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The value of Folate Receptor–Positive Circulating Tumor Cell as a diagnostic biomarker for lung cancer: a meta-analysis and system review

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INTRODUCTION

Review question / Objective To evaluate the diagnostic value of FR+CTC in lung cancer.

Condition being studied Lung cancer is one of the most common malignant tumors with the highest incidence worldwide. Many patients are diagnosed at an advanced stage, leading to poor prognosis and a high mortality rate. With the improvement of technology, the early diagnosis of lung cancer has attracted attention. However, some patients are still misdiagnosed with lung cancer and undergo non-essential surgery, which increases the medical burden of the population.

METHODS

Participant or population Normal and lung cancer patient.

Intervention Folate receptor-positive circulating tumor cells (FR+CTC) in normal and lung cancer patient.

Comparator Liquid biopsy.

Study designs to be included The related articles were searched from The PubMed, Embase, and Web of Science databases. Then Eligible studies were selected based on inclusion and exclusion criteria. Sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and area under the curve (AUC) were pooled with 95% confidence intervals (CI) by using RevMan 5.4 and STATA 17.0 software to assess the diagnostic value of FR+CTC for lung cancer.

Eligibility criteria The inclusion criteria were listed: (1). Study participants were lung cancer patients diagnosed by pathology; (2). Detection of FR-CTC expression in the participants' blood; (3). The

ability to give a complete list of true-positive, true-negative, false-positive, and false-negative sample sizes in the study or to be calculated by an apparent sample size that combined sensitivity, specificity, and area under the ROC curve (AUC).The exclusion criteria were: (1). Duplicate studies; (2). Reviews, abstracts, case reports, editorials, letters, and editorial articles; (3). Not a study of lung cancer with FR+ CTC; (4). Not a diagnostic study; (5). The study subject is not human; (6). Data are incomplete or calculated to be inconsistent with the original article; (7). Not a study in Chinese or English.

Information sources PubMed, Embase, and Web of Science.

Main outcome(s) 11 studies involving 3469 subjects were eligible after screening. The pooled sensitivity and specificity were 0.79 (95% CI: 0.76-0.82) and 0.84 (95% CI: 0.81-0.96), respectively, and the pooled positive and negative likelihood ratios were 4.90 (95% CI: 4.25-5.65) and 0.25 (95% CI: 0.22-0.29). The pooled diagnostic ratio was 19.70 (95% CI: 16.06-24.16). The area under the curve (AUC) of the pooled SROC was 0.89 (95% CI: 0.85-0.91). Sensitivity analysis showed that this result was stable after the one-by-one elimination of the study.

Quality assessment / Risk of bias analysis The quality of the included studies was assessed using the Quality Assessment of Diagnostic Accuracy Study-2 (QUADAS-2) diagnostic criteria scale. Two independent researchers conducted the assessment, and another aligned the findings in case of controversial views. The scale assesses the quality of included studies in four domains: patient selection, index testing, reference standards, and flow and timing, and lists 14 specific items that are evaluated with " Yes," "No," or "Unclear " for assessment.

Strategy of data synthesis A bivariate mixed-effects binary regression modeling framework was used to generate pooled sensitivities, combined specificities, positive likelihood ratios (PLR), negative likelihood ratios (NLR), diagnostic ratio ratios (DOR), the corresponding 95% confidence intervals (CI), and the confidence and prediction contours in summary subject operating characteristic (SROC) curves.
We additionally used Fagan's line plot to analyze the clinical value of FR+CTC in the diagnosis of lung cancer. Cochran's Q and $\chi 2$ were used for heterogeneity assessment, and $I2 > 50\%$ was defined as greater heterogeneity. P-values < 0.05 were considered statistically significant. The source of heterogeneity was then determined by meta-regression and subgroup analysis. In addition, sensitivity analysis was conducted to exclude each included study to determine whether the final results were stable. Finally, the asymmetry of the Deeks funnel plot assessed the publication bias in the enrolled studies.We used Stata software (version 17.0; Stata Corporation, College Station, TX, USA), RevMan (version 5.4.1; Copenhagen, Denmark; Cochrane Collaboration Network, 2020), and MetaDiSc (version 1.4) for meta-analysis.

Subgroup analysis We investigated the source of the heterogeneity by subgroup analysis stratified according to features including sample size (≥200 versus <200), period of publication (2018 and before versus after 2018), type of control group (benign disease versus benign disease and normal), threshold Settings(set in advance according to the manufacturer's recommended value versus the optimal solution based on the subject's operating curve).

Sensitivity analysis To identify whether the results of the meta-analysis were reliable, we performed a sensitivity analysis. The results were stable after excluding the included studies one by one, indicating that our pooled results were more reliable.

Country(ies) involved China.

Keywords Lung cancer,Biomarker,Folate Receptor,Circulating Tumor Cell,FR+CTC.

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