Systematic Review and Meta-Analysis

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The diagnostic value of circulating tumor cells for lung cancer

A systematic review and meta-analysis

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Abstract

Background: Circulating tumor cells (CTCs) have become a potential diagnostic tumor marker and have the potential for wide clinical applications. However, the diagnostic parameters vary among previous studies. A systematic review of the literature and meta-analysis were conducted to assess the diagnostic value of CTCs for lung cancer.

Methods: Eligible studies were searched in PubMed, Medline, Cochrane Library, and Embase databases. The included studies assessed the diagnostic value of CTCs in patients with lung cancer up to September 30, 2018. A total of 1601 patients in 8 studies were included in the meta-analysis. We calculated the pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and area under the curve (AUC) to investigate the diagnostic value of CTCs for lung cancer. STATA version 12.0 and Meta-DiSc version 1.4 software were used to analyze the data.

Results: The pooled sensitivity was 0.75 (95% CI: 0.73–0.78), the specificity was 0.89 (95% CI: 0.86–0.92), the PLR was 6.29 (95% CI: 3.98–9.96), and the NLR was 0.24 (95% CI: 0.14–0.42). Furthermore, the pooled DOR of CTCs for lung cancer was 27.73 (95% CI: 12.99–59.23). The summarized area under the ROC curve was 0.93 (95% CI: 0.90–0.95). The meta-regression analysis suggested that the heterogeneity was mainly attributed to the experimental methods. The results of the clinical diagnosis efficiency show that the diagnostic efficiency has increased significantly by testing CTCs for diagnosing lung cancer.

Conclusion: The results of this meta-analysis suggest that CTCs are associated with a high diagnostic value for lung cancer. These findings require large-scale prospective studies to verify and evaluate the diagnostic value in the future.

Abbreviations: AUC = area under SROC, CI = confidence interval, CTCs = circulating tumor cells, DOR = diagnostic odds ratio, FN = false negative, FP = false positive, NLR = negative likelihood ratio, PLR = positive likelihood ratio, QUADAS-2 = quality assessment of diagnostic accuracy studies tool-2, SROC = summary receiver operating characteristic curve, TN = true negative, TP = true positive.

Keywords: circulating tumor cells, lung cancer, meta-analysis

1. Introduction

Lung cancer, including small cell lung cancer and non-small cell lung cancer, is one of the most common malignant tumors worldwide.[1] The 5-year survival rate for early stage lung cancer is approximately 13 times greater than that for advanced stage lung cancer, and patients with early stage lung cancer have the opportunity to undergo surgery, which could significantly reduce the disease mortality.[2,3] Therefore, it is very important to diagnose and treat lung cancer in the early stage. If lung cancer can be diagnosed early and treated quickly, the prognosis of patients can be significantly improved.[4]

Circulating tumor cells (CTCs) enter the blood flow from the original tumor or metastases. It is an important cause of postoperative recurrence and distant metastasis in patients with malignant tumors.[5] In previous studies, CTCs have been used to evaluate the prognosis of malignancies and to monitor and direct personalized therapeutics.[6,7] Recently, CTCs have gradually demonstrated their value in the diagnosis of various cancers and have become a potential new diagnostic tumor marker. Moreover, compared with the traditional biopsy method, the use of CTCs as a diagnostic has the advantages of fewer side effects, simple operation, and repeatability.[8] However, the diagnostic parameters are varied among the previous studies. Therefore, we conducted a systematic review to investigate the diagnostic value of circulating tumor cells in lung cancer and to compare the diagnostic parameters according to the previous studies and patient characteristics.

2. Methods

2.1. Search strategy

The meta-analysis was conducted in accordance with the guidelines for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[9] A comprehensive search of the literature in PubMed, Medline, Cochrane Library, and Embase databases was

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conducted up to September 30, 2018. The following search strategy was used: ("circulating tumor cells" OR "circulating tumor cell" OR "CTCs" OR "CTC") and ("lung carcinoma" OR "lung cancer" OR "lung tumor" OR "lung neoplasm"). Subsequently, eligible literature was included for further screening.

2.2. Study selection

The literature search and study selection were independently conducted by 2 researchers (Ye and Li), and any inconsistencies were resolved by group discussion until a consensus was reached. Studies were included if the study met the following criteria: the study describes the testing of CTCs in the peripheral blood of patients who are diagnosed with lung cancer; all patients with lung cancer must be confirmed by pathological biopsy; the control group consists of benign pulmonary disease patients or healthy volunteers; and sensitivity, specificity, and critical values must be explicitly mentioned in the study. The exclusion criteria included the following: no definite diagnosis threshold; incomplete clinical data; duplicate reports; and animal experiments.

2.3. Data extraction and quality assessment

The following information was collected from the included studies: the name of the first author, publication year, country in which the study was performed, age, number of patients, cut-off value, the detection method for CTCs, the sensitivity and specificity of CTCs, and the AUC (the area under the receiver operating characteristic curve). The Quality Assessment of Diagnostic Accuracy Studies tool-2 (QUADAS-2) was used to evaluate the quality of the studies included in this meta-analysis independently by the 2 authors (YY and JJW).[10] All authors agreed to the final determinants of the literature to be considered. Because this is a systematic review and meta-analysis, the ethical approval and patient written informed consent are not required.

2.4. Statistical analysis

Review Manager (RevMan) version 5.3 was used for quality assessment, while other analyses were conducted using Stata version 12.0 statistical software (StataCorp, LLC., College Station, TX) and Meta-DiSc version 1.4 (Ramony Cajal Hospital, Madrid, Spain). The sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR) and corresponding 95% confidence intervals (CIs) were calculated from true positive (TP), false positive (FP), false negative (FN), and true negative (TN) results, which were extracted from each study before data pooling. Sensitivity, specificity, PLR, and NLR were summarized by the bivariate random effects meta-analysis,[11] and the summary receiver operating characteristic (sROC) curve and the area under the ROC curve were summarized by the hierarchical regression model. The Q-statistic and I-square were used to inspect the statistical heterogeneity across the eligible studies (P-values $\leq .05$ indicated statistically significant heterogeneity for the Q-statistic).[12] I^2 values of 25%, 50%, and 75% represented low, medium, and high heterogeneity, respectively.[13] A random-effects model was used if the heterogeneity was high (when the I^2 was $>50\%$ and the P-value was $\leq .05$); otherwise, the fixed effects model was used. Meta-regression analyses were conducted on the basis of the year of publication, age, country, and diagnostic methods.[14] Deeks asymmetry test was used to evaluate potential publication bias.[15] Fagan nomogram was used to evaluate the pre-test probability and post-test probability of the PLR and NLR.[16] A P-value $<.05$ was regarded as statistically significant, and all tests were 2-sided.

3. Results

3.1. Literature search

The selection process of studies is shown in Fig. 1. In total, 386 relevant studies were identified from a search of the above-mentioned databases using the search strategy as described above, of which 273 studies were excluded due to duplication. After carefully reading each article, 72 studies were excluded because they were letters, reviews, comments, nonhuman studies, or contained incomplete clinical data. Upon further review, 33 additional studies were excluded because there were missing index details or they were irrelevant to lung cancer. Finally, a total of 8 publications were enrolled for this meta-analysis.

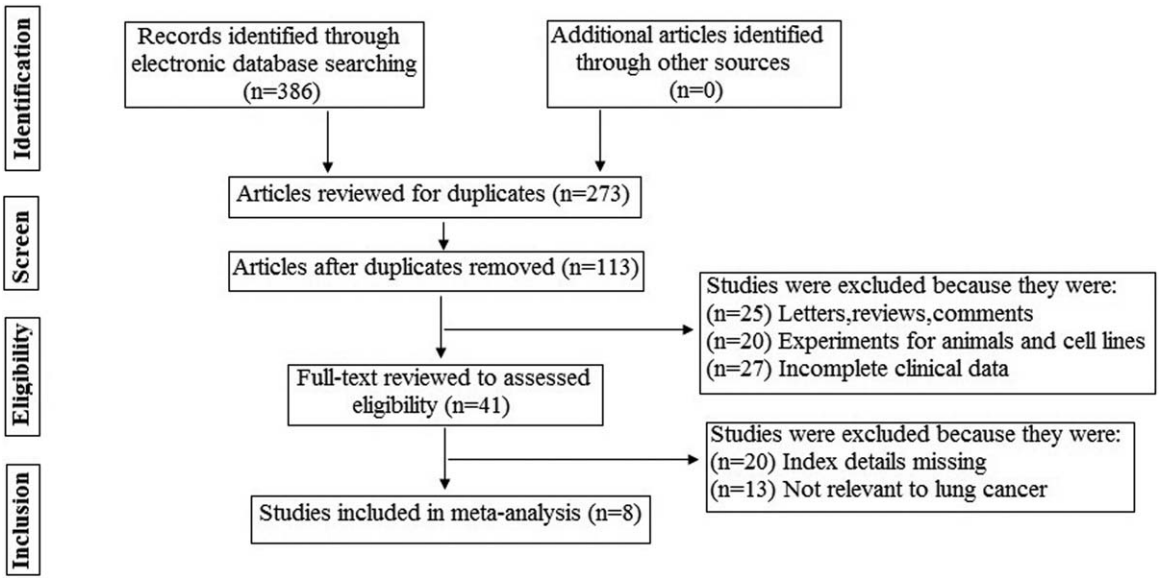

Figure 1. The flow chart of searching eligible articles process in this meta-analysis.

Table 1

Characteristics of the eligible studies in the meta-analysis.

Author	Year	Country	Case (control), n	Age	Method	AUC	Cut off	Sensitivity	Specificity
Chen	2014	China	50 (40)	59	FISH	0.917	2/3.2 mL	84.00%	97.60%
Tanaka	2009	Japan	125 (25)	–	CC	0.598	>1	30.40%	88.00%
Lou	2013	China	72 (44)	58.8	PCR	–	8.5 units	81.80%	93.20%
Yu	2013	China	153 (113)	59.4	PCR	0.823	8.64 units	73.20%	84.10%
Fiorelli	2015	Italy	60 (17)	65.5	IHC	0.9	>25	89.00%	100%
Zhong	2017	China	247 (70)	56.5	FISH	0.871	1.5	83.80%	86.50%
Qian	2018	China	250 (50)	–	MC	0.975	3.5/mL	86.00%	98.00%
Shen	2018	China	136 (149)	–	FISH	0.854	2/3.2mL	72.10%	89.30%

AUC = area under curve, CC = cell-counting, FISH = fluorescence in situ hybridization, IHC = immunohistochemistry, MC = microfluidic chip.

3.2. Study characteristics

The characteristics of the selected studies are listed in Table 1. Eight studies were published between 2009 and 2018, including 1093 lung cancer patients and 508 controls. Six studies were conducted in China,[17–22] 1 study was conducted in Italy,[23] and 1 study was conducted in Japan.[24] The quality of included studies was assessed by QUADAS-2 and some studies had moderately high scores. The quality assessment results of the included studies are shown in Fig. 2.

3.3. Meta-analysis

The summarized results for sensitivity, specificity, PLR, and NLR are presented in Fig. 3. The pooled sensitivity was 0.75 (95% CI: 0.73–0.78), the specificity was 0.89 (95% CI: 0.86–0.92), the

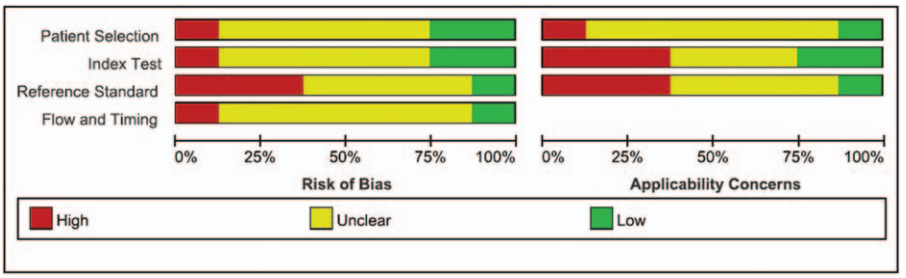

Figure 2. Bar charts of the quality assessment of included studies using the tool of Quality Assessment of Diagnostic Accuracy Studies 2 (QUADUA-2). (Left) Risk of bias. (Right) Applicability concerns.

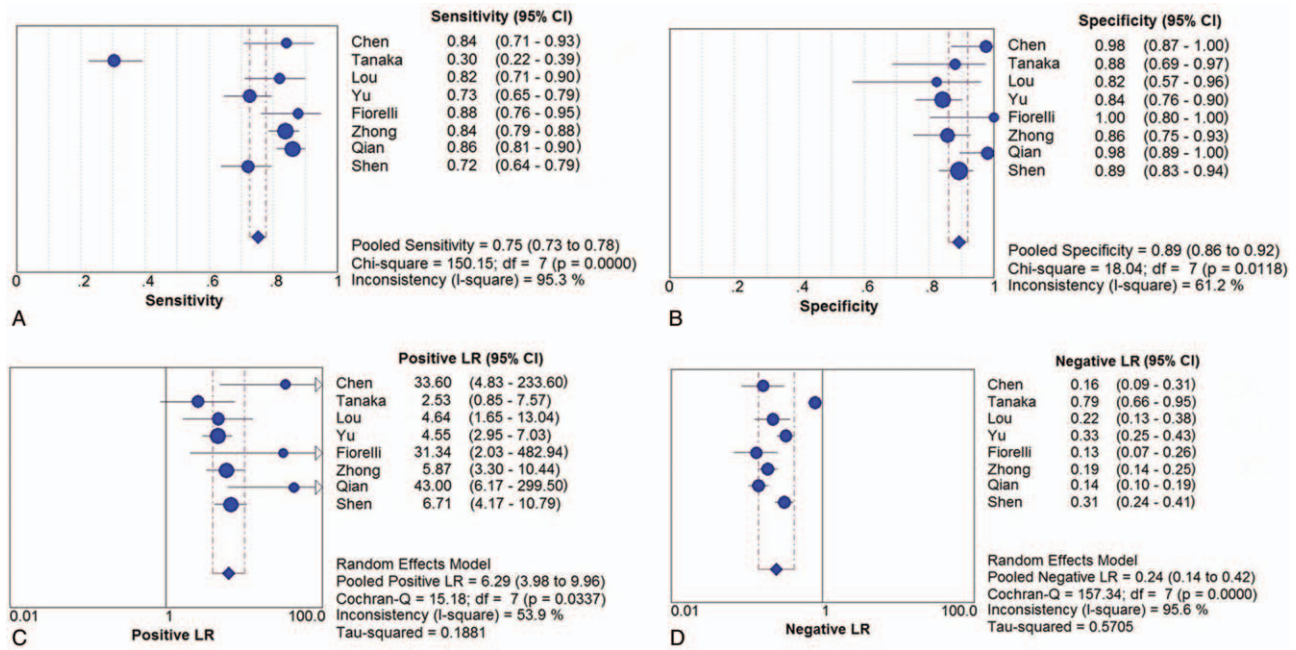

Figure 3. Forest plots for the sensitivity, specificity, PLR, and NLR. (A) Pooled sensitivity. (B) Pooled specificity. (C) Pooled PLR. (D) Pooled NLR. The point estimates from each study are shown as solid circle. The pooled estimates are shown as a solid diamond. Effect sizes were pooled by random-effect models. NLR = negative likelihood ratio, PLR = positive likelihood ratio.

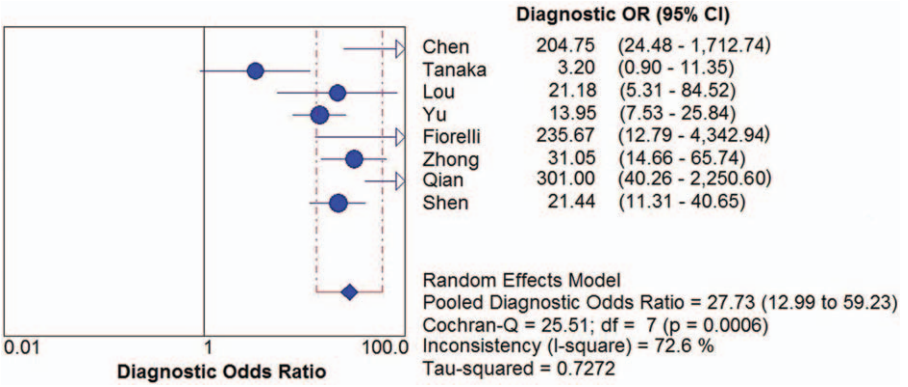

Figure 4. Forest plot for diagnostic odds ratio of CTCs in the diagnosis of lung cancer. CTC = circulating tumor cells.

PLR was 6.29 (95% CI: 3.98–9.96), and the NLR was 0.24 (95% CI: 0.14–0.42). Furthermore, the pooled DOR of CTCs for lung cancer was 27.73 (95% CI: 12.99–59.23) (Fig. 4). Finally, the summarized area under the ROC curve was 0.93 (95% CI: 0.90–0.95) (Fig. 5).

3.4. Heterogeneity analysis

Due to the high heterogeneity of the DOR, meta-regression analysis was conducted based on the year of publication, age, country, and diagnostic methods. The results suggested that the heterogeneity was mainly attributed to the diagnostic methods (Fig. 6) (Table 2).

3.5. Clinical diagnosis efficiency

Through the analysis of Fagan nomogram, we determined that the pre-test probability of the PLR was 20% and the post-test probability was 67%. The pre-test probability of the NLR was 20%, and the post-test probability decreased to 6% (Fig. 7).

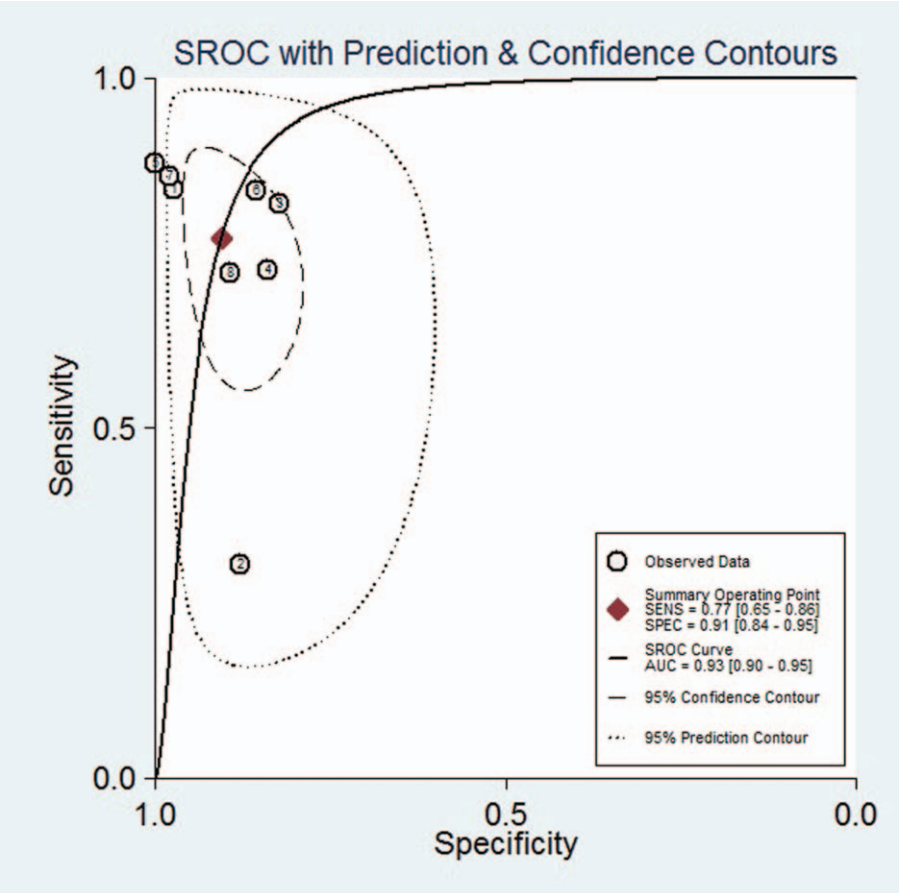

Figure 5. The summary receiver operator characteristic curve (sROC) with area under curve (AUC) of CTCs in the diagnosis of lung cancer for all studies. CTC = circulating tumor cells, sROC = summary receiver operating characteristic, AUC = area under curve.

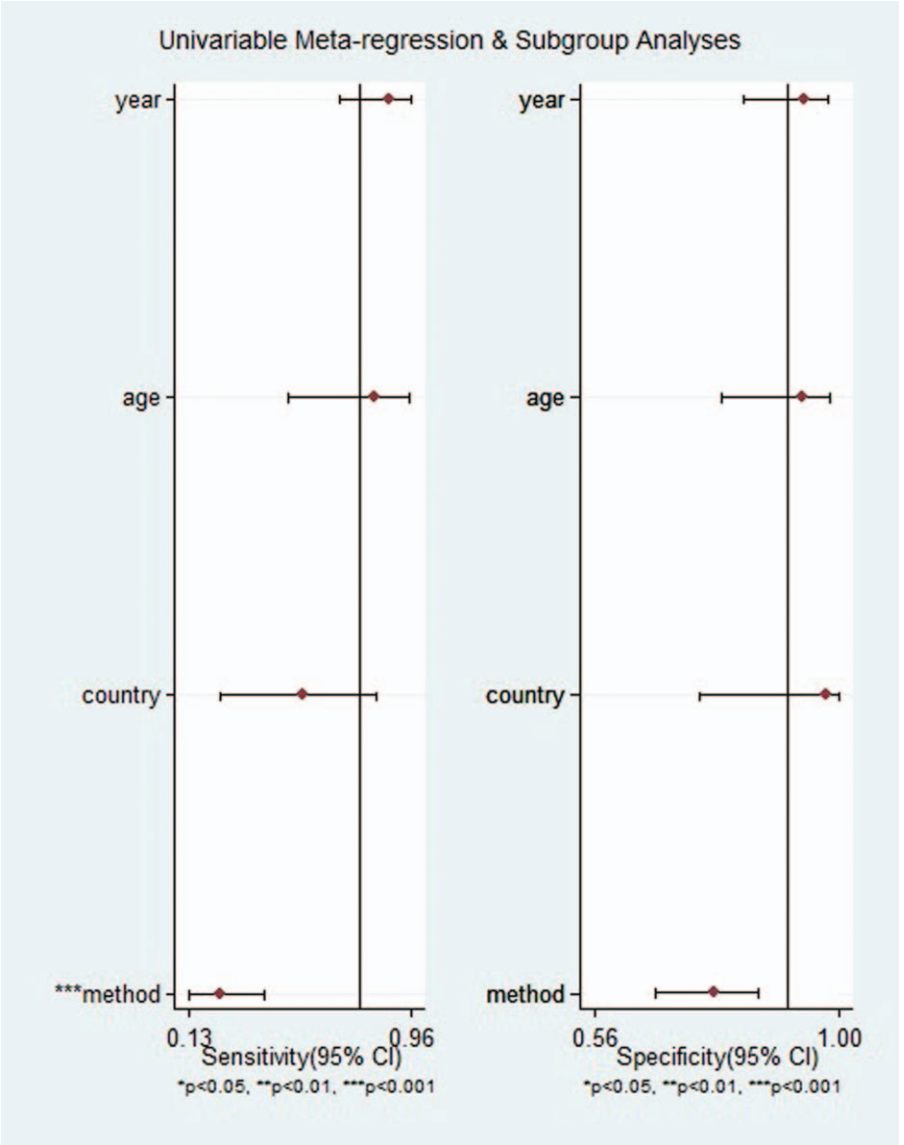

Figure 6. The meta-regression analyses of the enrolled studies. CI = confidence interval.

3.6. Publication bias

Deeks funnel plot asymmetry test was used to evaluate publication bias. The funnel plots of the studies were symmetrical, and the results of the test showed no evidence of publication bias ($P = .57$) (Fig. 8).

4. Discussion

Lung cancer is a common malignant tumor and is the main cause of cancer-related deaths worldwide.[25] Each year, approximately 1.8 million new cases of lung cancer occur worldwide, accounting for 23% of new cases of cancer. Due to the lack of effective diagnostic methods and specific clinical features, most patients are in advanced stages or metastatic after a definitive diagnosis, losing the opportunity for surgery, and facing a very low 5-year survival rate.[26] Compared with the traditional detection method, CTCs have shown improved sensitivity and specificity in the diagnosis of lung cancer.[27]

Table 2

Meta-regression.

Variable	Coefficient	Std. Err.	*P*-value	RDOR	(95%CI)
Country	1.84	1.67	.38	6.3	(0.00;8164.43)
Year	0.97	0.68	.29	2.65	(0.14;48.92)
Age	−1.56	0.82	.19	0.21	(0.01;7.02)
Method	−9.21	2.07	.04	0	(0.00;0.73)

CI = confidence interval; RDOR = relative diagnostic odds ratios.

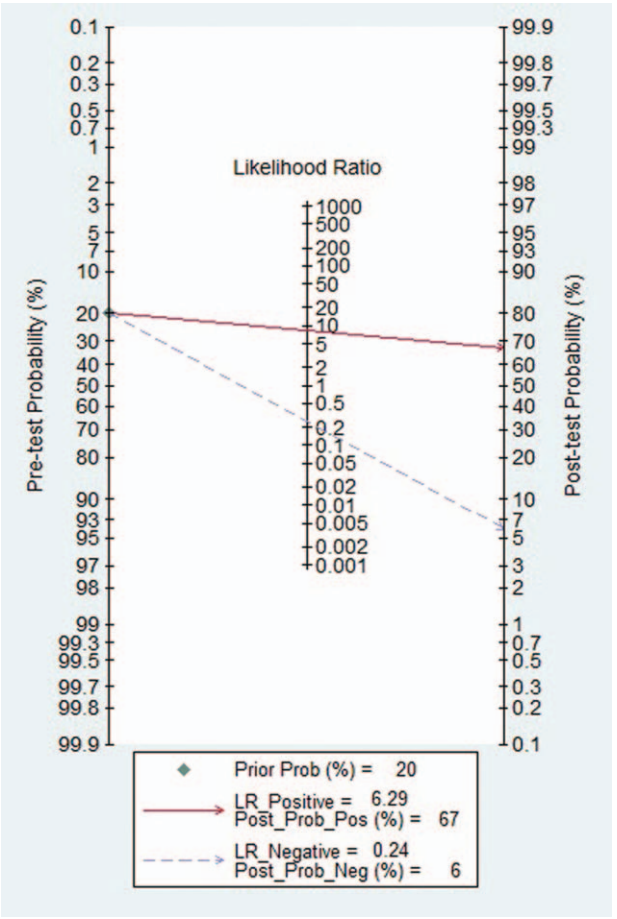

Figure 7. Fagan nomogram of CTCs in the diagnosis of lung cancer. CTCs = circulating tumor cells.

This meta-analysis evaluated the diagnostic value of CTCs for lung cancer, including 8 studies involving a total of 1601 patients. The pooled sensitivity of CTCs for the diagnosis of lung cancer was 0.75, the pooled specificity was 0.89, the missed diagnosis rate was 0.25, and the misdiagnosis rate was 0.11, which showed that the diagnostic efficiency was high. The results show that the PLR and NLR of CTCs for lung cancer were 6.29 and 0.24, respectively, which suggested an acceptable detection rate. Taken all together, it indicated that overall accuracy of lung cancer detection using CTCs was relatively good. Furthermore, the high DOR suggested a stronger discrimination ability for lung cancer. We used an sROC to summarize the overall test performance and an AUC to evaluate the overall diagnostic efficiency. The summarized area under the ROC curve was 0.93, which indicated a high diagnostic value.

The I^2 value of the heterogeneity test of the DOR was 72.6%, indicating high heterogeneity. Therefore, we use meta-regression analysis to explore the possible sources of heterogeneity. The *P*-value of the method was .04 (<.05), indicating that the method is the main source of heterogeneity. The results of the clinical diagnosis efficiency showed that it has increased significantly by testing CTCs for diagnosing lung cancer. The Fagan nomogram showed that the abnormal CTCs was suspicious for lung cancer increased the pretest probability of cancer from 20% to 67%, whereas a normal CTCs decreased the pretest probability from 20% to 6%. Compared with the diagnosis of lung cancer without CTCs, the diagnosis accuracy of lung cancer by CTCs is significantly increased. Therefore, combined with clinical information, detection of CTCs timely and effectively can help clinicians to treat and monitor the development of the disease and is beneficial to early diagnosis of lung cancer.

Based on the results of the current meta-analysis, we speculate that CTCs have high diagnostic value for lung cancer. Nevertheless, there are several limitations to this study. First,

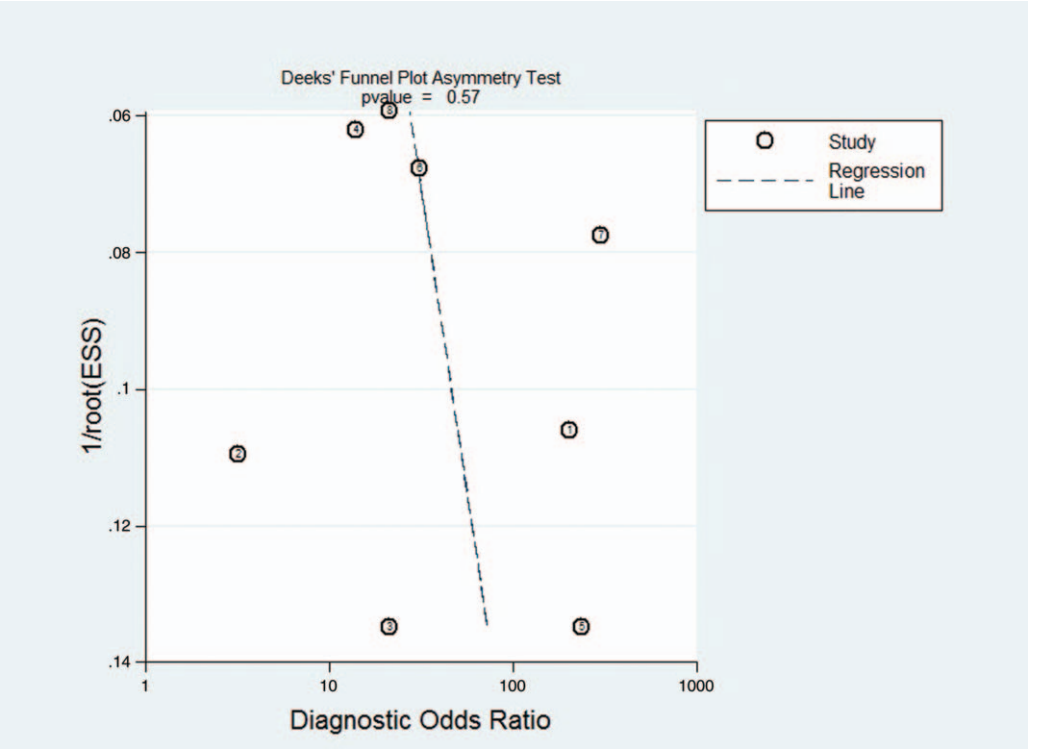

Figure 8. Deeks funnel plot for the assessment of publication bias.

there may have been publication bias because our study did not include unpublished articles and articles published in other languages. Second, we used summarized data for analysis, and a more detailed analysis was limited. Third, the small sample size in some of the included literature may have affected the determination of the diagnostic value of CTCs in the diagnosis of lung cancer.

5. Conclusion

The results of this meta-analysis suggest that CTCs are associated with a high diagnostic value for lung cancer. These findings require large-scale prospective studies to verify and evaluate the diagnostic value in the future.

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Formal analysis: Yun ye, Su-Liang Li.
Investigation: Su-Liang Li, Jian-Jun Wang, Bing Liu.
Resources: Jian-Jun Wang.
Supervision: Bing Liu, Yun Ye.
Methodology: Su-Liang Li, Yun Ye.
Software: Yun Ye.
Supervision: Yun Ye.
Validation: Bing Liu.
Writing – original draft: Su-Liang Li.
Writing – review and editing: Yun Ye, Su-Liang Li.

References

[1] Vallières E, Pintos J, Parent ME, et al. Occupational exposure to wood dust and risk of lung cancer in two population-based case-control studies in Montreal. Canada Environ Health 2015;14:1–9.
[2] Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin 2017;67:7–30.
[3] Yu JB, Soulos PR, Cramer LD, et al. Comparative effectiveness of surgery and radiosurgery for stage I non-small cell lung cancer. Cancer 2015;121:2341–9.
[4] Gelvan A, Risum S, Langer SW. Incidence and survival from lung cancer in Greenland is comparable to survival in the Nordic countries. Dan Med J 2015;62:A5033.
[5] Ilie M, Hofman V, Long E, et al. Current challenges for detection of circulating tumor cells and cell-free circulating nucleic acids, and their characterization in non-small cell lung carcinoma patients. What is the best blood substrate for personalized medicine? Ann Transl Med 2014;2:107.
[6] Hofman V, Ilie M, Long E, et al. Detection of circulating tumor cells from lung cancer patients in the era of targeted therapy: promises, drawbacks and pitfalls. Curr Mol Med 2014;14:440–56.
[7] Hayes DF, Cristofanilli M, Budd GT, et al. Circulating tumor cells at each follow-up time point during therapy of metastatic breast cancer patients predict progression-free and overall survival. Clin Cancer Res 2006;12 (14 pt 1):4218–24.
[8] Cabel L, Proudhon C, Gortais H, et al. Circulating tumor cells: clinical validity and utility. Int J Clin Oncol 2017;22:421–30.
[9] Moher D, Liberati A, Tetzlaff J, et al. PRISMA GroupPreferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med 2009;6:e1000097.
[10] Whiting PF, Weswood ME, Rutjes AW, et al. Evaluation of QUADAS, a tool for the quality assessment of diagnostic accuracy studies. BMC Med Res Methodol 2006;6:9.
[11] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
[12] Jackson D, White IR, Riley RD. Quantifying the impact of between-study heterogeneity in multivariate meta-analyses. Stat Med 2012;31:3805–20.
[13] Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
[14] Altman DG, Bland JM. Interaction revisited: the difference between two estimates. BMJ 2003;326:219.
[15] Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. J Clin Epidemiol 2005;58:882–93.
[16] Akobeng AK. Understanding diagnostic tests 2: likelihood ratios, pre- and post-test probabilities and their use in clinical practice. Acta Paediatr 2007;96:487–91.
[17] Chen YY, Xu GB. Effect of circulating tumor cells combined with negative enrichment and CD45-FISH identification in diagnosis, therapy monitoring and prognosis of primary lung cancer. Med Oncol 2014;31:240.
[18] Lou J, Ben S, Yang G, et al. Quantification of rare circulating tumor cells in non-small cell lung cancer by ligand-targeted PCR. PLoS One 2013;8: e80458.
[19] Yu Y, Chen Z, Dong J, et al. Folate receptor-positive circulating tumor cells as a novel diagnostic biomarker in non-small cell lung cancer. Transl Oncol 2013;6:697–702.
[20] Zhong CH, Tong D, Zhou ZQ, et al. Performance evaluation of detecting circulating tumor cells and tumor cells in bronchoalveolar lavage fluid in diagnosis of peripheral lung cancer. J Thorac Dis 2018;10(suppl):S830–7.
[21] Qian C, Wu S, Chen H, et al. Clinical significance of circulating tumor cells from lung cancer patients using microfluidic chip. Clin Exp Med 2018;18:191–202.
[22] Shen Q, Shen LS, Chen Q, et al. The value of circulating tumor cells detected by chromosome centromere probe identification in diagnosis of non-small cell lung cancer. Zhonghua Jie He He Hu Xi Za Zhi 2018;41:772–7.
[23] Fiorelli A, Accardo M, Carelli E, et al. Circulating tumor cells in diagnosing lung cancer: clinical and morphologic analysis. Ann Thorac Surg 2015;99:1899–905.
[24] Tanaka F, Yoneda K, Kondo N, et al. Circulating tumor cell as a diagnostic marker in primary lung cancer. Clin Cancer Res 2009;15:6980–6.
[25] Nanavaty P, Alvarez MS, Alberts WM. Lung cancer screening: advantages, controversies, and applications. Cancer Control 2014;21:9–14.
[26] Travis WD, Asamura H, Bankier AA, et al. The IASLC Lung Cancer Staging Project: proposals for coding T categories for subsolid nodules and assessment of tumor size in part-solid tumors in the forthcoming Eighth Edition of the TNM classification of lung cancer. J Thorac Oncol 2016;11:1204–23.
[27] Ning N, Zhan T, Zhang Y, et al. Improvement of specific detection of circulating tumor cells using combined CD45 staining and fluorescence in situ hybridization. Clin Chim Acta 2014;433:69–75.