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Diagnostic Value of TB-IGRA, PPD, TB-DNA-PCR and ADA in Tuberculous Pleural Effusion

Weijia Lin[1*], Zhi Liu[2], Yaping Zhang[1], Yanan Yu[1], Yang Liu[1], Ping Feng[1], Feng Li[1], Zhihua Zhang[1#]

[1]Department of Respiratory Medicine, The First Affiliated Hospital of Hebei North University, Zhangjiakou, China
[2]Department of Orthopaedics, The First Affiliated Hospital of Hebei North University, Zhangjiakou, China
Email: lwj1987lu@163.com, [#]ZZH19641229@163.com

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Abstract

Objective: To investigate the clinical diagnostic value of TB-IGRA (Tuberculosis-Interferon Gamma Release Assay), PPD (Intradermal Tuberculin Test), TB-DNA-PCR (Tuberculosis-Deoxyribonucleic-Polymerase Chain Reaction) and ADA(Adenosine Aeaminase) in tuberculous pleural effusion. **Methods:** 60 patients with tuberculous pleural effusion discharged from our department from January 1, 2018 to December 31, 2019 were selected. Moreover, the TB-IGRA in peripheral blood, PPD test, TB-DNA-PCR and ADA in pleural effusion were detected. Subsequently, the positive rate, negative rate, sensitivity and omission diagnostic rate of TB-IGRA, PPD, TB-DNA-PCR, ADA and combined TB-IGRA were calculated. **Results:** The positive rate and sensitivity of TB-IGRA, PPD, TB-DNA-PCR, and ADA were 95%, 71.67%, 5% and 86.67% respectively. The omission diagnostic rate was 5%, 28.33%, 95% and 13.33%. TB-IGRA showed the highest positive rate and sensitivity, and TB-DNA-PCR represented the highest omission diagnostic rate. The sensitivity of TB-IGRA + PPD was 98.33%, while the omission diagnostic rate was 51.67%. The sensitivity of TB-IGRA + TB-DNA-PCR was 95%, while the omission diagnostic rate was 5%. The sensitivity of TB-IGRA + ADA was 100%, while the omission diagnostic rate was 0%. In addition, the TB-IGRA + ADA had the highest sensitivity and the lowest omission diagnostic rate. **Conclusion:** TB-IGRA has high positive rate, high sensitivity and low omission diagnostic rate, which is superior to the traditional sputum test for tuberculosis. Notably, the combination of PPD, TB-DNA-PCR, ADA is capable of improving the diagnosis rate, and the diagnosis rate can reach 100% when combined with ADA, which is able to provide solid diagnostic value in clinical practice.

Keywords

TB-IGRA, PPD, TB-DNA-PCR, ADA, Diagnosis

*First author.
#Corresponding author.

1. Introduction

Pleural effusion is one of the common clinical diseases. In 2007, a multicenter investigation in the United States has revealed that the number of patients with pleural effusion is 1.5 million every year. Congestive heart failure is the most common cause, followed by parapneumonic pleural effusion and malignant pleural effusion. In the prospective single center clinical study among the British population by Walker *et al.* [1], infection and heart failure are the most common causes of nonmalignant pleural effusion. Moreover, according to the Taghizadeh *et al.* [2] retrospective analysis of the patient information in the national inpatient sampling (NIS) database system of the United States, malignant pleural effusion has been considered as a common and expensive disease in the United States. However, the overall data analysis of pleural effusion etiology, diagnosis and treatment, disease load in other countries is relatively less. In 2017, Beijing Chaoyang Hospital [3] conducted a retrospective single center clinical study on the Etiological Distribution of pleural effusion, involving a total of 1541 patients. The results revealed that the bacterial infection, malignant tumor, cardiac insufficiency and tuberculosis were the most common causes. In addition, the Mi yun teaching hospital of Capital Medical University [4] analyzed the etiology of 67 patients admitted with unilateral pleural effusion from January 2016 to December 2017, including 24 cases of tuberculous pleurisy, 11 cases of cardiac insufficiency, 18 cases of malignant pleural effusion, 3 cases of renal insufficiency and 11 cases of pneumonia. Tuberculosis and pneumonia are the main causes in developing countries [5], it found that the most common causes in developed countries are cardiac insufficiency, pneumonia and malignant tumor. As we all know, Zhangjiakou is a poor mountain area with a high incidence rate of tuberculous pleurisy, the phenomenon of returning to poverty due to illness is very common, therefore, early diagnosis plays a conducive role in early treatment with improving the cure rate, reducing the patients and social economic burden. Large data samples suggested that TB-IGRA had high sensitivity, accuracy and specificity in tuberculous pleural. However, since the traditional PPD, TB-DNA-PCR, ADA detection methods are low in sensitivity, it is urgent to find faster methods with higher sensitive, specific for diagnostic of tuberculous pleural.

2. Materials and Methods

2.1. Materials

From January 1, 2018 to December 31, 2019，60 discharged cases with tuberculous pleural effusion were selected.

2.2. Inclusion and Exclusion Criteria

Inclusion criteria: 1) discharge time: January 1, 2018 to December 31, 2019; 2) Length of hospitalization: > 24 hours; 3) The patient age: ≥ 18 years old; 4) Discharge diagnosis: Tuberculous pleurisy.

Exclusion criteria: 1) No pleural effusion confirmed by imaging; 2) Patients

discharged within 24 hours; 3) For those who were hospitalized repeatedly due to pleural effusion, only the data of the first hospitalization in this year were collected; 4) Discharge diagnosis was non tuberculous pleurisy.

3. Methods

All patients were tested by four detection methods of tuberculosis: TB-IGRA, PPD, TB-DNA-PCR and ADA.

3.1. TB-IGRA

In the morning, 6 to 10 mL of fasting peripheral venous blood was extracted under anticoagulation with heparin, meanwhile, the peripheral monocytes were isolated. In the four wells (blank control, test well A, test well B and positive control) of the microplate, 50 μL cell culture medium, ESAT-6 (antigen A), CFP-10 (antigen B), positive quality control solution, and then each well was added with 100 μL samples, all the wells were incubated in incubator. The microplate was washed with PBS, and then the enzyme labeled antibody was added into the microplate. Then the microplate was washed, and substrate reaction solution was added into the microplate. ELISPOT reader was used to read and count the number of spots, and the result was evaluated by following the instructions of the kit strictly. If the number of negative spots is ranged from 0 to 5, and the spots number of antigen A or antigen B test wells minus the spots number of negative wells is greater than 6, it will be considered as positive results. While, if the number of negative spots is more than 6, the number of test spots must be more than 2 times of the number of negative spots, it will be considered as positive results. If the above standards are not met and the positive control well is normal, the test result will be negative.

3.2. PPD

After subcutaneous injection of 5 IU tuberculosis protein derivative into the medial side of left forearm for 72 hours, the average diameter of induration was calculated by (transverse diameter + longitudinal diameter)/2. If there is no induration or the average diameter of induration is less than 10 mm, it is judged as negative (−); if it is more than 10 mm, it is judged as positive = (+).

3.3. Pleural Effusion TB-DNA-PCR

Drainage of pleural effusion was placed in sterile sputum box for examination. TB-DNA detection kit of Sun Yat-sen University Da'an gene Co., Ltd. was adopted, and the detection process was operated according to the instructions.

3.4. Pleural Effusion ADA

5 ml of pleural effusion drainage stored in the sterile sputum box was detected. The test kit of Beijing Century ward Biotechnology Co., Ltd. was adopted, and the detection process was operated according to the instructions.

3.5. Observation Index [6]

The positive rate, negative rate, sensitivity and omission diagnostic rate of TB-IGRA, PPD, TB-DNA-PCR, ADA and combined with TB-IGRA.

3.6. Statistical Method [7] [8]

SPSS 20.0 statistical software was employed to process data. The measurement data were showed by $\overline{x} \pm s$, while the enumeration data were represented in%.

4. Results

1) General results

In 60 cases of tuberculous pleural effusion, there were 27 males and 33 females, aged from 19 to 86 years old, with an average age of (59.48 1 ± 13.732).

2) The positive and negative rates of TB-IGRA, PPD, TB-DNA-PCR and ADA were compared

A total of 60 cases were included in this study. The positive cases of TB-IGRA were 57 cases (95%), and the negative cases were 3 cases (5%). The positive cases of PPD were 43 cases (71.67%), and the negative rate was 17 cases (28.33%). The TB-DNA-PCR positive cases were 3 cases (5%), and negative cases were 57 cases (95%). The positive cases of ADA were 52 cases (86.67%), and the negative cases were 8 cases (13.33%) (Table 1, Figure 1).

3) The sensitivity and omission diagnostic rate of TB-IGRA, PPD, TB-DNA-PCR, ADA and combined with TB-IGRA were compared

The sensitivity of TB-IGRA was 95% while the omission diagnostic rate was 5%. The sensitivity of PPD was 71.67% while the omission diagnostic rate was 28.33%. The sensitivity of TB-DNA-PCR was 5% while the omission diagnostic rate was 95%. The sensitivity of ADA was 86.67% while the omission diagnostic rate was 13.33%. TB-IGRA showed the highest sensitivity and TB-DNA-PCR represented

Table 1. The positive rate and negative rate of four tuberculosis detection indexes.

	TB-IGRA	PPD	TB-DNA-PCR	ADA
Number of positive cases	57	43	3	52
Number of negative cases	3	17	57	8
Positive rate	95%	71.67%	5 %	86.67 %
Negative rate	5%	28.33 %	95%	13.33%

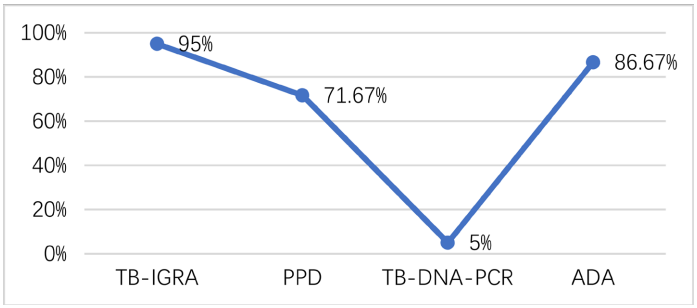

Figure 1. The positive rate and negative rate of four tuberculosis detection indexes

the highest omission diagnostic rate.

The sensitivity of TB-IGRA + PPD combination detection was 98.33% while the omission diagnostic rate was 51.67%. The sensitivity of TB-IGRA + TB-DNA-PCR was 95% while the omission diagnostic rate was 5%. The sensitivity of TB-IGRA + ADA was 100% while the omission diagnostic rate was 0%. Notably, the TB-IGRA + ADA showed the highest sensitivity and the lowest omission diagnostic rate. (Table 2, Figure 2 and Figure 3)

Table 2. Sensitivity and omission diagnostic rate of four tuberculosis detection indexes (%)

	sensitivity	omission diagnostic rate
TB-IGRA	95 (57/60)	5 (3/60)
PPD	71.67 (43/60)	28.33 (17/60)
TB-DNA-PCR	5 (3/60)	95 (57/60)
ADA	86.67 (52/60)	13.33 (8/60)
TB-IGRA+PPD	98.33 (59/60)	1.67 (1/60)
TB-IGRA + TB-DNA-PCR	95 (57/60)	5 (3/60)
TB-IGRA+ADA	100 (60/60)	0 (0/60)

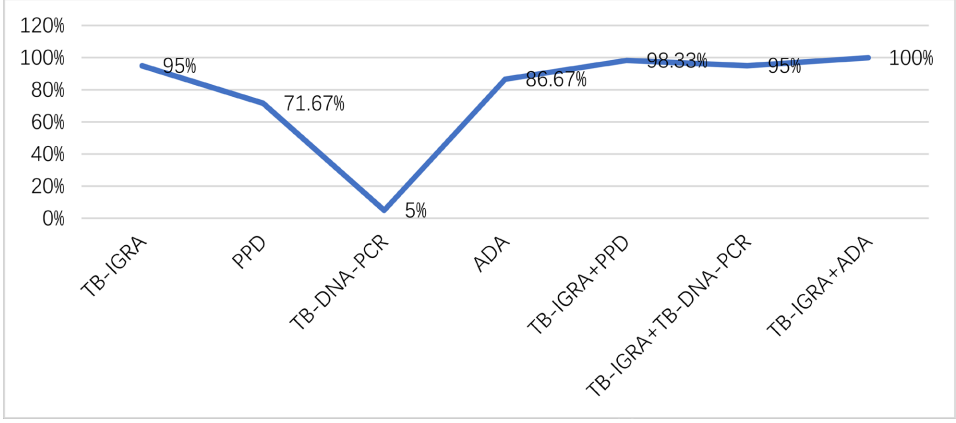

Figure 2. Sensitivity of four tuberculosis detection indexes.

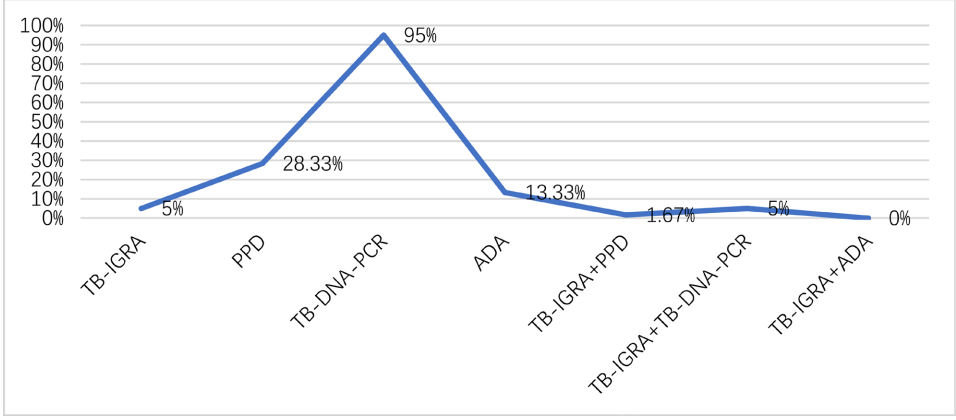

Figure 3. The omission diagnostic rate of four tuberculosis detection indexes.

5. Conclusions

Tuberculous pleural effusion is a type of pulmonary tuberculosis [9] [10], which is caused by Mycobacterium tuberculosis invading the pleura [11], the main clinical manifestations of the patients are chest tightness, shortness of breath, chest pain, low-grade fever, perspire during sleep, and the gold standard for the diagnosis of which is detecting the tuberculosis in pleural effusion, however, the positive rate of this method is low, most of the diagnosis depends on clinical manifestations. [12]. Traditional diagnostic methods for pulmonary tuberculosis have the characteristics of low sensitivity and unsatisfying specificity. For example, the culture time of *Mycobacterium tuberculosis* is long and the positive rate is low, and tuberculin test is prone to be a false positive or false negative results. The detection of Mycobacterium tuberculosis specific cellular immune response (TB-IGRA) [13] is a diagnostic method of tuberculosis developed in recent years, which has been proved to be a sensitive and specific detection method in Mycobacterium tuberculosis infection, especially, it can be early diagnosed before bacteriological results and typical imaging findings. Therefore, it has been employed as a common method for tuberculosis detection in European and American countries. Moreover, it has been recorded into the 2018 edition of the guideline for TB diagnosis [14] [15]. In addition, many studies have shown that [16] TB-IGRA has represented a satisfying diagnostic efficacy in pulmonary tuberculosis. Notably, combined with classical PPD, TB-DNA-PCR and ADA, it is capable of improving the positive rate of diagnosis and reducing the rate of the omission diagnostic rate.

A total of 60 cases were included in this study. The positive rate and sensitivity of TB-IGRA, PPD, TB-DNA-PCR and ADA were 95%, 71.67%, 5% and 86.67% respectively. The rate of the omission diagnostic rate was 5%, 28.33%, 95% and 13.33%. TB-IGRA showed the highest positive rate and sensitivity, and TB-DNA-PCR represented the highest omission diagnostic rate. The sensitivity of TB-IGRA + PPD was 98.33% while the omission diagnostic rate was 51.67%. The sensitivity of TB-IGRA + TB-DNA-PCR was 95% while the omission diagnostic rate was 5%. The sensitivity of IGRA + ADA was 100% while the omission diagnostic rate was 0%. TB-IGRA + ADA showed the highest sensitivity and the lowest omission diagnostic rate.

In conclusion, TB-IGRA shows the high positive rate, high sensitivity and low omission diagnostic rate relatively, which is more satisfying and applicable than the traditional sputum examination of tuberculosis. When it is combined with PPD, TB-DNA-PCR、ADA, the diagnosis rate can be improved, when combined with ADA, the diagnosis accuracy can reach 100%, which has made up for their own shortcomings and represented a promising clinical application value in the auxiliary diagnosis of tuberculous pleurisy.

Project Name

2018 Key project plan of medical science research in Hebei Province 20180869,

2021Key R & D plan of Zhangjiakou City, Hebei Province 2021046D.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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