Diagnostic Utility of Pleural Fluid Carcinoembryonic Antigen and CYFRA 21-1 In Patients With Pleural Effusion: A Systematic Review and Meta-Analysis

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Pleural effusions (PE) are the most common complications that may be produced by a wide variety of diseases. A large number of studies exploring the role of carcinoembryonic antigen (CEA) and cytokeratin fragment 19 (CYFRA 21-1) marker in differential diagnosis of PE have been published, employing differing methodologies with sometimes conflicting results. A comprehensive systematic review would be useful to synthesize the currently available bulk of information. The objective of this work was to assess and compare the overall value of pleural fluid CEA and CYFRA 21-1 in differential diagnosis of PEs with a meta-analysis. All the English and Chinese published studies for differential diagnosis of PEs by pleural fluid CEA and CYFRA 21-1 were collected. Methodological quality of the included studies was evaluated. Pooled sensitivity and specificity were calculated, the threshold effect and the possible sources of heterogeneity were also analyzed. Summary receiver operating

characteristic (SROC) curve analysis was used to compare the differential diagnostic ability of pleural fluid CEA and CYFRA 21-1. A total of 19 studies were included in the meta-analysis, with a total of 3,228 subjects. Pooled sensitivity and specificity of CEA and CYFRA 21-1 were 45.9% (43.2–48.5%) and 97.0% (96.0–97.8%), and 47.3% (44.0–50.6%) and 91.8% (89.5–93.7%), respectively. Both CEA and CYFRA 21-1 have a threshold effect, the main source of heterogeneity was from variable assay methods. The areas under the SROC curve (AUCs) of CEA and CYFRA 21-1 were 0.7691 and 0.8213, respectively. There was no statistical significance between the AUC of CEA and CYFRA 21-1 ($P > 0.05$). Both CEA and CYFRA 21-1 have good performance in the differential diagnosis of PE, when compared with CEA, CYFRA 21-1 has no advantage. *J. Clin. Lab. Anal.* 21:398–405, 2007.

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INTRODUCTION

Pleural effusions (PE) are the most common complications that may be produced by a wide variety of diseases. Approximately 20% of PE are due to malignancy, and 50% of these are due to primary lung cancer (1). It is important to differentiate the etiology of the effusion to decide appropriate treatment; however, current methods are either insufficient or invasive. Cytology is a standard method for the diagnosis of malignant effusion. Although repeated thoracenteses can increase the sensitivity of cytology, usually it is only 50–70%. Blind pleural biopsy, which is the alternative method in the case of negative cytology results, has

limited additional diagnostic value (7%) (2). Thoracoscopy has a considerable high sensitivity, but in addition to being expensive, it is also an invasive method, which may cause many complications such as pneumothorax, pleural shock, hemothorax, subcutaneous emphysema, and possible cancer implantation in 4% of patients (2,3).

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Although rather insensitive for the early diagnosis of cancer, tumor markers are a reliable diagnostic aid in advanced stages (4,5). Because malignant PE are almost always metastatic manifestations of malignant tumors elsewhere, the chance of tumor marker elevation in such patients seems far from negligible.

A large number of studies exploring the role of carcinoembryonic antigen (CEA) and cytokeratin fragment 19 (CYFRA 21-1) marker in differential diagnosis of pleural effusion have been published employing differing methodologies with sometimes conflicting results. A comprehensive systematic review would be useful to synthesize the currently available bulk of information.

The objective of this review was to assess and compare the overall diagnostic value of pleural fluid CEA and CYFRA 21-1 in differential diagnosis of PE with a meta-analysis, which to our knowledge, has not previously been studied.

MATERIALS AND METHODS

Data Sources

A systematic literature search identified articles published between 1996 and 2007 that contained quantitative data. Articles were retrieved from the electronic bibliographic databases (PubMed, Cancerlit, Embase, Cochrane Library, China Bio-medicine Database [CBMdisc], and China National Knowledge Infrastructure [CNKI]) using the following search terms "CEA," "carcinoembryonic antigen," "CYFRA 21-1," "cytokeratin fragment," "pleural fluid," and "pleural effusion." The references of the articles identified were hand-searched for relevant articles.

Study Selection

The studies were included in the meta-analysis if they fulfilled the following inclusion criteria:

1. Involvement of a population with benign or malignant PE.
2. All assays were performed using commercially available kits.
3. Effusions were considered malignant if one of the following criteria was met:
 - a. demonstration of malignant cells at cytological examination or in a biopsy specimen;
 - b. histologically proven primary malignancy with exclusion of any other cause known to be associated with PE.
4. Presence of data regarding sensitivity and specificity values or the possibility of deriving such values from the results analysis.
5. Published article was written in English or Chinese.

The studies were excluded if they met the following exclusion criteria:

1. Subjects are the healthy population.
2. The definition of malignant PE was not consistent with the inclusion criteria or the definition was not clear.
3. If there were duplicate studies, the one which was published earlier or had a smaller sample size was excluded.

Data Abstraction and Quality Assessment

Two reviewers (P.G. and Y.C.) independently screened the titles, abstracts, and full text to identify eligible studies. Disagreements between the reviewers were resolved by consensus. Data retrieved from the studies included methodological quality and outcome data (true-positive, false-positive, true-negative, false-negative). We assessed the quality of the included studies by using criteria selected from the quality assessment of diagnostic accuracy studies (QUADAS) checklist for assessment of quality of diagnostic studies (6): study design (prospective or retrospective); patient collection (consecutive or not); blinding (blind or not interpretation of index test); assay method; study size; cutoff point, etc.

Statistical Analysis

The pooled sensitivity, pooled specificity, and their 95% confidence interval (CI) were calculated by the DerSimonian Laird method. A chi-squared test for heterogeneity between each studies was reported. In cases of cutoff threshold effect, the relationship between sensitivity and specificity was evaluated by using the Spearman correlation coefficient ρ . Possible sources of heterogeneity were investigated by metaregression, which used a generalization of Littenberg and Moses linear model weighted by the inverse of the variance. The accuracy measure used is the diagnostic odds ratio (dOR), which indicates the change in diagnostic performance of the test under study per unit increase in the covariate. We also use Moses' linear model to draw a summary receiver operating characteristic (SROC) curve, which summarized the joint distribution of sensitivity and specificity. The area under the SROC curve (AUC) was calculated. The difference of AUC between CEA and CYFRA 21-1 was tested by Z test. Values of $P < 0.05$ were considered statistically significant. All analyses were undertaken using Meta DiSc statistical software (version 1.4; Ramón y Cajal Hospital, Madrid, Spain) (7) and SPSS (version 11.0; SPSS Inc., Chicago, IL).

RESULTS

Study Characteristics and Quality

Out of 253 articles in English and 110 articles in Chinese identified in the literature search, 21 articles met

TABLE 1. Main characteristics of 19 studies

Reference	Location	Storage temperature (°C)	Study design	Blinding	Patients collection	Follow-up	Study size	Malignancy (%)
Romero S (8)	Spain	−20	Prospective	—	Yes	—	115	42 (36.52)
Villena V (9)	Spain	−20	Prospective	Yes	—	Yes	207	65 (31.40)
San Jose ME (10)	Spain	−40	—	—	—	—	271	88 (32.47)
Cynowska B (11)	Poland	−20	Retrospective	Yes	—	—	35	22 (62.86)
Miedouge M (12)	France	−80	Retrospective	—	—	Yes	336	215 (63.99)
Ferrer J (13)	Spain	—	Prospective	—	Yes	—	122	43 (35.25)
Lai RS (14)	Taiwan	−70	Retrospective	—	—	—	126	72 (57.14)
Riantawana P (15)	Thailand	—	—	Yes	Yes	—	176	78 (44.32)
Alatas F (16)	Turkey	−20	—	Yes	—	—	74	44 (59.46)
Dejsomritrutai W (17)	Thailand	—	—	Yes	—	—	62	27 (43.55)
Paganuzzi M (18)	Italy	−80	—	—	Yes	Yes	106	72 (67.92)
Hernandez L (19)	Spain	−20	Prospective	Yes	Yes	—	383	130 (33.94)
Villena V (21)	Spain	−20	Prospective	Yes	—	Yes	252	101 (40.08)
Porcel JM (22)	Spain	−70	—	Yes	—	—	416	243 (58.41)
Uostun H (23)	Turkey	−20	Prospective	—	—	—	81	41 (50.62)
Li CS (24)	China	−20	—	Yes	—	—	62	32 (51.61)
Lee JH (25)	Korea	−80	—	Yes	—	—	50	34 (68.00)
Shitrit D (26)	Israel	−20	Prospective	Yes	—	—	116	44 (37.93)
Porcel JM (28)	Spain	−80	—	Yes	—	—	238	135 (56.72)

TABLE 2. The assay methods, cutoff point, TP, FP, TN, and FN of CYFRA 21-1

Reference	Assay methods	Cutoff (ng/mL)	TP	FP	FN	TN
Lee JH (25)	RIA	45	20	3	14	13
Porcel JM (22)	ECLIA	175	53	0	190	173
Shitrit D (26)	ELISA	3.3	26	14	18	58
Romero S (8)	ELISA	50	16	13	26	60
Alatas F (16)	ELISA	8	40	3	4	27
Dejsomritrutai W (17)	ELISA	55	20	1	7	34
Miedouge M (12)	ELISA	163	92	1	123	120
Ferrer J (13)	IRMA	150	10	0	33	79
Cynowska B (11)	IRMA	3.3	20	12	2	1
Paganuzzi M (18)	ELISA	41.9	56	7	16	27
Lai RS (14)	RIA	50	41	3	31	51
Li CS (24)	ELISA	3.3	27	3	5	27

TP, true-positive; FP, false-positive; TN, true-negative; FN, false-negative; RIA, radioimmunoassay; ECLIA, electrochemiluminescent immunoassay; ELISA, enzyme-linked immunosorbent assay; IRMA, immunoradiometric assay.

the inclusion criteria for this review (8–28) (only one in Chinese). Of these, two articles were excluded, because of data duplication (25) and the unavailability of sensitivity or specificity value (27). So at the end of the process, the final analysis included 19 studies, with a total of 3,228 subjects, whose main characteristics are detailed in Table 1.

A total of 12 articles were studies of the diagnostic value of pleural fluid CYFRA 21-1, 15 articles were studies of the diagnostic value of pleural fluid CEA. Among them, both CEA and CYFRA 21-1 were

TABLE 3. The assay methods, cutoff point, TP, FP, TN, and FN of CEA

Reference	Assay methods	Cutoff (ng/mL)	TP	FP	FN	PN
Lee JH (25)	RIA	5	28	1	6	15
Porcel JM (22)	ECLIA	50	70	0	173	173
Shitrit D (26)	CLIA	5	28	1	16	71
Romero S (8)	MEIA	3	24	1	18	72
Alatas F (16)	CLIA	3	23	7	21	23
Miedouge M (12)	MEIA	6	129	1	86	120
Paganuzzi M (18)	MEIA	5	22	3	50	31
Lai RS (14)	RIA	10	43	3	29	51
Villena V (21)	RIA	40	35	0	66	151
Hernandez L (19)	MEIA	4.8	64	6	66	247
Riantawana P (15)	MEIA	10	60	6	18	92
San Jose ME (10)	MEIA	7.2	27	13	61	170
Villena V (9)	RIA	40	28	0	37	142
Uostun H (23)	MEIA	6	24	4	17	36
Porcel JM (28)	ECLIA	50	39	1	96	102

TP, true-positive; FP, false-positive; TN, true-negative; FN, false-negative; CLIA, chemiluminescence immunoassay; MEIA, microparticle enzyme immunoassay.

evaluated in seven articles (8,12,16,18,22,25,26). The assay methods, cutoff point, true-positive, false-positive, true-negative, and false-negative of CEA or CYFRA 21-1 in each article are listed in Tables 2 and 3.

Sensitivity and Specificity of CEA or CYFRA 21-1

We identified 15 articles that assessed the sensitivity and specificity of pleural effusion CEA; the sensitivity varied from 28.8% to 82.4% and the specificity varied

Fig. 1. Sensitivity, specificity, and 95% CI of CEA.

Fig. 2. Sensitivity, specificity, and 95% CI of CYFRA 21-1.

from 76.7% to 100%. The range of sensitivity and specificity of CYFRA 21-1 of 12 articles were 21.8–90.9% and 7.7–100%, respectively. The Forrest plots with sensitivities, specificities, and their 95% CI from various studies are shown in Figs. 1 and 2. Pooled sensitivity and pooled specificity of CEA and CYFRA 21-1 were calculated by the DerSimonian Laird method (see Table 4); the entire heterogeneity test used the chi-squared test, results show that both CEA and CYFRA 21-1 have heterogeneity between each test ($P < 0.05$).

TABLE 4. Pooled sensitivity, pooled specificity, and chi-squared value of CEA and CYFRA 21-1

	Pooled sensitivity (95% CI)	χ^2 value (P value)	Pooled specificity (95% CI)	χ^2 value (P value)
CEA	45.9% (43.2–48.5)	152.10 (0.000)	97.0% (96.0–97.8)	71.53 (0.000)
CYFRA 21-1	47.3% (44.0–50.6)	201.12 (0.000)	91.8% (89.5–93.7)	135.52 (0.000)

Threshold Effect

Computation of Spearman correlation coefficient (ρ) was between the logit of sensitivity and logit of

1–specificity. ρ of CEA and CYFRA 21-1 are 0.268 and 0.644, respectively; both have a positive correlation, which suggests a threshold effect (6).

Possible Sources of Heterogeneity

Possible sources of heterogeneity across the studies were explored using meta-regression analysis with the following covariants as predictor variables: study design, patient collection, blinding, assay method, and study size. Results are shown in Table 5, covariants of assay method had highest dOR in CEA and CYFRA 21-1, which suggest that various assay methods are probably the sources of heterogeneity for CEA and CYFRA 21-1 in PE.

SROC and AUC

Figures 3 and 4 present the SROC of CEA and CYFRA 21-1. Owing to the significant heterogeneity of sensitivity and specificity, an asymmetrical SROC curve was used for pooling. The AUC of CEA and CYFRA 21-1 are 0.7691 and 0.8213, respectively. Z test shows that the z value is 0.45 ($P>0.05$), which suggests that the

AUC of CEA and CYFRA 21-1 had no statistical significance.

DISCUSSION

Etiological diagnosis of PE is still a common problem in clinical practice. Usually, the first diagnostic step of differential diagnosis of PE is to examine the pleural fluid obtained by thoracenteses. If cancer cells are found in the pleural fluid, the diagnosis of malignancy is established. However, if a malignancy is suspected and the pleural fluid cytology is negative, as usually occurs in 50% of cases, the clinical management is controversial. Since thoracenteses is still a simple and safe procedure , more and more investigations have focused on the detection and use of reliable tumor markers as an alternative; however, the results have been inconclusive.

The most widely studied and recommended tumor marker is CEA. CEA is a glycoprotein component of the glycocalyx of the endodermic epithelium, which is present to a high degree in a wide variety of tumors. It has been suggested that decreased lymphatic drainage due to the obstruction of the lymphatics by malignant cells and pleural invasion may increase pleural fluid CEA levels (13). Lee et al. (25) suggested that CEA has a good performance at diagnosis of malignant PE; the sensitivity and specificity are 68% and 93%, respectively. But some studies did not recommend PE CEA as

TABLE 5. dOR of covariants in metaregression

	CEA	CYFRA 21-1
Study design	1.02	0.37
Patients collection	0.43	0.33
Blinding	0.80	0.98
Assay method	2.60	2.32
Study size	1.00	1.00

Fig. 3. SROC and AUC of CYFRA 21-1.

Fig. 4. SROC and AUC of CEA.

a differential diagnosis method, because of its low sensitivity (29%) (22). CYFRA 21-1, soluble fragments of cytokeratin 19, is expressed by all histologic types of lung cancer, especially squamous lung cancer (14). The higher levels of CYFRA 21-1 in the effusion may also be due to impaired lymphatic drainage or pleural seeding of the tumor. Since 50% of malignant PE is caused by lung cancer and most advanced stage patients of lung cancer will have malignant PE, some experts suggest CYFRA 21-1 may be a promising tumor marker in this field. This opinion is also supported by several studies (17,18). However, like CEA, CYFRA 21-1 also has various performances in different studies. Porcel JM et al. (28) reported that in all 416 PE patients, the sensitivity of CYFRA 21-1 was only 22% when specificity was at 100%. Furthermore, when CEA was compared with CYFRA 21-1, some studies even came to the opposite conclusion (8,13,14,18,22,25,26).

Although there are numerous studies focusing on the diagnostic value of pleural fluid CEA or CYFRA 21-1, most of them only have limited study size, and it is difficult to get a compelling conclusion. To our knowledge, this study it is the first time a meta-analysis has been used to synthesis various studies data to get a convincing answer toward the question of whether CEA or CYFRA is useful for diagnosis of malignant PE.

In our study, we used the Spearman correlation coefficient to analyze the threshold effect, and both CEA and CYFRA 21-1 had positive correlations, which

suggested a potential threshold effect. Then chi-squared test and metaregression were used to explore the overall heterogeneity and the possible sources of heterogeneity, which may include variation in study design, patient collection, blinding, assay method, study size, etc. between each study; results showed that both CEA and CYFRA 21-1 had significant heterogeneity, and the main sources of it may be from various assay methods. Unlike other diagnostic meta-analyses, our study uses SROC curve instead of pooled sensitivity or pooled specificity to assess the diagnostic value of CEA or CYFRA 21-1. Because pooled sensitivity or pooled specificity is usually used in the homogeneity study, it is difficult to get an overall summary of test performance or a global measure of overall test accuracy. In our study, both CEA and CYFRA 21-1 showed significant heterogeneity, so it is not suitable for use for pooled sensitivity or pooled specificity. Besides, even when we used pooled sensitivity and pooled specificity, we found that, compared with CYFRA 21-1, CEA had high specificity but lower sensitivity, so it was still difficult to draw a definite conclusion.

The SROC curve has been recommended to represent the performance of a diagnostic test, based on data from meta-analysis, and the area under the SROC curve (AUC) is not only useful to summarize the curve, but also quite robust to heterogeneity (29, 30). A study (31) showed that to demonstrate excellent accuracy, the AUC should be in the region of 0.97 or above. An AUC of 0.93 to 0.96 is very good; 0.75 to 0.92 is good. An

AUC less than 0.75 can still be reasonable, but the test has obvious deficiencies in its diagnostic accuracy. In our study, the AUC of CEA and CYFRA 21-1 were 0.7691 and 0.8213, respectively, which was between 0.75 and 0.92. This result showed that both pleural fluid CEA and CYFRA 21-1 have good accuracy in terms of differential diagnosis of PE. But when using the Z test, it showed that the AUC of CEA and CYFRA 21-1 had no statistical significance, which indicated that although the AUC of CYFRA 21-1 was higher than CEA, yet compared with CEA, CYFRA 21-1 had no advantage in terms of diagnosis of malignant PE.

Some limitations in our analysis need to be appreciated. First, we did not search for unpublished data, which probably caused publication bias. Second, because in clinical practice, malignant PE are caused by different cancers, the combination of several tumor markers in the pleural fluid may be helpful as a complementary tools in the differential diagnosis of PE. But up to now, the relevant studies concerning the combination of tumor marks are not enough to do a meta-analysis.

CONCLUSION

In patients with pleural effusion, both pleural fluid CEA and CYFRA 21-1 were useful noninvasive methods to diagnose malignant PE. When compared with CEA, CYFRA 21-1 had no advantage.

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