CEA and ADA in Pleural Fluid for Differential Malignant Pleural Effusion and Tuberculous Pleural Effusion

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Research Article

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Abstract

Objective This study aimed to establish a predictive model based on the clinical manifestations and laboratory findings in pleural fluid of patients with pleural effusion for the differential diagnosis of malignant pleural effusion (MPE) and tuberculous pleural effusion (TPE).

Methods Clinical data and laboratory indices of pleural fluid were collected from patients with malignant pleural effusion and tuberculous pleural effusion in Zigong First People's Hospital between January 2019 and June 2020 and were compared between the two groups. Independent risk factors or Independent protective factors for malignant pleural effusion were investigated using multivariable logistic regression analysis. Receiver operating characteristic curve (ROC) analysis was performed to assess the diagnostic performance of factors with independent effects, and combined diagnostic models were established based on two or more factors with independence effect. ROC curve was used to evaluate the diagnostic ability of each model, and the fit of the each model was measured using Hosmer-Lemeshow goodness-of-fit test.

Results Patients with MPE were older than those with TPE, the rate of fever of patients with MPE was lower than that of patients with TPE, and these differences were statistically significant ($p < 0.05$). Carcinoembryonic antigen (CEA), neuron-specific enolase (NSE), cytokeratin-19 fragment antigen (CYFRA21-1), cancer antigen 125 (CA125), and glucose (GLU) levels in the pleural fluid were higher, but total protein (TP), albumin (ALB) and Adenosine deaminase (ADA) levels in the pleural fluid were lower in MPE patients than in TPE patients, and the differences were statistically significant ($P < 0.05$). In multivariate logistic regression analysis, CEA and NSE levels in the pleural fluid were independent risk factors for MPE, whereas ADA levels in pleural fluid and fever were independent protective factors for MPE. The differential diagnostic value of pleural fluid CEA and pleural fluid ADA for MPE and TPE were higher than that of pleural fluid NSE [$p < 0.05$] and the area under the ROC curve was 0.901, 0.892, and 0.601, respectively. Four different binary logistic diagnostic models were established based on pleural fluid CEA combined with pleural fluid NSE, pleural fluid ADA or (and) fever. Among them, the model established with the combination of pleural fluid CEA and pleural fluid ADA ($\text{logit}(P) = 0.513 + 0.457 \times \text{CEA} - 0.101 \times \text{ADA}$) had the highest diagnostic value for malignant pleural effusion, and its predictive accuracy was high with an area under the ROC curve of 0.968 [95% confidence interval (0.947, 0.988)]. But the diagnostic efficacy of the diagnostic model could not be improved by adding pleural fluid NSE and fever.

Conclusion The model established with the combination of CEA and ADA in the pleural fluid has a high differential diagnostic value for malignant pleural effusion and tuberculous pleural effusion, and NSE in the pleural fluid and fever cannot improve the diagnostic efficacy of the diagnostic model.

Background

Cancer is the leading killer that threatens human health. In most countries, cancer is ranked first or second in the list of causes of death^[1]. Among them, lung cancer is the malignancy with the highest mortality rate in the world^[2], and malignant pleural effusion is a common complication of advanced lung cancer. Malignant pleural effusions often indicate a poor prognosis for patients, and the median survival of patients with untreated malignant pleural effusions is only 4 months^[3]. Early and correct diagnosis of malignant pleural effusion is of great value for the selection of clinical treatment strategies and the improvement of patients' survival quality. Given that the primary diseases of malignant pleural effusion and tuberculous pleural effusion are both wasting diseases and patients mostly have weight loss and dyspnea, their differential diagnosis is extremely challenging for clinicians. Currently, the differential diagnostic techniques for both are limited. The diagnosis of malignant pleural effusion is based on pleural effusion cytology and pleural biopsy as the gold standard. But there are disadvantages such as low sensitivity, invasiveness, and heavy reliance on the diagnostic experience of pathologists^[4]. While the Mycobacterium tuberculosis culture technique, as the gold standard for the diagnosis of tuberculous pleural effusion, suffers from a low positivity rate and long culture time. Therefore, we analyzed the clinical manifestations and laboratory findings of pleural effusions in patients with malignant pleural effusions and tuberculous pleural effusions. It is proposed to screen the differential diagnostic biomarkers or models of both and improve the differential diagnosis of malignant pleural effusion and tuberculous pleural effusion.

1. Materials And Methods

1.1 Research subjects

According to the inclusion and exclusion criteria, clinical data and laboratory findings of patients who underwent pleurodesis in Zigong First People's Hospital from January 2019 to June 2020 were collected. Clinical data included gender, age, smoking, alcohol consumption, fever, and clinical diagnosis. Laboratory indicators included CEA, NSE, CYFRA21-1, CA125, TP, chloride ion (CL), GLU, ALB, ADA, and lactic dehydrogenase (LDH) in pleural effusion. Inclusion criteria were: patients with a clear diagnosis of tuberculous pleural effusion or malignant pleural effusion. Exclusion criteria were: (1) patients with incomplete clinical data or laboratory indicators; (2) patients who had received anti-tuberculosis treatment or anti-tumor therapy.

1.2 Instruments and reagents

CEA, NSE, and CA125 levels in pleural effusion were measured using a chemiluminescence immunoassay on a Diasorin Liaison® XL automated immunoassay analyzer (Diasorin S.p. A, Saluggia, Italy), and the test reagents were Liaison matching products. CYFRA21-1 in pleural effusion was measured using a chemiluminescence immunoassay on a Mindray CL6000i automated immunoassay analyzer (Mindray Medical International Ltd.), the test reagents were Mindray matching products. TP, CL, GLU, ALB, ADA, LDH in pleural effusion were evaluated with an automatic biochemical analyzer (model

7600; Hitachi Ltd., Tokyo, Japan). The test kits of TP, GLU, ALB, ADA, LDH were Maccura Biotechnology products (Maccura Biotechnology Co., Ltd., China). The test reagent of CL was a Hitachi matching product.

1.3 Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics (IBM SPSS Statistics for Mac, Version 26.0. Armonk, NY, USA) Inc., Chicago, IL or Empower Stats and R project version 3.6.3 (<http://www.r-project.org/>). Normality of data was assessed using Kolmogorov-Smirnov test. Data were expressed as mean (standard deviation) if normally distributed, otherwise, as median (quartiles). Independent samples t-test or Mann-Whitney U-test was used to compare between two groups for the measures. The chi-square test was used to compare between the two groups for the count data, and the data were expressed as counts (%). Multivariate logistic regression analysis was performed to identify significant independent factors. Logistic regression was performed with independent risk (or protective) factors as independent variables and malignant pleural effusion as dependent variables to establish different diagnostic models. The Hosmer-Lemeshow test was used to test the model fit. ROC curves were used to evaluate the diagnostic efficacy of independent risk factors and diagnostic models. Comparisons between diagnostic indicators and models were performed using the diagnostic test and ROC analysis in Empower Stats.

2. Results

2.1 Clinical manifestations and laboratory tests

A total of 241 patients with pleural effusion were entered into the study according to the inclusion and exclusion criteria, including 136 patients in the malignant pleural effusion (MPE) group and 105 patients in the tuberculosis pleural effusion (TPE) group. The age of patients with malignant pleural effusion was older than that of patients with tuberculous pleural effusion, but the fever rate was the opposite, and the difference was statistically significant ($P<0.05$). Pleural fluid CEA, NSE, CYFRA21-1, CA125, and GLU levels were higher in patients with malignant pleural effusion than in patients with tuberculous pleural effusion, but pleural fluid TP, ALB, and ADA levels were lower in patients with malignant pleural effusion, with statistically significant differences ($P<0.05$) (Table 1).

Table 1

Clinical findings and laboratory results between patients with MPE and TPE

	MPE (n=136)	TPE (n=105)	<i>P</i> value
Male [number (%)]	84 (61.76%)	74 (70.48%)	0.158
Age [years, X (SD)]	67.71 (11.63)	49.09 (19.47)	0.000
Fever [number (%)]	11 (8.09%)	39 (37.14%)	0.000
Smoking [number (%)]	75 (55.15%)	52 (49.52%)	0.386
Drinking [number (%)]	31 (22.79%)	28 (26.67%)	0.488
CEA [ng/ml, M (IQR)]	35.40 (3.09,337.00)	0.80 (0.47,1.27)	0.000
NSE [µg/L, M (IQR)]	12.60 (6.67,22.32)	8.55 (5.50,16.05)	0.016
CYFRA21-1[ng/m, M (IQR)]	70.40(20.35,176.00)	20.00(11.08,38.23)	0.000
CA125 [U/ml, M (IQR)]	1000.00(750.00,1397.00)	882.00(425.00,1000)	0.005
TP [g/L, M (IQR)]	41.01(33.95,46.35)	47.10(40.87,50.30)	0.000
CL [mmol/L, M (IQR)]	106.20(102.13,108.88)	105.60(102.80,108.75)	0.996
GLU [mmol/L, M (IQR)]	6.10(5.10,7.28)	5.30(4.30,6.40)	0.002
ALB [g/L, M (IQR)]	23.40(18.84,27.90)	27.00(23.25,29.35)	0.001
ADA [U/L, M (IQR)]	8.05(6.50,10.75)	35.30(22.80,45.80)	0.000
LDH [U/L, M (IQR)]	327.50(198.25,476.25)	321.00(219.00,546.50)	0.585

2.2 Risk factors for malignant pleural effusion

A binary logistic regression (Forward; LR method) analysis was performed with sex, age, fever, CEA, NSE, CYFRA21-1, CA125, TP, GLU, ALB, and ADA as independent variables and malignant pleural effusion as the dependent variable. Fever, CEA, NSE, and ADA entered the regression variance and were independent risk factors for malignant pleural effusion (Table 2)

Table 2

Results of binary logistic regression analysis

	Partial regression coefficient	Standard error	Wald χ^2 value	odds ratio/ β value [95%CI]	<i>P</i> value
Fever	-1.952	0.872	-2.240	0.142 (0.026, 0.783)	0.025
CEA	0.519	0.190	2.732	1.670 (1.158, 2.436)	0.006
NSE	0.050	0.020	2.570	1.052 (1.012, 1.093)	0.010
ADA	-0.134	0.034	-3.906	0.875 (0.818, 0.935)	0.000

2.3 Diagnostic model and ROC curve analysis

Four dichotomous logistic diagnostic models were established for the joint diagnosis of malignant pleural effusion based on CEA in combination with NSE, ADA or (and) fever [i.e., model CEA_NSE (logit (P) = $-2.342 + 0.743 \times \text{CEA} + 0.022 \times \text{NSE}$), model CEA_ADA (logit (P) = $0.513 + 0.457 \times \text{CEA} - 0.101 \times \text{ADA}$), model CEA_NSE_ADA (logit (P) = $0.205 + 0.443 \times \text{CEA} + 0.052 \times \text{NSE} - 0.130 \times \text{ADA}$), model FEVER_ALL (logit (P) = $0.497 + 0.486 \times \text{CEA} + 0.046 \times \text{NSE} - 0.124 \times \text{ADA} - 1.549 \times (\text{FEVER}=1)$)]. The Hosmer-Lemeshow test was performed for the above four models, and the *P* values were 0.268, 0.302, 0.078, and 0.432, respectively, suggesting a good fit for all four models. The ROC curve was used to evaluate the diagnostic efficacy of CEA, NSE, ADA, and the above four models for malignant pleural effusion using the tuberculous pleural effusion group as a control (Figure 1, Table 3). Among the above models, the model CEA_ADA had the highest diagnostic value for malignant pleural effusion, and its predictive accuracy was high with an area under the ROC curve of 0.968 [95% confidence interval (0.947, 0.988)]. But the diagnostic efficacy of the diagnostic model could not be improved by adding pleural fluid NSE and fever (Figure 1, Table 3).

Table 3

Diagnostic performance of each parameter and model for identifying MPE

	AUC	AUC (95%CI)	Cut off value	Specificity	Sensitivity	PPV	NPV
CEA	0.901	(0.856, 0.945)	2.90	0.950	0.779	0.950	0.779
NSE	0.601	(0.521, 0.680)	11.10	0.647	0.564	0.674	0.534
ADA	0.892	(0.842, 0.943)	15.05	0.867	0.919	0.899	0.892
CEA_NSE	0.901	(0.853, 0.949)	0.45	0.929	0.835	0.938	0.814
CEA_ADA	0.968	(0.947, 0.988)	0.41	0.890	0.967	0.915	0.957
CEA_NSE_ADA	0.974	(0.956, 0.992)	0.42	0.882	0.963	0.915	0.957
FEVER_ALL	0.977	(0.960, 0.994)	0.36	0.894	0.973	0.922	0.962
Abbreviations: AUC: area under the curve, PPV: positive predictive value, NPV: negative predictive value.							

3. Discussion

Malignant pleural effusions and tuberculous pleural effusions are common types of clinical exudate. Malignant pleural effusion can lead to dyspnea, pain, cachexia, and decreased physical activity, and it can occur in almost all malignant diseases, especially pulmonary malignancies, which account for 1/3 of clinical cases^[5]. In contrast, tuberculous pleural effusions are mostly inflammatory exudates from tuberculous pleurisy. Both are predominantly associated with lymphocytic exudate and their differential diagnosis is challenging in clinical work. The treatment strategies and prognosis of the two are very different. Therefore, early and accurate diagnosis is crucial for the treatment of pleural effusion. In this study, a predictive model for the differential diagnosis of malignant pleural effusion and tuberculous pleural effusion was established by the clinical presentation of patients, tumor markers, and biochemical markers in the pleural effusion.

The rate of fever is significantly higher in tuberculous pleural effusion than in malignant pleural effusion. And the fever is an independent risk factor for tuberculous pleural effusion, which is consistent with a previous report^[6]. The age of patients with malignant pleural effusion is higher than that of patients with tuberculous pleural effusion. The reason for this is that most malignant pleural effusions are caused by malignant tumors metastasizing to the pleura, and aging is one of the main risk factors for malignancy^[7, 8]. The levels of tumor markers in the pleural fluid such as CEA, NSE, CYFRA21-1, and CA125 in patients with malignant pleural effusion, were higher than those in tuberculous pleural effusion, which may be

related to increased secretion of malignant tumor cells. In them, pleural fluid CEA levels were significantly higher in patients with malignant pleural effusion than in tuberculous pleural effusion, in agreement with ElSharawy, D.E et al^[9], whose area under the ROC curve for the diagnosis of malignant pleural effusion was 0.901. Pleural fluid CEA has a good diagnostic value in lung cancer-related malignant pleural effusion in the Chinese population especially^[10]. Pleural fluid glucose levels are higher in patients with malignant pleural effusions than in tuberculous pleural effusions. The reason may be that impaired Glut1 expression after CD3/CD28 stimulation in memory T lymphocytes in malignant pleural effusion leads to insufficient glucose uptake, which results in a relative increase in pleural fluid glucose levels^[11]. Pleural fluid protein levels were lower in patients with malignant pleural effusion than in patients with tuberculous pleural effusion, in agreeing with the report of Alejandra González et al^[12]. After binary multiple regression analysis, only CEA and NSE in the pleural fluid were independent risk factors for malignant pleural effusion, while ADA in pleural fluid and fever were independent protective factors for malignant pleural effusion. Among the tumor markers in pleural fluid, the diagnostic value of CEA for malignant pleural effusion was significantly higher than that of NSE, and their area under the ROC curve was 0.901 and 0.601, respectively, similar to that reported by Zhang H et al^[13]. Among the tumor markers in pleural fluid, CEA has the highest diagnostic value for malignant pleural effusion. When the CEA in pleural fluid was higher than 2.9 µg/ml, its diagnostic sensitivity for malignant pleural effusion was 77.9% and its specificity was 95.0%. CEA in pleural fluid can also be used to differentiate between malignant pleural effusions with high levels of ADA and tuberculous pleural effusions with high levels of ADA^[14]. The increased ADA levels in tuberculous pleural effusions may reflect macrophage activation downstream of CD4+ lymphocyte activation in pleural fluid^[15]. The differential diagnostic value of ADA in pleural fluid for tuberculous pleural effusion and malignant pleural effusion with an area under the ROC curve of 0.892 is comparable to that of CEA in pleural fluid. And a critical value of less than 15.05 U/L, similar to that reported by Huo Z et al^[16], but lower than 26.5 U/L reported by Chang KC et al^[17] and Dalil Roofchayee N et al^[18]. The reason may be that the incidence of tuberculosis varies from region to region or that different control populations were selected for different studies. The activity of ADA decreases with age, probably due to the lower degree of an inflammatory response to tuberculosis in older than in younger patients^[19]. The diagnostic model of CEA combined with ADA in pleural effusion has a higher diagnostic value than CEA alone for malignant pleural effusion, in agreement with Krishnan VG et al^[20]. The area under the ROC curve of the combined diagnostic model was 0.986, and the sensitivity, positive predictive value, and negative predictive value were above 90%. However, when NSE and fever were added to the model, there was no significant improvement in the diagnostic efficacy of malignant pleural effusion. When the following conditions exist: (1) patients who refuse to undergo further invasive examinations; (2) patients who cannot undergo medical thoracoscopy because of low volume or dense separation of pleural effusion. CEA combined with ADA in pleural effusion is useful for the differential diagnosis of malignant pleural effusion and tuberculous pleural effusion.

Our research had some limitations. First, this study is a single-center study, and the extrapolation of the model may have some limitations. Second, the diagnostic model in this study is based on the test index

of pleural effusion obtained by puncture, which is less practical for patients with contraindications to pleural effusion puncture.

4. Conclusion

The levels of CEA and NSE in pleural effusion are independent risk factors for malignant pleural effusion, while the levels of ADA in pleural effusion and fever are independent risk factors for tuberculous pleural effusion. The prediction model based on CEA and ADA in pleural effusion can well differentiate the diagnosis of malignant pleural effusion and tuberculous pleural effusion.

Abbreviations

MPE: malignant pleural effusion; TPE: tuberculous pleural effusion; ROC: receiver operating characteristic curve; CEA: Carcinoembryonic antigen; NSE: neuron-specific enolase; CYFRA21-1: cytokeratin-19 fragment antigen; CA125: cancer antigen 125; GLU: glucosetotal; TP: total protein; ALB: albumin; ADA: adenosine deaminase; CL: chloride ion; LDH: lactic dehydrogenase.

Declarations

Acknowledgment

None

Author's contributions

Jianhong Yu made substantial contributions to the conception and design of the manuscript.

Qirui Cai Huang made substantial contributions to the construction of the measurement protocol.

The authors read and approved the final manuscript.

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Availability of data and materials

The datasets supporting the conclusions of this article are included within the article.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Zigong First People's Hospital, China.

All participants' guardians signed an informed consent form in advance.

Consent for publication

Not applicable.

Competing interests

None declared.

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Figures

Figure 1

ROC curves of CEA, NSE, and ADA alone and in combination