/28	11/41	378d	2 w, 3m, 6m, 12m, 18m, 24 m	3.649(1.844-7.22)
Qiu et al.[16]	2021	China	NA	65	NA	ATG-Seq	NSCLC	- A	14/18	20/67	88d	within 30 d, once every 3 m	NA
Xia L et al.[17]	2021	China	NA	51.2	35.4m	NGS	NSCLC	-	21/26	49/303	NA	3 d, 1 m, once every 3 m to 6m	4.2(2.6–6.7)
Waldeck et al.[18]	2022	Germany	70	33	26.2m	NGS	NSCLC	-	4/4	4/12	NA	1 w, 2 w, once every 3 m	NA
Yue DS et al.[19]	2022	China	62.5	22.73	17.67m	NGS	NSCLC	B- A	5/7	3/17	205d	3–8 d, once every 2 m to 3m	7.41(0.91–60.22)
Li N et al.[20]	2022	China	NA	NA	30.7m	NGS	NSCLC	- A	6/12	20/104	261d	within 30 d, once every 3 m to 6m	2.42(1.11–5.27)

d, day; w, week; m, month; R, recurrence; +, ctDNA positive; –, ctDNA negative; n, number

NA, not available; NGS, next-generation sequencing; RFS, recurrence-free survival,

ADC, adenocarcinoma; NSCLC, Non-Small-Cell Lung Cancer

Methods and Materials

Search strategy

We used ' Circulating Tumor DNA ', ' ctDNA ', ' Cell Free Tumor DNA ', ' Non-Small-Cell Lung Carcinoma ', ' Carcinoma, Non-Small-Cell Lung Cancer ', ' NSCLC ' as the main search terms. Systematic literature retrieval was conducted on PubMed, Web of Science, Cochrane Library and Embase databases. All articles published up to February 2022 were searched by two authors independently. The reference lists of related studies were manually searched to find other publications that might be of interest. The researchers looked through the body of the study and references for articles that might qualify in order to uncover studies that were not published or could not be located by keyword search. The ethical approval requirement was dropped because it was a meta-analysis of previous studies.

Inclusion and exclusion criteria

Select eligible studies according to the following criteria : (1) NSCLC patients were confirmed by pathological examination ; (2) NSCLC patients underwent radical resection of lung cancer ; (3) ctDNA is used to assess and predict tumor recurrence ; (4)Sufficient information was provided to calculate recurrent RR. Exclusion criteria are as follows : (1) Published in the conference summary, case reports and reviews ; (2) Blood samples cannot be continuously collected after operation ; (3) Non-English studies ; (4) Research using the same population or overlapping data ; (5) Patients with pathological type not NSCLC.

Data extraction

Data extraction and evaluation were independently completed by the two authors. Any controversy was discussed with another author until consensus was reached. The following was useful basic information for the study and extracted by the two independent authors: the first author's name, publication date, region, follow-up time ,median age, ctDNA detection method, tumor stage, sample size, postoperative ctDNA positive or negative number, postoperative ctDNA positive or negative recurrence, collection time, NOS score. If feasible, the preoperative ctDNA HR (95% CI) of RFS is also extracted. The above information and data were described and recorded in the basic characteristics form. RFS was defined as the time interval from the surgery to the first verified recurrence (local or distant) or death for any cause.

Quality assessment

We used STATA 16.0 statistical software to analyze the data. RR and 95% CI of recurrence were calculated by the number of ctDNA positive and negative patients and the number of recurrence, and the random effect model was used. Combine RR and analyze the results according to RR and 95% CI. We also used the random effect model to calculate the HR (95% CI) of RFS of the total RFS in the ctDNA positive group and negative group. When P value is greater than 40%, heterogeneity is considered to be meaningful. Although the number of included studies was insufficient, we evaluated the publication bias of this study, using funnel plot and Egger’s linear regression test. All p-values were double-sided and $p < 0.05$ was considered statistically significant.

Results

Study Characteristics

A total of 551 articles were reviewed in the initial search. 381 papers were collected after reviewing titles and abstracts. Following a thorough reading of the entire text as well as qualitative analysis and review, 18 papers were found to meet the standards. Three papers did not provide comprehensive data after extensive reading and investigation, while five articles did not meet the inclusion criteria. As a result, following a thorough review of these articles, 10 studies including 799 patients published between 2017 and 2022 were eventually enrolled in our meta-analysis. Seven of the 10 studies were conducted in China, with one each in the United States, the United Kingdom, and Germany.The literature selection process is shown in Fig. 1. The quality of included studies was assessed using NOS scale. The characteristics and quality scores of these studies were shown in Table 1.

Figure 1 Flow diagram of the selection progress

Meta-analysis of the correlation between ctDNA and postoperative recurrence in NSCLC

A total of 10 studies including 799 patients were summarized for meta-analysis of ctDNA in predicting recurrence in NSCLC. The RR of NSCLC recurrence had low heterogeneity ($P = 0.158$, $I^2 = 31.3\%$), so we used the fixed effects model to calculate the final analysis. As shown in the Fig. 2, the combined RR was 3.75 (95% CI : 1.98–4.72, $P < 0.05$, Fig. 2), which indicated that patients with postoperative ctDNA positive had a higher postoperative recurrence rate in NSCLC than postoperative ctDNA negative. In addition, Meta-analysis of 4 studies with available data showed that preoperative peripheral blood ctDNA positive showed poor prognosis of RFS with combined HR = 3.40(95%CI: 2.72–4.69, $P < 0.05$, Fig. 3).

Figure 2 Forest plot of the correlation between postoperative ctDNA positive and recurrence in NSCLC patients

Figure 3 Forest plot of correlation between preoperative ctDNA positive and recurrence in NSCLC patients

Publication Bias

We used funnel plot and Egger's linear regression test to evaluate publication bias. Eventually, No publication bias was found in our study (Egger's test $P = 0.2056 > 0.05$). The funnel plot is shown in Fig. 4.

Figure 4 The funnel plot

Discussion

With the continuing progress of ctDNA technology in targeting various malignancies, ctDNA technology has brought new ideas for tumor detection and treatment guidance after first reported in 1989 by Stroun et al [21]. Although ctDNA detection method and detection time are still debatable,The importance of ctDNA technolog cannot be overlooked in clinical practice.

As far as we know, the effect of ctDNA on the prognosis of postoperative RFS in patients with NSCLC is still uncertain.In order to further demonstrate the role of ctDNA in NSCLC and its influence on postoperative prognosis of NSCLC patients. We performed a meta-analysis with 799 patients in 10 studies in our study. The results demonstrated that the ctDNA positive group had a higher predictive effect on postoperative NSCLC recurrence than the ctDNA negative group with the pooled RR = 3.75, $P < 0.05$. The RFS of NSCLC patients in the preoperative ctDNA positive group was lower than the preoperative ctDNA

negative group (HR = 3.40, P < 0.05), according to data from four trials. The presence of ctDNA may be an independent predictive factor for postoperative NSCLC recurrence, according to the findings of this meta-analysis.

ctDNA is fragmented DNA obtained from tumors and circulated in the bloodstream, and it frequently carries mutations, deletions, insertions, copy number aberrations, methylation, and other gene mutation information[22]. As a result, ctDNA has the potential to detect cancer that has gone undetected and to track tumor-specific alterations. The ease of plasma collection allows for continuous monitoring of the ctDNA level in order to anticipate the mutation state vertically and to assess the risk of recurrence. Therefore, ctDNA has become a widely used indicator of MRD[23].

The detection of ctDNA was compared to the traditional radiological monitoring method in seven trials from this meta-analysis, and the former was found to be 6.7 months ahead of the latter (the longest 12.6 months, and the shortest 88 days). Abbosh et al proposed a median lead time of 151 days for ctDNA in the TRACERx project, which was the first to report it[11]. Despite the fact that the patients, clinical phases, and adjuvant treatment strategies in each study were all different, the final results showed that ctDNA technology beat radiography methods in diagnosing tumor recurrence. Because routine imaging cannot detect MRD and recurrence, and repeated CT scan can be harmful to the patient's health, the final decision of treatment is impacted by the physician's level of experience and subjective considerations. Based on the aforementioned, it is believed that ctDNA technology can be used in conjunction with radiographic techniques for tumor surveillance.

Although ctDNA technology can be used to monitor MRD after tumor surgery, the guidelines have recommended relevant ctDNA monitoring time for colon cancer, but there is no clear standard for postoperative ctDNA detection and follow-up time for NSCLC[12, 24]. The variable detection period may raise the risk of false positive results and lead to excessive adjuvant therapy. According to Chen et al's research, ctDNA decays rapidly after tumor excision, and ctDNA detection on the third day after resection can be utilized as the baseline value for postoperative NSCLC monitoring[13]. Li et al used dynamic monitoring and discovered that the positive group had a obvious shorter RFS than the ctDNA negative patients. Different collection and follow-up time in this study are shown in Table 1.

According to the survey, even after surgical treatment, 5-year OS of NSCLC patients from 92% of stage Ia1 to 26% of stage IIIb[25]. So, even in early conditions, the clinical requirement for adjuvant therapy is increasing in order to eradicate MRD. However, up to now, adjuvant chemotherapy in patients with NSCLC following surgery has given only 4–5 percent of the absolute survival benefits compared to observation or best supportive treatment[26]. Because the present TNM staging paradigm may not effectively detect MRD, it may lead to erroneous postoperative treatment decisions. ctDNA samples from 330 perioperative patients were evaluated in Xia L et al study[17]. The findings revealed that ctDNA-based MRD outperformed clinical pathological indicators like TNM stage in predicting RFS, and that ctDNA-based MRD positive patients would benefit from adjuvant therapy. The other two studies suggested that the state of ctDNA after adjuvant treatment was closely related to RFS, and adjuvant treatment had beneficial effects on postoperative ctDNA positive patients[16, 27], after comparing the benefits of adjuvant treatment in postoperative ctDNA positive and negative groups.

Our meta-analysis has some limitations that need to be addressed. first, the number of enrolled trials is tiny, as is the total sample size and the sample size gap in each study, both of which inevitably lead to some biases. Second, standardizing the detection of ctDNA, stratifying the recurrence risk of patients based on the results of ctDNA detection at different times, and formulating corresponding follow-up strategies for different patients to guide postoperative adjuvant therapy remain significant challenges in clinical practice. Finally, each study differs in terms of illness stages and ctDNA technique. This dilemma demonstrates that future research should focus on ctDNA detection technologies and risk classification of different patients in order to better understand the critical role of ctDNA monitoring in the prognosis of NSCLC and guide the management of following diseases.

Conclusion

In conclusion, the findings of our meta-analysis of 799 individuals from 10 trials suggest that ctDNA is a promising biomarker for predicting NSCLC recurrence after surgery. According to our findings, NSCLC patients who tested positive for ctDNA had a shorter RFS. ctDNA testing may supplement current radiation and blood biomarker monitoring for postoperative NSCLC patients, and it should be given enough attention to assist patients' postoperative treatment selection and prognosis. In the future, more well-designed and larger trials will be needed to further confirm the clinical role of ctDNA to improve patient’s prognosis.

Abbreviations

RFS Recurrence-free survival

NSCLC Non-small cell lung cancer

HR Hazard ratio

CI Confidence interval

ctDNA Circulating tumor DNA

MRD Molecular Residual Disease

NGS Next-generation Sequencing

Declarations

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Authors ' contributions

Yifan Li and Qifan Yin designed this study, analyzed the data and wrote manuscripts. Peng Qie, Shaohui Han, Xiaoning Li, Guibin Zhang and Shaohui Zhou participated in collecting the data. Huien Wang made important academic contributions and made critical revisions to the manuscript. All authors reviewed and approved the manuscript.

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Availability of data and materials

All relevant data is included in the manuscript. The data described in this article can be provided according to the reasonable requirements of the corresponding authors.

Compliance with ethical standards

Ethical approval for this type of study and formal consent were not required. This study does not involve any human participants or animals.

Competing interests

The authors declare that they have no competing interests.

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Figures

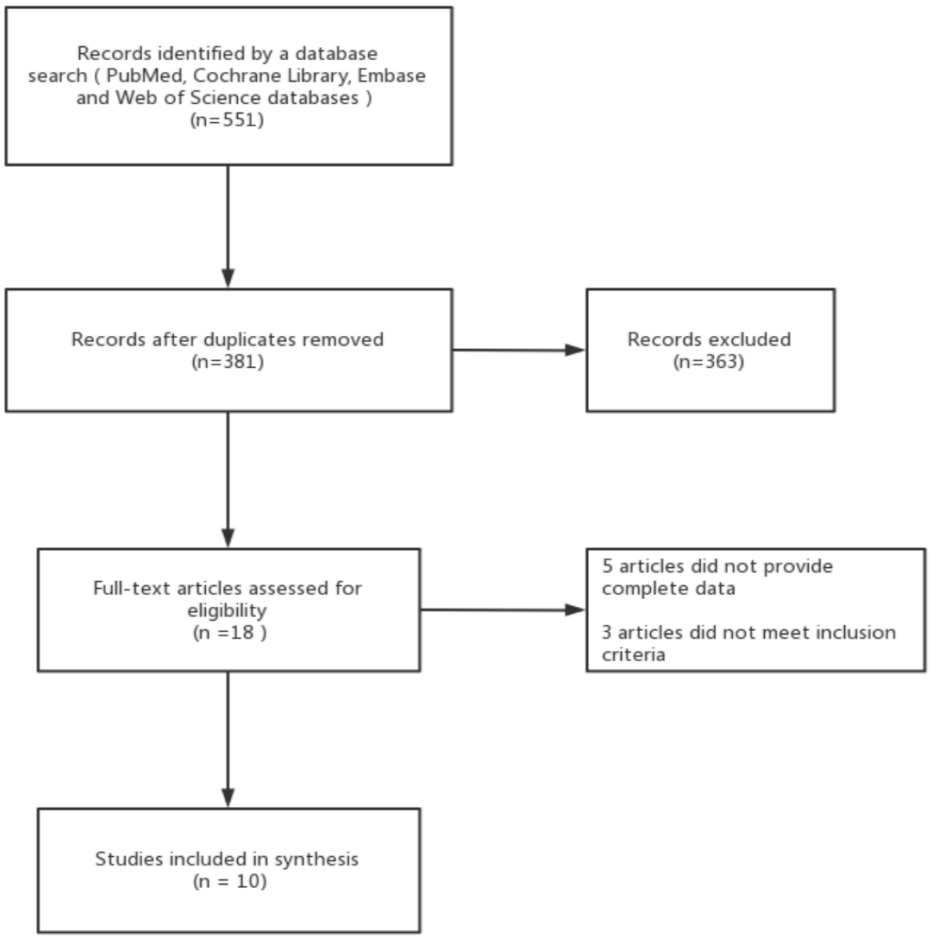

Figure 1

Flow diagram of the selection progress

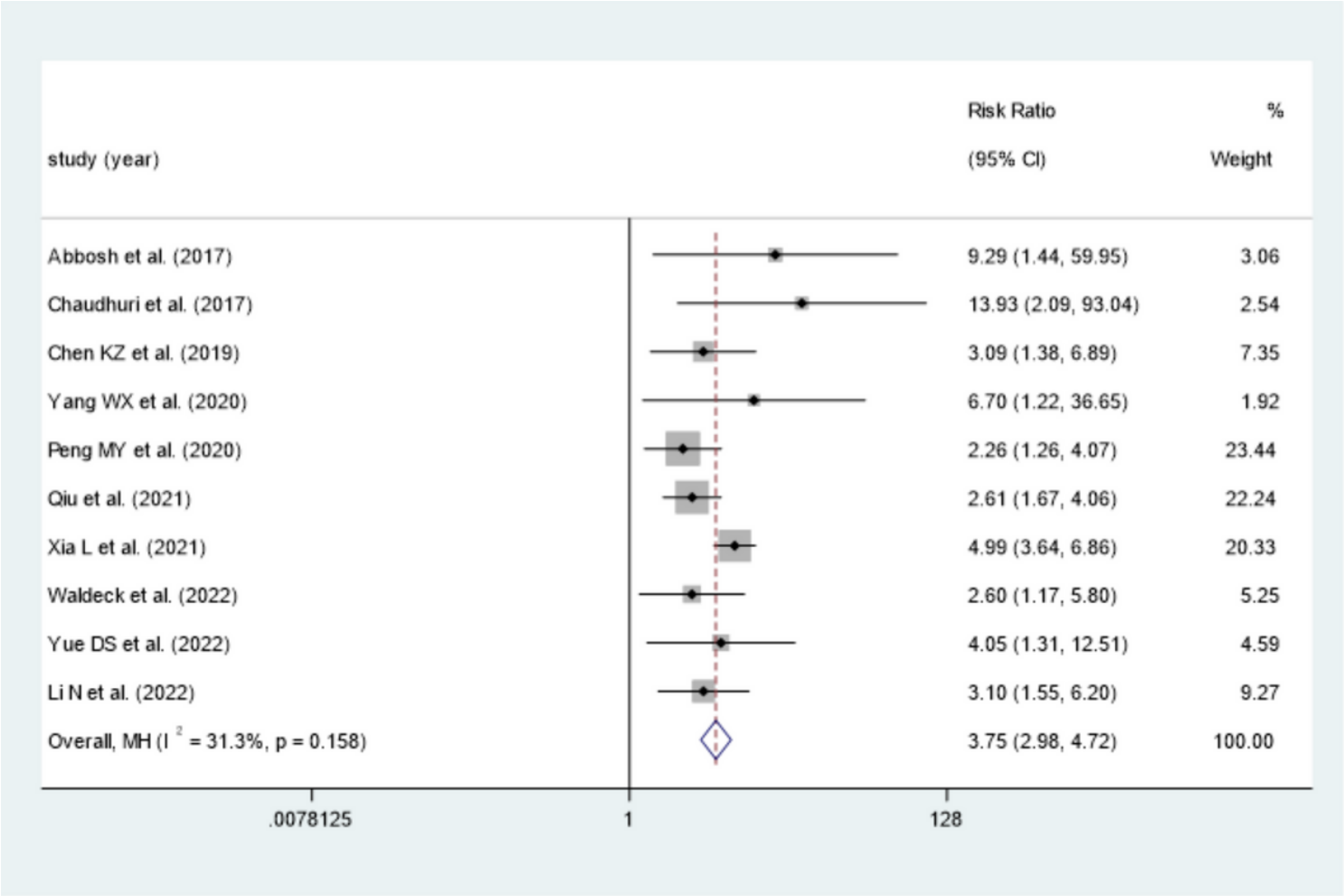

Figure 2

Forest plot of the correlation between postoperative ctDNA positive and recurrence in NSCLC patients

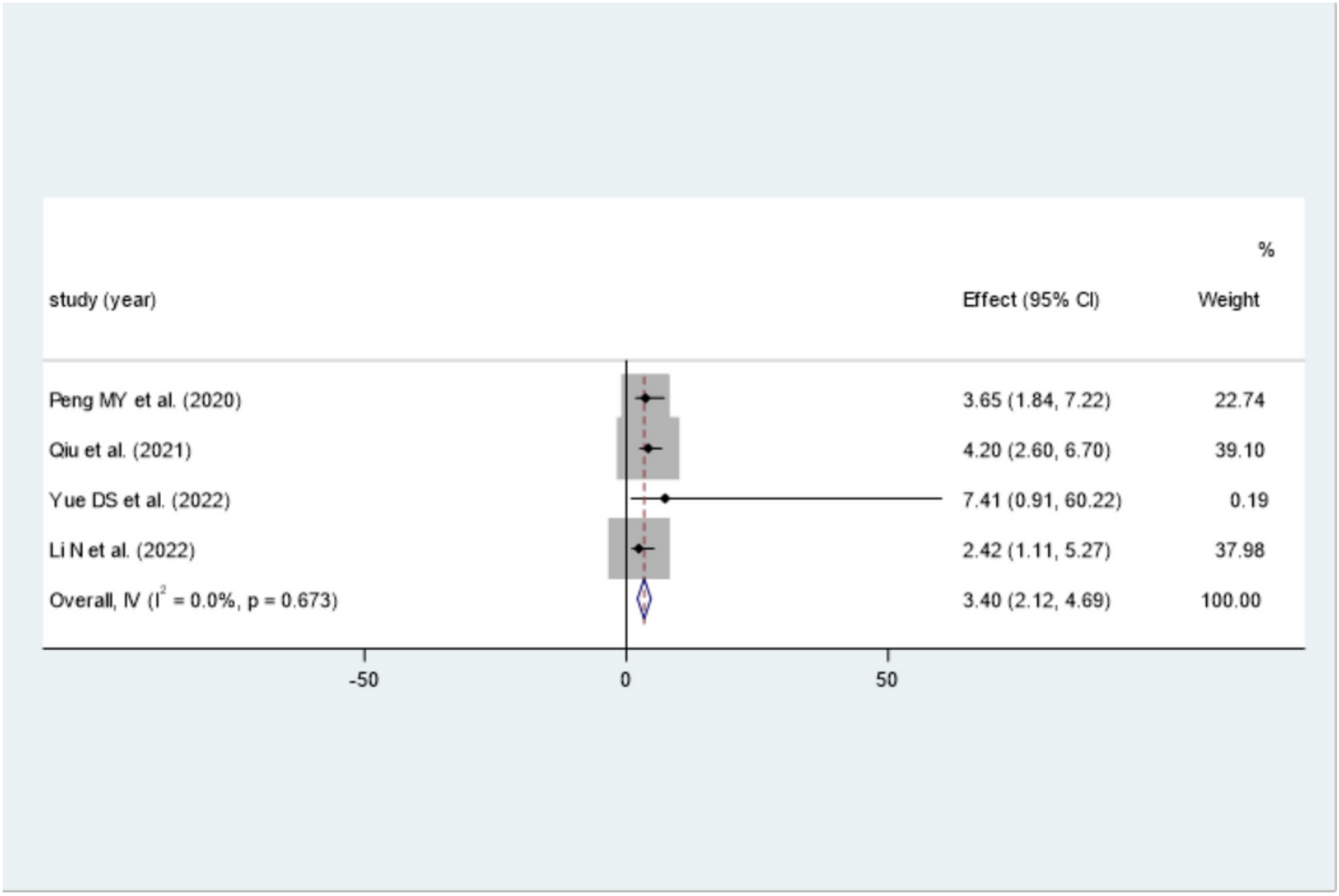

Figure 3

Forest plot of correlation between preoperative ctDNA positive and recurrence in NSCLC patients

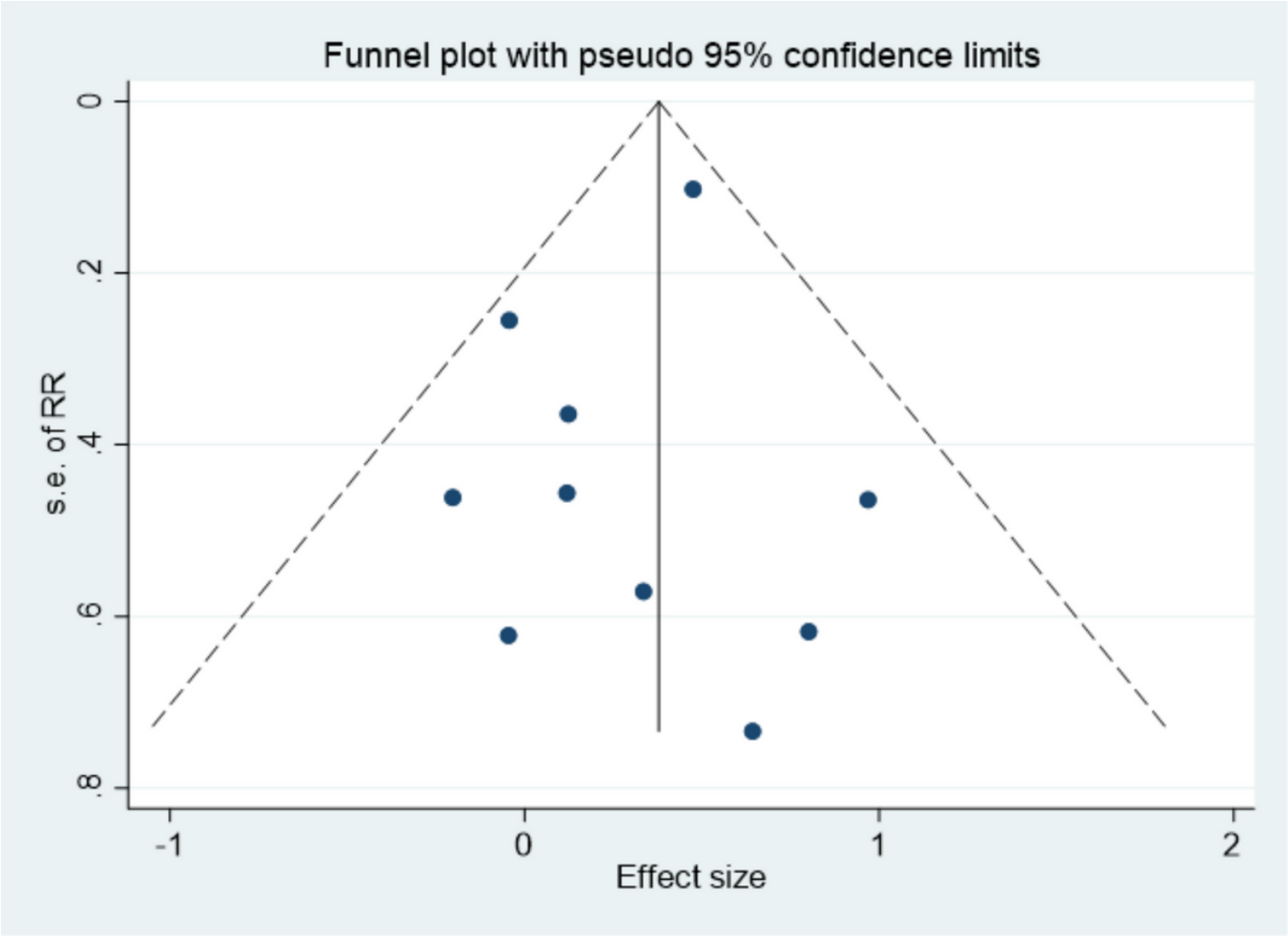

Figure 4

The funnel plot