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Original Research

Combined detection of CEA and CA125 for the diagnosis for lung cancer: A meta-analysis

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Abstract: This study aimed to systematically evaluate the value of combined detection of serum CEA and CA125 concentrations for the diagnosis of lung cancer. Related studies regarding the diagnosis of lung cancer were searched in PubMed, Embase, CNKI, and Wanfang using a computer. The number of patients who were true-positive, false-positive, false-negative, and true-negative were extracted from each study. Meta-analysis was performed using the Meta-Disc l.4, RevMan 5.3. Seven studies involving 2,216 cases were finally included. Regarding the diagnosis of lung cancer, the sensitivity, specificity, and diagnostic odds ratio of combined CEA and CA125 detection were higher than those of CEA detection alone. The area under the curve (AUC) of combined detection was 0.90, whereas the independently detected AUC was 0.73. Combined CEA and CA125 detection has higher diagnostic efficiency for lung cancer than CEA detection alone. The significance of combined serum CEA and CA125 detection in lung cancer is confirmed.

Key words: Diagnosis; Meta-analysis; Lung cancer; CA125; CEA.

Introduction

Lung cancer is the leading type of cancer worldwide. It is difficult to diagnose at the early stage; thus, most of the patients admitted to the hospital have been in the process of progression or metastasis, and the treatment outcome is often poor, with the five-year survival rate of <15% (1, 2). Therefore, early diagnosis and treatment are effective ways to improve the survival rate of patients with lung cancer. Tumor markers have important reference values for the diagnosis of lung cancer. Clinical tumor markers commonly associated with lung cancer are CEA, CA125, SCC, NSE, and CYFRA21-1; however, a single indicator to detect lung cancer has limitations. Therefore, this study adopts the systematic method of evaluation by combining the CEA and CA125, two kinds of tumor markers individually used to evaluate and assess lung cancer.

Materials and Methods

Search strategy

PubMed, Embase, CNKI, Wanfang, and Weipu Chinese technology journal database were searched for lung cancer-related studies. The search terms were lung cancer, CEA, CA125, and tumor marker. A comprehensive search of the relevant literature from 2000 to October 1, 2017, was conducted by combining the keywords and free words.

Inclusion criteria

Literature includes Chinese or English. The study subjects are patients with lung cancer, including those with squamous cell carcinoma or adenocarcinoma, and the control subjects are healthy individuals or patients with benign lung disease. The gold standard is a histopathological examination. True-positive (TP), false-negative (FN), false-positive (FP), and true-negative (TN) findings can be obtained. The method used is a serological test.

Exclusion criteria

Studies with incomplete data on TP, FP, FN, and TN; with cases not confirmed by the gold standard; with no control group; published and used the same data (duplicate studies); and those that were evaluated as low-quality literature were excluded.

Data extraction and analysis

Two researchers screened the literature independently, and any disagreement was resolved by consulting the experts or through discussion. The two evaluators searched the literature according to the exclusion criteria set in order to independently select literature and extract and cross-check the data to ensure the quality and consistency of evaluation results. Meta-analysis was performed using Meta-Disc l.4, RevMan 5.3.

Heterogeneity analysis

(1) Threshold effect: When there is a threshold effect

caused by the heterogeneity of the sensitivity (SEN) calculation and negative correlation with the specificity (SPE), the result on the summary receiver operating characteristic (SROC) curve distribution is "JianBei" point (3), i.e., the fitting SROC curve and area under the ROC curve (AUC) (4). (2) Non-threshold effect: Using the Q test to analyze the heterogeneity of the diagnostic odds ratio (DOR), the heterogeneity size was evaluated using the I^2 value. If the heterogeneity test results are $P > 0.05$ and $I^2 < 50\%$, the heterogeneity is considered small, and the fixed effect model is adopted. If $I^2 > 50\%$, the results of multiple independent studies are considered highly heterogeneous, and the stochastic effect model is adopted (5) and subgroup analysis is performed to determine the reasons for heterogeneity.

Meta-analysis

(1) The random effects model is adopted to extract the study data (TP, FP, FN, and TN), to merge and calculate separate and combined detection of CEA, CA125, and CEA, with SEN, SPE, and their 95% confidence interval (95% CI). (2) Using Moses' constant linear model to fit the SROC curve (6), the accuracy of the diagnostic test was evaluated using the DOR, AUC, and Q *.

Results

Characteristics of included studies

At first, 215 Chinese and English papers were retrieved, and the final screening included seven papers (7-13), which were published in 2003–2016. A total of 1,023 cases of lung cancer and 1,193 cases in the control group were involved. All included literature had separate results of CEA detection alone and combined.

Quality evaluation of the included literature

The risk deviation assessment method of the Cochrane system was used to evaluate the quality of the included literature (Figures 1 and 2). All included literature had results of CEA detection alone and combined. The heterogeneity of CEA was independently detected with the I2=82.6% (P = 0.0000) (Figure 5). Distribution of "shoulder arm" points on the SROC curve was shown (Figure 5), indicating the heterogeneity of the threshold effect. The heterogeneity of CEA and CA125 was combined to detect I2=94.8% (P = 0.0000) (Figure 9). Distribution of "shoulder arm" was not shown on the SROC curve (Figure 10), and the presence of non-threshold was indicated.

Diagnosis SEN, SPE and DOR

The SEN, SPE, and DOR of CEA were 0.59 (95% CI: 0.56–0.62), 0.80 (95% CI: 0.78–0.82), and 7.29 (95% CI: 4.26–12.47), respectively. The SEN, SPE, and DOR of combined CA125 and CEA tests were 0.78 (95% CI: 0.75–0.80), 0.84 (95% CI: 0.82–0.86), and 23.62 (95% CI: 7.69–72.55), respectively. Compared with the independent detection of CEA, the combined detection with SEN, SPE, and DOR was significantly higher, suggesting that the detection ability of combined detection was stronger (Figures 3–5 and 7 –9).

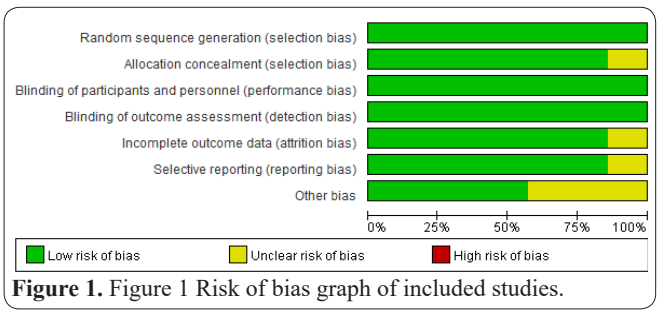

Figure 1. Figure 1 Risk of bias graph of included studies.

Area under the ROC curve analysis, AUC, and Q*

Independently, AUC= 0.73, Q*=0.68 (Figure 6). The AUC= 0.90 and Q*=0.83 (Figure 10) of the combined detection of CEA and CA125 and the combined detec-

Figure 2. Risk of bias summary of included studies.

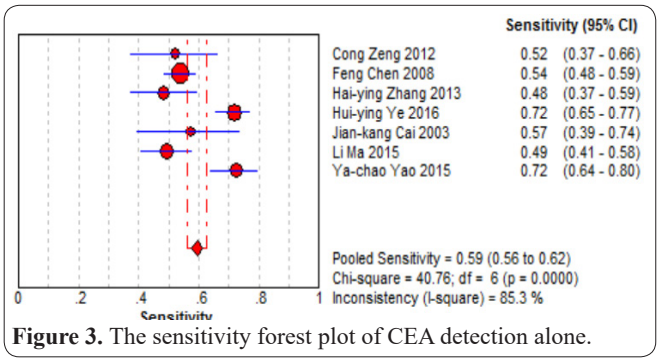

Figure 3. The sensitivity forest plot of CEA detection alone.

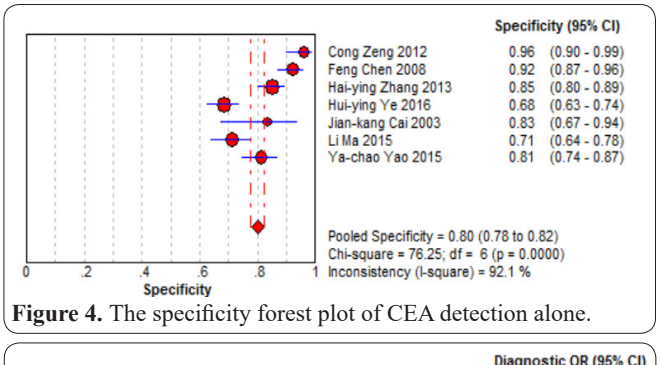

Figure 4. The specificity forest plot of CEA detection alone.

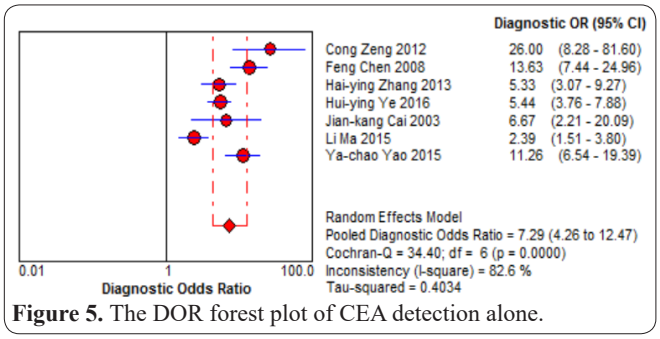

Figure 5. The DOR forest plot of CEA detection alone.

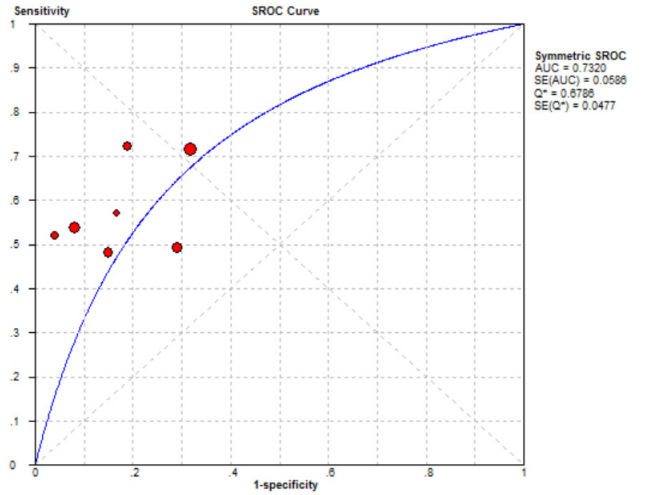

Figure 6. Area under the ROC curve for CEA in the diagnosis of lung cancer.

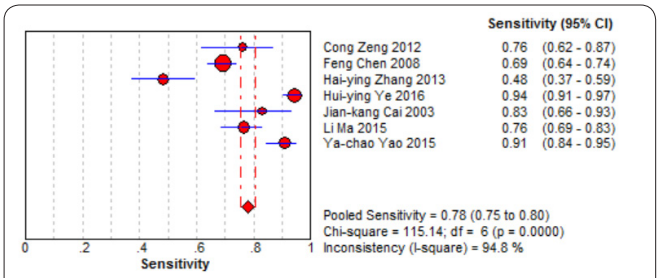

Figure 7. The sensitivity forest plot of combined detection of CEA and CA125 detection.

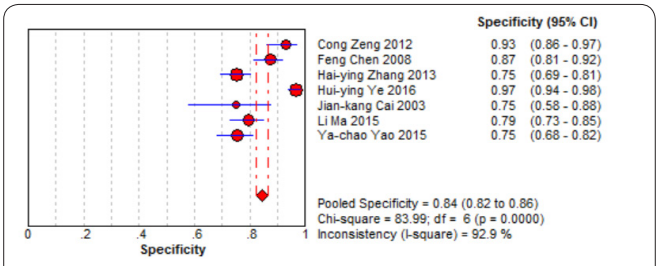

Figure 8. The specificity forest plot of combined detection of CEA and CA125.

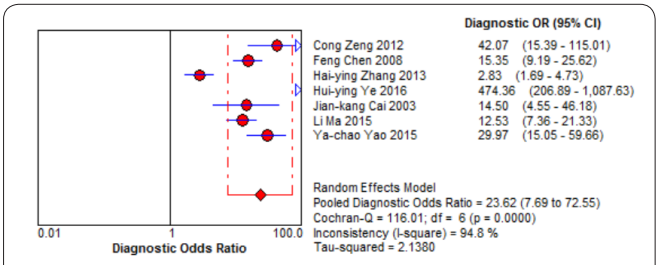

Figure 9. The DOR forest plot of combined detection of CEA and CA125.

tion of AUC and Q* value of CEA and CA125 are both higher than that of the independent detection of CEA, indicating the high accuracy of combined detection.

Subgroup analysis

In the combined CEA and CA125 tests, the threshold effect caused the heterogeneity; therefore, a subgroup analysis on the number of possible factors, such as health status, should be performed to determine the detection of SEN and influence of SPE. In addition, to determine whether the seven articles included healthy subjects as the control group, a separate subgroup analysis was performed and showed that the combined

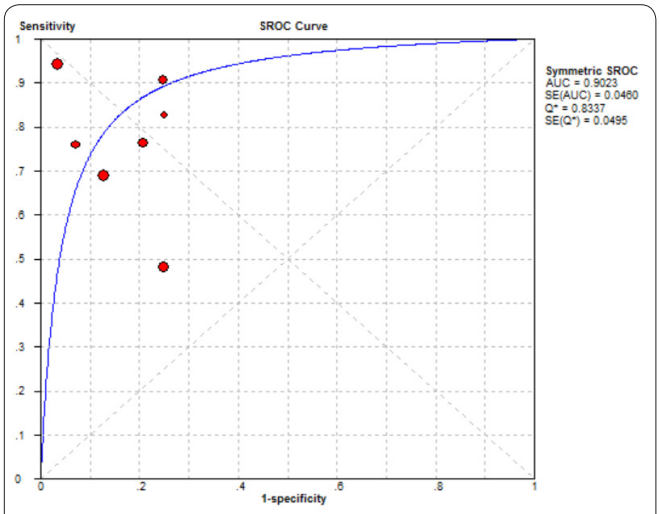

Figure 10. The area under the ROC curve of combined detection of CEA and CA125 for the diagnosis of lung cancer.

detection of CEA and CA125 in normal healthy subjects were lower in subgroups with SEN, SPE, and DOR, indicating that the heterogeneity factors can be thought of as the control group.

Discussion

Lung cancer is a kind of malignant tumor with the highest incidence and mortality rates worldwide (14). According to the statistics, the 5-year survival rate of patients with early stage of lung cancer is about 60%. However, those with advanced lung cancer only had 5–20% (15). Therefore, early diagnosis and surgical resection are significant to improve the survival rate of patients. The tumor marker is a substance produced by abnormally occurring tumor cells or stimulated by the host's response to the tumor. They are prevalent in tumor patients, tissues, blood, and fluids and can be detected using immunological or biochemical methods. Tumor markers play an important role in the diagnosis and typing of lung cancer. Tumor markers used to diagnose lung cancer have high SEN and SPE in order to detect the early stage, the pathological type, and the staging of cancer.

In 1965, Gold (16) et al. extracted CEA, a kind of acidic glycoprotein, from colon cancer. It can perform adhesive reaction between the cancer cells and extracellular matrix collagen, which plays a key role in the growth and metastasis of tumors.

CEA cannot be detected in the serum of normal adults and is highly expressed and specific in gastrointestinal malignancy. In the recent years, the diagnostic value of lung cancer becomes more significant. Previous research showed that CEA had better diagnostic value for lung cancer (17, 18). CEA is a kind of broad-spectrum tumor marker that is found in many kinds of tumors, but its SPE and SEN are not high. Therefore, its role in the early diagnosis of cancer is not obvious; thus, its use as a tumor marker is greatly limited.

CA125 is a kind of mucin glycoprotein with relatively large molecular weight, i.e., >200 kDa. It can be produced by the monoclonal antibody OC125 in the immune laboratory with the epitopes of mucin as the protein fraction and not in the sugar chain. Originally, CA125 is mainly used for the diagnosis of pancreatic,

endometrial, and ovarian cancers. Recent studies have found that the serum levels of CA125 also increased in patients with lung cancer, but its SEN is low (19). The expression level of CA125 in the serum and pathological staging of lung cancer was positively correlated and is related to the pathological type of lung cancer. CA125 is highly clinically significant for the diagnosis, condition monitoring, pathological classification, and prognosis of lung cancer.

A total of seven studies were included in this meta-analysis. The AUC value of the SROC curve is used to measure the accuracy of a diagnostic method. The closer the AUC is to 1, the better the diagnostic result is. The AUC of 0.5–0.7 indicates low accuracy, 0.7–0.9 indicates certain accuracy, and >0.9 indicates high accuracy. The combination of CEA and CA125 for the diagnosis of lung cancer can improve the AUC value to 0.9134, with higher accuracy. Limitations of this study are as follows: Most studies in this meta-analysis were conducted in China, which may lead to some publication bias to the system evaluation. Thus, more relevant high-quality studies are needed.

Comprehensive data analysis can conclude that the combined detection of CEA and CA125 relative to individual detection significantly improved the diagnostic accuracy of lung cancer and has a certain significance for the early diagnosis of lung cancer.

Acknowledgments
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Conflicts of interests
None

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