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An efficient scoring model for diagnosis of tuberculous pleural effusion

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ABSTRACT

Background: Due to the low efficiency of single clinical feature or laboratory variable in the diagnosis of tuberculous pleural effusion (TBPE), The diagnosis of TBPE is still challenging. This study aimed to build an efficient scoring diagnostic model based on laboratory variables and clinical features to differentiate TBPE from non-tuberculous pleural effusion(non-TBPE).

Methods: A retrospective study of 125 patients (63 with TBPE; 62 with non-TBPE) were undertaken. Univariate analysis was used to select the laboratory and clinical variables relevant to the model composition. The statistically different variables were selected to undergo binary logistic regression. Variables B coefficients were used to define a numerical score to calculate a scoring model. A receiver operating characteristic (ROC) curve was used to calculate the best cut-off value and evaluate the performance of the model.

Results: Six variables were selected in the scoring model: Age ≤ 46 years old (4.96 point), Male (2.44 point), No cancer (3.19 point), Positive T-cell Spot (T-SPOT) results (4.69 point), Adenosine Deaminase (ADA) ≥ 24.5U/L (2.48 point), C-reactive Protein (CRP) ≥ 52.8mg/L (1.84 point). With a cut-off value of total score was 11.038 points, the sensitivity, specificity and accuracy of the scoring model was 93.7%, 96.8% and 99.2% respectively.

Conclusion: The scoring model was efficient to differentiate TBPE from non-TBPE.

KEYWORDS: Tuberculosis; Pleural effusion; Tuberculous pleural effusion; Scoring model

Introduction

Tuberculosis (TB) affects about nine million people and 1.5 million deaths worldwide every year [1]. In 2016, tuberculosis claimed 1.3 million lives among HIV-negative people, exceeding the total number of deaths caused by HIV and becoming the first killer among infectious diseases [2]. On Sep 26, 2018, all UN Member States promised to end the global tuberculosis epidemic by 2030 in the UN General Assembly High Level meeting [3]. Currently, pleural tuberculosis (PT) has been a most common type of extrapulmonary tuberculosis, and its frequency of all TB varies greatly in different countries. PT accounts for more than 20% of all TB cases in Africa [4, 5], 6.5 to 8.7% in China [6, 7], 8.7% in Brazil [8], and 3.7% in the United States [9]. PT appears to be the main cause of pleural effusion (PE) in countries with a high prevalence of tuberculosis (e.g. in India) [10].

Tuberculous pleural effusion (TBPE) accounts for about 40% of PE cases in China [11, 12]. For patients with TBPE, untimely anti-tuberculosis treatment will affect its prognosis. The diagnostic criteria of TBPE is dependent on bacteria culture and histopathology, but the diagnostic sensitivity is limited and time consuming. Thoracoscopic Pleural Biopsy is an effective method in the diagnosis of TBPE, but its application is limited because of its invasiveness, complexity and technical difficulty

[5, 13, 14]. Moreover, the diagnostic value of single clinical biomarker of TBPE is limited, including erythrocyte sedimentation rate (ESR), blood T-cell spot (T-SPOT), adenosine deaminase (ADA) and lymphocyte ratio, so the diagnosis of TBPE is still challenging. Thus, our study aimed to build an efficient scoring diagnostic model based on laboratory variables and clinical features to differentiate TBPE from non-TBPE.

Methods

Study subjects

A retrospective study was conducted in the period 2016–2021 after approval by the Ethics Committee of Dongguan People's Hospital. All the enrolled patients met the indications of thoracic puncture or thoracoscopic pleural biopsy and signed the informed contents. The patients selected in the study should meet the following criteria: (1) Adult group; (2) Presence of PE on chest radiographs and ultrasonography; (3) Complete data in clinical were available for all patients. Finally, a total of 125 PE patients were included in this study.

Diagnostic Criteria

TBPE diagnosis was confirmed when PE met at least one of the following criteria: (1) pleural fluid/sputum/bronchial aspirate/bronchoscopic brushing specimen were positive for acid-fast bacilli or positive culture or positive polymerase chain reaction (PCR) for Mycobacterium tuberculosis. (2) Positive acid-fast staining or epithelioid caseous granuloma in pleural or lung tissue [15-17].

Malignant Pleural Effusion (MPE) was diagnosed when pleural histopathology demonstrated malignant lesions or when cytological examination of pleural effusion demonstrated malignant cells.

Empyema cases with negative M. tuberculosis culture were confirmed according to ATS guidelines [18]. Parapneumonic effusion (PPE) was caused by pneumonia which was confirmed based on the criteria of the American Thoracic Society (ATS) [19]. Thoracoscopic pleural biopsy was performed in patients with unknown etiology of PE. Except for the cases with TBPE, all the other cases were classified as non-TBPE group.

All patients underwent a standard thoracocentesis procedure to collect pleural effusion samples and blood was collected by venupuncture before intervention procedures. Record items include: sex, age, clinical symptoms (cough, fever, chest pain, night sweats), T-SPOT, ESR, C-reactive protein (CRP), PE lymphocyte ratio, PE protein, PE lactate dehydrogenase (LDH), ADA, PE location, presence of cancer or not. Patients who had incomplete data were excluded in this study. the statistical analysis was performed using the data from the first pleural fluid sample before treatment. Hematological data were collected from the blood samples taken nearest to the first thoracentesis.

T-SPOT TB test was measured using Enzyme-Linked Immunospot (T-SPOT TB assay kit, Oxford Immunotec Co., Ltd., Abingdon, UK). Pleural effusion protein was measured using Colorimetric Determination (Dry tablets assay kit, Ortho-Clinical Diagnostics Co., Ltd., New York, USA). The activity of ADA was measured using peroxidase assay (ADA assay kit, Beijing Leadman Biochemistry Co., Ltd., Beijing,

China). LDH levels were measured using the lactic acid substrate method (LDH assay kit, Beckman Coulter Laboratory Systems Co., Ltd., Suzhou, China). CRP level was measured using Quantitative Immunofluorescence method (Boditech Biotechnology Co., Ltd., Guangxi, China). ESR was measured using an Italian Microsed-System Automatic Blood Sedimentation Instrument. Differential cell counts in PE were counted manually.

Statistical analysis

The analyses were carried out using SPSS 22.0 software (SPSS Inc., Chicago, IL, USA). Continuous data are reported as median, with first and third quartiles. Mann–Whitney U test was used for comparisons between groups. Chi-square test was used for the analysis of categorical variables. The results with p values less than 0.05 were considered as statistical significance. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy and Youden index were calculated to estimate the diagnostic performance of the indicators. In addition, receiver operating characteristic (ROC) curve was plotted to evaluate the diagnostic value of continuous data for TBPE, and the continuous variable was converted into a binary variable according to the cut-off value corresponding to the maximum value of the Youden Index. The factors with statistically significant differences between the two groups were selected in the binary logistic regression. A goodness-of-fit test of the binary logistic regression model was evaluated by Hosmer and Lemeshow test. Variables B coefficients were used to define a numerical score to calculate a scoring

model. A receiver operating characteristic (ROC) curve was used to calculate the best cut-off value and evaluate the performance of the scoring model.

Results

Clinical and laboratory findings of the 125 patients with PE

In this study, a total of 125 patients (63 with TBPE; 62 with non-TBPE) were enrolled according to the selection criteria. The demographic and clinical characteristics were collected from the patient's medical records and summarized in **Table 1**. It was no significant difference between two groups in cough, chest pain, night sweats, pleural fluid protein and LDH ($p > 0.05$), But there were significant differences among age, male, cancer diagnosis, pleural fluid location, fever, ESR, CRP, T-SPOT, pleural fluid lymphocyte ratio and ADA ($p < 0.05$). The mean age of TBPE group was lower than that of non-TBPE group. TBPE predominated in men (46/63, 73.0%) who with unilateral pleural effusion (62/63, 98.4%). MPE accounts for most of the non-TBPE (43/62, 69.4%). The proportion of fever, positive T-SPOT and the mean values of ESR, CRP, pleural fluid lymphocyte ratio, ADA in patients with TBPE was higher than that of patients with non-TBPE.

The diagnostic performance of single indicator for TBPE

ROC curve was used to evaluate the diagnostic value of continuous data (**Figure 1A and 1B**), and the continuous variable was converted into a binary variable according to the cut-off value corresponding to the maximum value of the Youden Index (**Table**

133 **2**). The diagnostic performance, including Sensitivity, Specificity, Positive predictive
134 value (PPV), Negative predictive value (NPV) and Accuracy, were calculated and
135 summarized in **Table 3**.
136
137 ***The multivariate logistic regression of binary variables and the establishment of the***
138 ***scoring model***
139 The factors with statistically significant differences between two groups were
140 selected in the logistic regression, using forward selection method to select indicators
141 to enter the final model. At last, ESR≥27.5 mm/h, fever, lymphocyte ratio≥91.5%,
142 unilateral pleural effusion was eliminated by the model, And age≤46.5 years, male, no
143 cancer, positive T-SPOT, CRP≥52.8 mg/L, ADA≥24.5 U/L were accepted into the final
144 binary logistic regression model. Hosmer and Lemeshow test Confirmed a good
145 goodness-of-fit test of the binary logistic regression model(P=0.499). Variables B
146 coefficients were used to define a numerical score to calculate a scoring model (table4).
147
148 ***The diagnostic performance of scoring model***
149 The total score is equal to the sum of the score of the Variables in **Table 4** when
150 matching the scoring criteria. The calculation equation as follow: Y (total score) =Age
151 score +Gender score +Cancer score +T-SPOT score +CRP score +ADA score. ROC
152 curve was used to calculate the best cut-off value. When total score≥11.038, The area
153 under the curve (AUC) value was 0.992 (95%CI: 0.982–1.000) (**figure 2**). The
154 performance of the total scoring model for diagnosis TBPE were Summarized in **table**

5.

Discussion

There are many causes of pleural effusion. Since the high prevalence of TB was occurred in China, TBPE accounts for about 40% of pleural effusion [11, 12]. Currently, the diagnostic performance of clinical feature or laboratory variable in diagnosing TBPE was poor, therefore it's urgent need to find a new method to diagnose TBPE. Our study had built an efficient scoring diagnostic model by using logistic regression based on laboratory variables and clinical features to differentiate TBPE from non-TBPE.

A total of 15 indicators were included in this study. There were no any symptoms were introduced into the final binary logistic regression model, which shows that clinical symptoms had no significant diagnosis value to the TBPE. And the results was similar to the previously reported data [20]. In terms of pleural effusion tests, unilateral pleural effusion, pleural effusion protein, LDH, and pleural effusion lymphocytes ratio ultimately failed to enter the final model, and it may due to TBPE and MPE are dominated by unilateral lymphocytic exudates [21], and most of the PE in this study were MPE. ESR, a non-specific indicator for the diagnosis of TBPE, as expected, was eventually eliminated by the regression model, even though there was difference in univariate analysis between two groups.

Finally, six indicators of age, sex, cancer, CRP, T-SPOT and ADA were included in the diagnostic scoring model by multivariate binary logistics regression, which showed that those six indicators made a great contribution to the diagnosis. In terms of

age, the non-TBPE group was significantly older than the TBPE group, which may attribute to the elderly-onset of cancer that was the main causes of non-TBPE. Our result showed that TBPE predominated in men (46/63; 73.0%), while MPE predominated in females (37/62; 59.6%), and it was similar to the previously reported data of Roberta et al [21]. Consistent with the previously studies [22], we also demonstrated the potential diagnostic value of CRP for TBPE. The sensitivity and specificity of ADA, had a good diagnostic performance in diagnosis of TBPE, were above 90% in diagnosing TBPE, and T-SPOT also showed a good diagnostic value for the diagnosis of TBPE that the sensitivity and specificity were 93.7% and 77.4% respectively. Above results were similar to the previous studies [20, 23, 24].

Hosmer and Lemeshow test confirmed a good goodness-of-fit test of the binary logistic regression model (p = 0.499). The performance of the scoring model for diagnosis TBPE were evaluated by ROC cure, when total score ≥ 11.038, the AUC value was 0.992 (95%CI: 0.982–1.000), the sensitivity, specificity, PPV, NPV were 93.7%, 96.8%, 100% and 93.9% respectively, the diagnostic performance of the scoring model was better than the reported data of Petborom et al [20, 25]. Our scoring model can aid to diagnosis TBPE and provide more evidence for anti-tuberculosis treatment, but we need to track the effect of treatment to verify the accuracy of the diagnostic model follow-up. When anti-tuberculosis treatment is ineffective, a thoracoscopic pleural biopsy should be used to further confirm the diagnosis. For medical units with limited sanitary conditions, the diagnostic model can help to find TBPE, so that patients can be referred to specialist hospitals for earlier treatment.

The retrospective study has the selection bias, for example, patients with incomplete data were excluded from the study which leading to a reduction in the number of cases. Some test indicators, such as cytokines, CD4 and CD8 were not included in our study because of the small number of people tested. Therefore, the establishment of a better TBPE diagnostic scoring model requires a prospective study, multi-center study to achieve.

Conclusions

The diagnostic score model established by logistic regression combined with multiple indicators improves diagnostic performance. It is significantly higher than a single index of laboratory variables or clinical features in diagnosing TBPE. In brief, establishing a scoring model for the diagnosis of TBPE provide a more economical, effective, and faster diagnostic method based on routine clinical data to assist clinicians in making better clinical decisions.

Abbreviations

TB: Tuberculosis; TBPE: Tuberculous Pleural Effusion; ROC: Receiver Operating Characteristic; T-SPOT: T-cell Spot; ADA: Adenosine Deaminase; CRP: C-reactive Protein; PT: Pleural Tuberculosis; PE: pleural effusion; ESR: Erythrocyte Sedimentation Rate; LDH: Lactate Dehydrogenase; PPV: Positive Predictive Value; NPV: Negative Predictive Value.

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Authors' contributions

All listed authors meet the requirements for authorship. SW, HW and PZ conceived and designed the study. SL, NF and WM collected clinical information. SW, SL and NF analyzed the data. SW wrote the manuscript. All authors critically reviewed and approved the final manuscript.

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Availability of data and materials

Most of the data was included in the submission. The more details of the data were available from the corresponding authors on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Dongguan People's Hospital, and the institutional review board approved a waiver of patient informed consent.

Consent for publication

Not applicable.

Competing interests

No potential conflict of interest was reported by the authors.

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Table 1. Clinical and laboratory findings of the 125 patients with PE

	Total(n=125)	TBPE (n=63)	Non-TBPE(n=62)	p Value
Age(years)	58.0(38.0-70.5)	42.0(29.0-65.0)	67.0(53.0-74.0)	0.000
Male	71(56.8%)	46(73.0%)	25(40.3%)	0.000
Cancer	44(35.2%)	1(1.6%)	43(69.4%)	0.000
Unilateral PE	116(92.8%)	62(98.4%)	54(87.1%)	0.017
Cough	101(80.8%)	52(82.5%)	49(79.0%)	0.656
Fever	41(32.8%)	33(52.4%)	8(12.9%)	0.000
Chest pain	50(40.0%)	30(47.6%)	20(32.3%)	0.080
Night sweats	4(3.2%)	3(4.8%)	1(1.6%)	0.619
In blood:				
ESR (mm/h)	35.0(21.5-56.0)	40.0(28.0-60.0)	30.0(12.0-45.7)	0.031
CRP (mg/L)	36.1(13.2-90.8)	76.5(30.1-131.3)	18.1(8.4-41.0)	0.000
T-SPOT	73(58.4%)	59(93.7%)	14(22.6%)	0.000
In PE:				
L%	90(77.5-96.0)	93.0(84.0-98.0)	85.0(67.7-94.0)	0.000
Protein(g/L)	64.7(53.0-79.6)	69.5(58.5-81.6)	61.7(50.4-77.5)	0.063
ADA(U/L)	26.7(8.6-41.7)	40.9(33.6-49.3)	9.5(7.1-12.9)	0.000
LDH(U/L)	306.2(216.2-571.4)	415.1(262.0-610.7)	269.4(207.7-392.9)	0.299

Note: Data in the table are expressed either as a frequency (percentage) or a median (interquartile range); PE: pleural effusion; TBPE: tuberculous pleural effusion; non-TBPE: non-tuberculous pleural effusion; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; T-SPOT: T-cell spot; L%: lymphocyte ratio; ADA: adenosine deaminase.

Table 2. Youden Index and cut-off value of continuous data

	Youden Index	cut-off value
Age (years)	0.443	46.5
ESR (mm/h)	0.23	27.5
CRP (mg/L)	0.457	52.8
L%	0.264	91.5
ADA (U/L)	0.856	24.5

Note: ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; L%: lymphocyte ratio; ADA: adenosine deaminase.

Table 3. The diagnostic performance of single indicator for TBPE

	Sensitivity	Specificity	PPV	NPV	Accuracy
Age≤46.5 years	0.556	0.887	0.833	0.663	0.720
Male	0.730	0.597	0.648	0.685	0.664
No cancer	0.984	0.694	0.765	0.977	0.840
Fever	0.524	0.871	0.805	0.643	0.696
Unilateral PE	0.984	0.129	0.534	0.889	0.560
Positive T-SPOT	0.937	0.774	0.808	0.923	0.856
ESR≥27.5 mm/h	0.762	0.468	0.593	0.659	0.616
CRP≥52.8 mg/L	0.651	0.806	0.774	0.694	0.728
L%≥91.5%	0.603	0.661	0.644	0.621	0.632
ADA≥24.5 U/L	0.937	0.919	0.922	0.934	0.928

Note: PPV: positive predictive value; NPV: negative predictive value; PE: pleural effusion; T-SPOT: T-cell spot; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; L%: lymphocyte ratio; ADA: adenosine deaminase.

Table 4. Score for diagnosis based on the B coefficient of the variables

Variable	Scoring criteria	B coefficient	Score
Age	Age≤46.5years	4.96	4.96
Gender	Male	2.44	2.44
Cancer	No cancer	3.19	3.19
T-SPOT	Positive T-SPOT	4.69	4.69
CRP	CRP≥52.8mg/L	1.84	1.84
ADA	ADA≥24.5U/L	2.48	2.48

Note: T-SPOT: T-cell spot; CRP: C-reactive protein; ADA: adenosine deaminase.

Table 5. The performance of scoring model

	Scoring model
cut-off value	≥11.038
Youden Index	0.905
Sensitivity	0.937
Specificity	0.968
Accuracy	0.992
PPV	1.000
NPV	0.939

Note: PPV: positive predictive value; NPV: negative predictive value.

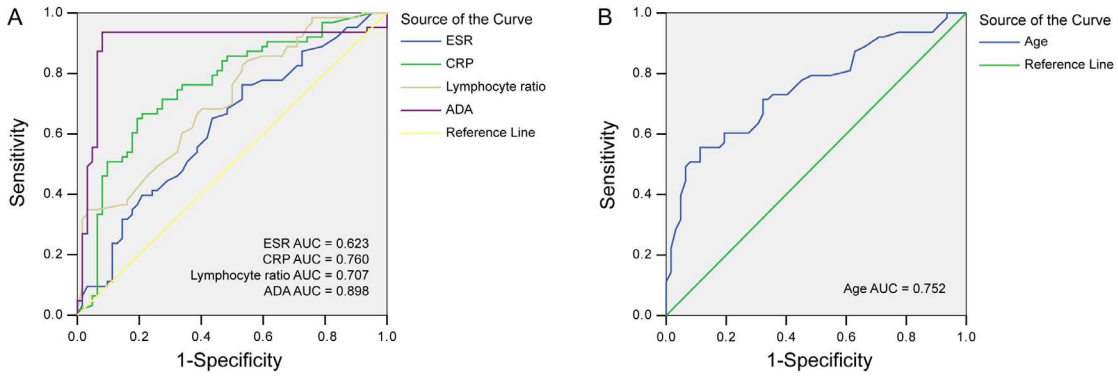

Figure 1. The diagnostic value for TBPE. (A) The diagnostic value of ESR, CRP, Lymphocyte ratio and ADA for TBPE, the AUC value was 0.623, 0.760, 0.707 and 0.898 respectively; AUC: area under the curve. (B) The diagnostic value of Age for TBPE, the AUC value was 0.752.

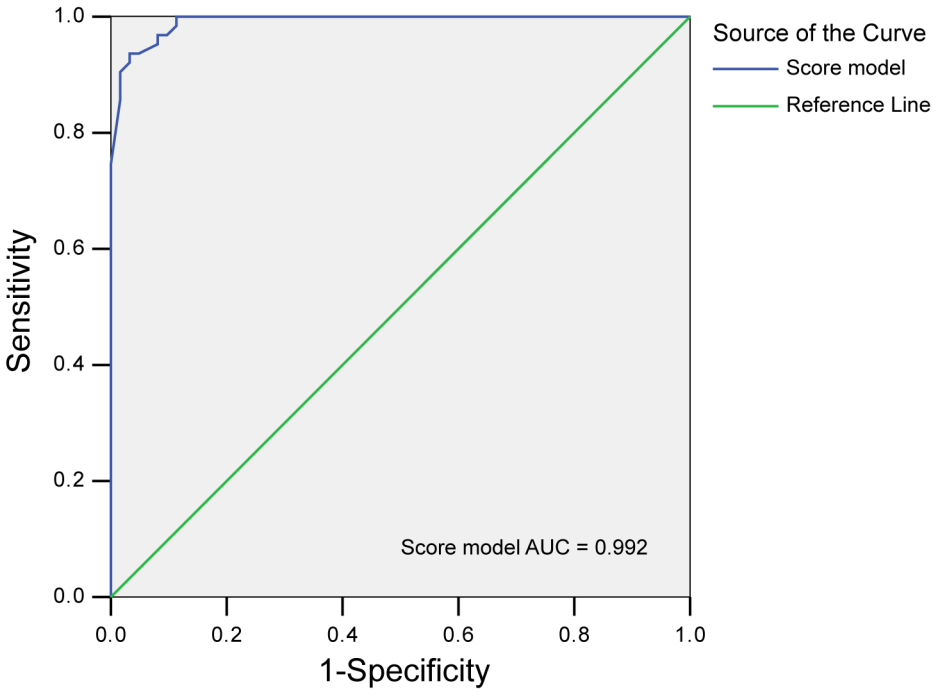

Figure 2. The diagnostic value of Scoring model for TBPE. The AUC value was 0.992; AUC: area under the curve.