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Improved early diagnosis of difficult cases of tuberculous pleural effusion by combination of thoracoscopy with immunological tests

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ABSTRACT

Introduction: Although pleural effusion is a common clinical manifestation, the differential diagnosis of the cause of pleural effusion is often challenging, especially in the early differentiation of tuberculous pleurisy (TP) from other pleural effusion. The aim of this study was to evaluate the performance of commonly used laboratory tests for the early diagnosis of difficult cases of pleural effusion.
Methods: Patients with undiagnosed pleural effusion were enrolled and subjected to five laboratory tests including thoracoscopy, pleural fluid adenosine deaminase assay (ADA), serum tuberculosis antibody test (TB-antibody), tuberculin skin test (TST), and T-SPOT.TB assay. The diagnosis of TP was established based on pleural histology and mycobacterial culture. The different tests were compared for diagnostic performance.
Results: A total of 106 patients were enrolled; their mean age was 53 years and 70.8% were male. Seventy-two (68%) of them were confirmed to have TP. When used individually, the five laboratory tests showed highly variable performance parameters, including sensitivity ranging from 46% to 92% and specificity ranging from 33% to 82%. When used in different combinations, thoracoscopy combined with TST or TB-antibody showed the optimal performance parameters, with a sensitivity of 80.8% and a specificity of 85.7%.
Conclusions: The results of this study suggest that the combination of thoracoscopy with TST or TB-antibody test is the best choice for the early diagnosis of difficult cases of TP in high TB burden countries.

Introduction

Tuberculosis (TB) remains one of the most severe bacterial infectious diseases globally, posing a great threat to the public health of seven billion people (Dabernat et al., 2014). The World Health Organization estimated that TB caused 1.7 million deaths and 10.4 million incident cases worldwide in 2016, including 0.9 million incident cases in China (World Health Organization, 2017). Although the global TB mortality rate showed a decline of 3% per year and the TB incidence decreased about 2% per year in 2016 compared to 2015, TB remains one of the top 10 causes of death worldwide (GBD Tuberculosis Collaborators, 2018). Tuberculous pleural effusion, also known as tuberculous pleurisy (TP), is a common manifestation of extrapulmonary TB, which accounts for about 3–25% of all TB cases (Light, 2010; Kataria and Khurshid, 2001).

The early diagnosis of TP is crucial for initiating timely effective treatment and promoting favorable outcomes. However, in clinical practice, distinguishing TP from other causes of pleural effusion is often challenging. The definite diagnosis of TP still depends primarily on the demonstration of positive *Mycobacterium tuberculosis* culture in pleural tissue or fluid samples (Gopi et al., 2007; Harada et al., 2008). This method not only lacks sensitivity but is also time-consuming, often leading to a missed or delayed diagnosis. (Light, 1999; World Health Organization, 2015; Udwadia and Sen, 2010). Alternative methods include pleural biopsy via thoracoscopy (Wang et al., 2015), pleural fluid adenosine deaminase assay (ADA) (Liang et al., 2008), tuberculosis antibody test (TB-antibody) (Steingart et al., 2011), tuberculin skin test (TST) (Kunter et al., 2003), and the T-SPOT.TB assay (Chung et al., 2011). These methods have improved the diagnosis of TP, particularly the speed of diagnosis. However, these methods, when used individually, still lack sufficient sensitivity or specificity to be useful for the

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differential diagnosis of TP (Liang et al., 2008; Liu et al., 2016; Sriram et al., 2011; Diacon et al., 2003). Given that each of these methods has advantages and disadvantages, it was hypothesized that a combination of different methods may offer greater diagnostic capability than is offered by a single method. To test this hypothesis, a single-center retrospective case-series study was conducted to evaluate the diagnostic performance of several common laboratory tests for the diagnosis of TP when used either individually or in different combinations, and to determine the optimal scheme for improved early diagnosis of TP.

Methods

Study population

This research project was approved by the Human Research Ethics Committee of the First Affiliated Hospital of Chongqing Medical University, China. Written informed consent was obtained from all patients for participation in this study. A chart review was conducted of all hospitalized patients with a suspected diagnosis of TP between January 2014 and December 2016 at the First Affiliated Hospital of Chongqing Medical University, Chongqing, China. Although all patients received comprehensive laboratory tests, including chest computed tomography (CT), TST, acid-fast staining of respiratory tract samples, pleural biochemical and cytological examinations, and serum pleural carcinoembryonic antigen assays, the cause of the pleural effusion was uncertain.

Patients were included in this study if they met all of the following criteria: (1) either sex and age ≥18 years; (2) presence of symptoms resembling TB, including cough, night sweats, fever, loss of weight, chest pain, and hemoptysis; (3) presence of pleural effusion on chest X-ray; (4) not confirmed to have TP. Patients were excluded if they met any of the following criteria: (1) presence of active pulmonary TB and/or under anti-TB therapy; (2) under immunosuppression therapy; and (3) HIV-seropositive.

Diagnostic criteria

A definite diagnosis of TP was based on a positive culture of *M. tuberculosis*, or a histopathological demonstration of granulomas in pleural tissue biopsy, or a good response to anti-TB chemotherapy over at least 1 year of follow-up (Kataria and Khurshid, 2001; Villena Garrido et al., 2014). The degree of pleural effusion was divided into three grades: large with a fluid volume ≥1500 ml; moderate with a volume of 500–1500 ml; minimal with a volume of ≤500 ml.

Thoracoscopy procedures

Thoracoscopy was performed by qualified respiratory physicians using a semi-rigid pleuroscope (Olympus LTF240) in a thoracoscope chamber. Prior to thoracoscopy, patients with contraindications (such as acute coronary syndrome, significant bleeding tendency, severe respiratory distress syndrome, etc.) were excluded based on preoperative assessment. The preoperative assessment included vital signs, exercise tolerance, routine blood test, coagulation function test, liver and kidney function tests, arterial blood gas analysis, myocardial injury markers, and electrocardiogram. During the thoracoscopy procedure, patients were closely monitored for blood pressure, heart rate, respiratory rate, and arterial oxygenation, and were given constant supplemental oxygen via nasal catheter. The incision was usually made between the fourth and eighth intercostal space of the axillary line. After moderate sedation and local anesthesia, a semi-rigid pleuroscope was inserted into the pleural cavity through the small incision in the chest wall. The visceral, diaphragmatic, and parietal pleura were carefully inspected, with all possible abnormalities recorded. The quantity and characteristics of pleural effusion were recorded. Pleural biopsies were implemented with flectional biopsy forceps in all suspected areas under direct visual control. Pleural effusion specimens were collected for *M. tuberculosis* culture, biochemistry, and cytological examination. Prior to incision closure, a chest drainage tube was inserted to drain fluid and air in the pleural cavity. Chest radiography was done routinely until the removal of the chest drainage tube.

Other laboratory tests

M. tuberculosis culture was performed using a pleural fluid sample and the BACTEC MGIT 960 culture system (Becton, Dickinson and Company, USA). The pleural fluid ADA level was measured colorimetrically using an ADA assay kit (Maccura Biotech, China). Serum TB-antibody was assessed using an immunochromatographic test system (Alere Inc., China). The T-SPOT.TB assay was performed using a commercial kit from Oxford Immunotec Ltd (UK). The TST was performed using 5 IU of tuberculin pure protein derivative (Xiangrui Biological Products Co. Ltd, China). All of these tests were performed following the respective manufacturer's instructions.

Statistical analysis

Both descriptive and inferential statistical methods were used to analyze the data with MedCalc software (version 13.0.0; Ostend, Belgium) and GraphPad Prism software (version 7.0.1; La Jolla, USA). The diagnostic performance parameters were calculated for each test, including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). The receiver operating characteristic (ROC) curve was computed using the default settings of the MedCalc software. Variance and diagnostic performance parameters were computed with 95% confidence intervals (CI).

Results

Clinical characteristics of study participants

A total of 106 patients with suspected TP were recruited. Their mean age was 53 years (range 17–86 years) and 75 (70.8%) were male (Table 1). Eighty-one (76.4%) of them had unilateral pleural effusion and 25 (23.6%) had bilateral pleural effusion. The proportions of large, moderate, and minimal degrees of pleural effusion were 57.5%, 28.3%, and 14.2%, respectively. Ninety-three (87.8%) patients showed yellow pleural effusion, while the other 13 (12.3%) had bloody pleural effusion. Based on CT imaging, 65 (61.3%) showed external lung atelectasis caused by pleural effusion, 38 (35.8%) showed pleural thickening, and 27 (25.5%) had enlarged mediastinal lymph nodes (Table 2). Based on thoracoscopy, pleural nodules appeared in 86 (81.1%) patients, pleural adhesion in 29 (27.4%), hyperemia in 12 (11.3%), and necrosis in six (5.7%), as shown in Table 3.

Of the 106 patients, 72 (67.9%) were determined to have TP based on the diagnostic criteria in this study, while 34 (32.1%) patients had non-TB pleural effusion, including 20 cases with malignant pleural effusion and 14 cases with other unknown causes.

Of the 72 patients with TP, 34 (47.2%) were current smokers, and only seven (9.7%) had a history of close contact with a TB patient. None of the patients were HIV-positive, suffered from other immunodeficiency diseases, or was using immunosuppressive agents. The mean number of times the patient had undergone thoracocentesis was two times for TP patients (before thoracoscopy) and 2.5 times for non-TB patients. The most common clinical symptoms in TP patients were cough (61.1%), chest pain (37.5%), fever (25.0%), dyspnea (11.1%), and night sweats (5.6%), as presented in Table 1.

Table 1
Clinical characteristics of the study population.[a]

Clinical characteristics	All patients (n = 106)	TB patients (n = 72)	Non-TB patients (n = 34)	p-Value
Age (years)	53.1 ± 16.5	50 ± 16.7	59.8 ± 13.7	0.003
Male	75 (70.8%)	53 (73.6%)	22 (64.7%)	0.352
BMI (kg/m^2)	22.3 ± 3.4	22.1 ± 3.0	22.7 ± 4.0	0.586
Smoker	53 (50.0%)	34 (47.2%)	19 (55.9%)	0.410
HIV infection	0 (0%)	0 (0%)	0 (0%)	
Close contact with TB	7 (6.6%)	7 (9.7%)	0 (0%)	0.007
Symptoms				
Cough	63 (59.4%)	44 (61.1%)	19 (55.9%)	0.613
Chest pain	38 (35.8%)	27 (37.5%)	11 (32.4%)	0.610
Fever	28 (26.4%)	18 (25.0%)	10 (29.4%)	0.634
Dyspnea	14 (13.2%)	8 (11.1%)	6 (17.6%)	0.358
Night sweats	5 (4.7%)	4 (5.6%)	1 (2.9%)	0.558
Hemoptysis	2 (1.9%)	1 (1.4%)	1 (2.9%)	0.588
Weight loss	2 (1.9%)	0 (0%)	2 (5.9%)	0.160
Duration of symptoms (days)	46.4 ± 56.1	36.9 ± 48.8	66.4 ± 64.7	0.024
Count of thoracocentesis	2.1 ± 1.2	1.9 ± 1.2	2.5 ± 1.2	0.050

TB, tuberculosis; BMI, body mass index.
[a] Data are presented as the number (%) or mean ± standard deviation.

Table 2
Clinical characteristics of pleural effusion and CT imaging.[a]

Clinical characteristics	All patients (n = 106)	TB patients (n = 72)	Non-TB patients (n = 34)	p-Value
Side of pleural effusion				
Right	47 (44.3%)	34 (47.2%)	13 (38.2%)	0.280
Left	34 (32.1%)	24 (33.3%)	10 (29.4%)	
Bilateral	25 (23.6%)	14 (19.4%)	11 (32.4%)	
Quality of pleural effusion				
Small	15 (14.2%)	13 (18.1%)	2 (5.9%)	0.053
Moderate	30 (28.3%)	21 (29.2%)	9 (26.5%)	
Large	61 (57.5%)	38 (52.8%)	23 (67.6%)	
Appearance of pleural effusion				
Yellow	93 (87.8%)	65 (90.3%)	28 (82.4%)	0.451
Bloody	13 (12.3%)	7 (9.7%)	6 (17.6%)	
CT imaging				
Pulmonary atelectasis	65 (61.3%)	39 (54.2%)	26 (76.5%)	0.021
Pleural thickening	38 (35.8%)	23 (31.9%)	15 (44.1%)	0.226
Mediastinal lymphopathy	27 (25.5%)	16 (22.2%)	11 (32.4%)	0.292

CT, computed tomography; TB, tuberculosis.
[a] Data are presented as the number (%).

Table 3
Thoracoscopic manifestations in TB and non-TB pleural effusion.[a]

Thoracoscopic manifestations	All patients (n = 106)	TB patients (n = 72)	Non-TB patients (n = 34)	p-Value
Pleural nodules	86 (81.1%)	59 (81.9%)	27 (79.4%)	0.758
Pleural adhesion	29 (27.4%)	22 (30.6%)	7 (20.6%)	0.267
Hyperemia	12 (11.3%)	8 (11.1%)	4 (11.8%)	0.922
Necrosis	6 (5.7%)	5 (6.9%)	1 (2.9%)	0.410

TB, tuberculosis.
[a] Data are presented as the number (%).

In terms of the postoperative complications of thoracoscopy, short-term chest pain occurred in 86 (81.1%) patients, fever in 19 (17.9%), pneumothorax in five (4.7%), and subcutaneous emphysema in one (0.9%) (Table 4). These postoperative reactions were all transient and mild.

Performance parameters of different diagnostic tests

All 106 patients were subjected to pleural fluid ADA assay, TB-antibody test, T-SPOT.TB assay, TST, and thoracoscopy.

For pleural fluid ADA levels, the ROC curve was used to determine the optimal cut-off ADA level to distinguish TB and non-TB patients. When the cut-off ADA level was set at more than 13.8 U/l, the optimum area under the curve (AUC) was 0.728 (95% CI 0.633–0.810), as shown in Figure 1.

The diagnostic performance parameters of ADA and all other tests are shown in Table 5. For individual tests, thoracoscopy showed the highest sensitivity (91%), but a relatively low specificity (67%). The TST showed a relatively high specificity (82%) and a relatively low sensitivity (45%). T-SPOT.TB exhibited a relatively high sensitivity (80%) and the lowest specificity (33%).

Table 4
Main postoperative complications of medical thoracoscopy.[a]

Complications	All patients (n = 106)	TB patients (n = 72)	Non-TB patients (n = 34)	p-Value
Pain	86 (81.1%)	55 (76.4%)	31 (91.2%)	0.039
Fever	19 (17.9%)	12 (16.7%)	7 (20.6%)	0.627
Pneumothorax	5 (4.7%)	4 (5.6%)	1 (2.9%)	0.558
Subcutaneous emphysema	1 (0.9%)	1 (1.4%)	0 (0%)	0.495

TB, tuberculosis.
[a] Data are presented as the number (%).

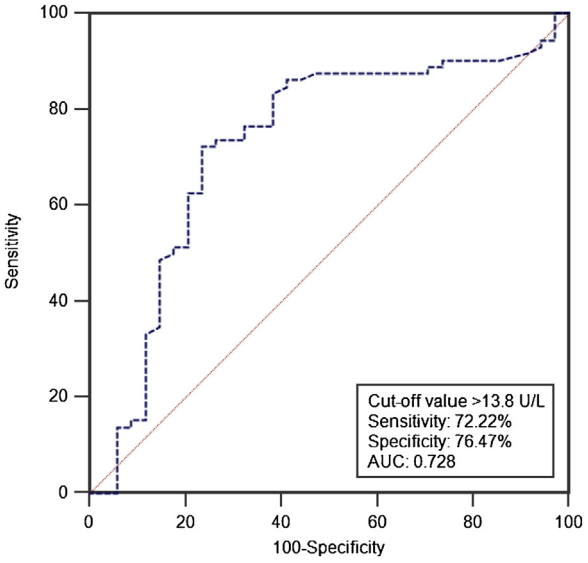

Figure 1. Receiver operating characteristic (ROC) curve of the adenosine deaminase assay for the diagnosis of tuberculous pleurisy; AUC = 0.728 (95% CI 0.633–0.810).

TST and thoracoscopy showed the highest PPV (88% and 85%, respectively). The sensitivity and specificity of ADA were both relatively low (72% and 76%, respectively).

When comparing different combinations of these tests, the combination of thoracoscopy with TST or TB-antibody showed the optimal performance parameters, with a sensitivity of 81%, specificity of 86%, PPV of 93%, and NPV of 64%.

Discussion

Despite the availability of various diagnostic tests, the early diagnosis of TP remains highly challenging with significant uncertainty. To address this challenge, 106 patients with suspected TP were enrolled and used to evaluate the diagnostic performance of five commonly used, relatively rapid laboratory tests in order to identify the best choice of diagnostic strategy for TP.

The five tests evaluated in this study showed a great degree of variability in sensitivity and specificity in individual testing; none of them demonstrated superior performance in both sensitivity and specificity compared to the others. While thoracoscopy had the highest sensitivity (92%) and NPV (79%), the TST showed the highest specificity (82%) and PPV (88%). Compared to a previous study on the performance of thoracoscopy (reporting a sensitivity of 71.4% and a specificity of 100%) (He et al., 2015), a higher sensitivity (92%) but a lower specificity (68%) were observed in the present study. Despite its high specificity and PPV, the TST displayed the lowest sensitivity (46%) and NPV (35%). The sensitivity of TST observed in this study appears to be substantially lower than that reported previously (65%), although its specificity appears to be higher (82%) than that reported previously (68%) (Kunter et al., 2003). The sensitivity of the T-SPOT.TB observed in this study (80%) is within the range reported previously (72–89%) (Aggarwal et al., 2015; Jiang et al., 2007), while its specificity in this study (33%) is much lower than found in previous reports (78–97%) (Aggarwal et al., 2015; Jiang et al., 2007). The TB-antibody test showed low sensitivity (48%) and intermediate specificity (76%) in this study, which lie within the highly variable ranges reported in a meta-analysis, in which the sensitivity ranged from 0% to 100% and specificity from 59% to 100% when testing with active pulmonary and extrapulmonary TB (Steingart et al., 2011; She and Litwin, 2015).

In this study, ADA showed intermediate levels of both sensitivity (72%) and specificity (76%), which appeared to be substantially lower than the sensitivity of 92% and specificity of 90% reported previously (Liang et al., 2008). The optimal cut-off level of ADA (13.8 U/l) was determined based on ROC curve analysis of 106 patients. This cut-off level is lower than the range of 40–60 U/l reported in previous studies (Burgess et al., 1996; Krenke and Korczyński, 2010; Wang et al., 2012; Keng et al., 2013; Gui and Xiao, 2014). A possible explanation for this difference is that there is a much higher morbidity related to TB in China than in Europe. Another possibility is that the patients in the present study (with a mean age of 53 years) were older than those included in previous studies (with a mean of 33.8–49 years) (Wang et al., 2012; Burgess et al., 1995; Hassanein et al., 2010; Yildiz et al., 2011; Medford et al., 2010). This possibility is supported by a linear regression analysis that showed that ADA activity decreases with age in TP patients, presumably due to a lesser degree of responsive inflammatory

Table 5
Diagnostic performances of ADA, TB-antibody, TST, T-SPOT.TB, thoracoscopy, and their combinations for tuberculous pleurisy.

Diagnosis method[a]	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
ADA (>13.8U/l)	72.22% (60.4–82.1%)	76.47% (58.8–87.1%)	86.7% (75.3–94.1%)	56.5% (41.1–71.1%)
TB-antibody	48.08% (35.1–61.31%)	76.19% (54.91–89.37%)	83.33% (66.44–92.66%)	37.21% (24.38–57.14%)
TST	45.83% (32.58–59.71%)	82.35% (58.97–83.81%)	88% (70.04–95.83%)	35% (22.13–50.49%)
T-SPOT.TB	80% (37.55–98.97%)	33.33% (1.71–88.15%)	66.67% (30–94.08%)	50% (25.6–97.44%)
Thoracoscopy	91.67% (82.99–96.12%)	67.65% (50.84–80.87%)	85.79% (76.2–91.83%)	79.31% (61.61–90.15%)
Thoracoscopy + TST	43.75% (30.7–57.72%)	94.2% (73.02–99.7%)	95.45% (78.2–99.77%)	37.21% (24.38–52.14%)
Thoracoscopy + TB-antibody	44.23% (31.6–57.66%)	84% (65.35–93.6%)	85.19% (67.52–94.08%)	42% (29.38–55.77%)
Thoracoscopy + TST/TB-antibody	80.77% (68.1–89.2%)	85.71% (65.36–95.02%)	93.33% (82.14–97.71%)	64.29% (45.83– 79.29%)

ADA, adenosine deaminase assay; TB, tuberculosis; TST, tuberculin skin test; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.
[a] Serial combination is indicated by '+', while parallel combination is indicated by '/'. Other combinations are not listed in this table due to their low performance parameters.

reaction to TB in the elderly compared to young patients (Zarić et al., 2008).

As the diagnostic performance was highly variable among the five tests evaluated, the performances of combinations of the different tests were compared and it was found that the combination of thoracoscopy with TST or TB-antibody showed the optimal performance parameters, with a sensitivity of 81%, specificity of 86%, PPV of 93%, and NPV of 64% (Table 5). The performance of this combination relies largely on the high sensitivity of thoracoscopy and the high specificity of the TST. Despite its high sensitivity, thoracoscopy has the disadvantage of being an invasive operation in addition to the need for moderate anesthesia and sedation. Nevertheless, no serious adverse reactions during the thoracoscopy operation and subsequent follow-up were observed in this study (Table 4), suggesting that thoracoscopy is a safe procedure, as has been reported by others (Agarwal et al., 2013; Casal et al., 2009; El-Hadidy and Rezk, 2016). Although difficult study subjects with an uncertain diagnosis of TP were enrolled, the combination of thoracoscopy with TST or TB-antibody was able to achieve a diagnosis with a sensitivity of 81% and a specificity of 86%, which represents a substantial improvement in the early diagnosis of TP.

This study has the following limitations. First, the study was conducted in a single hospital with a relatively small sample size; thus, the results may not be generalized to other populations. Second, the patient population involved in this study came from a region with a high TB burden; thus the results may not be applicable to other areas, especially those with a low TB burden. Third, the patients enrolled in this study were all difficult cases with an uncertain diagnosis, which may have given rise to an under-estimation of the true sensitivity and specificity of the diagnostic tests.

In conclusion, the diagnostic performances of five relatively rapid laboratory tests for TP were evaluated using a panel of 106 patients with suspected TP. When used individually, the tests showed highly variable performance parameters. When used in different combinations, thoracoscopy combined with TST or TB-antibody showed the optimal performance parameters, suggesting its potential as a valuable tool for the early diagnosis of TP.

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The authors declare that no funding was received for this study.

Ethics statement

This work was approved by the Institutional Review Board of the First Affiliated Hospital of Chongqing Medical University. The authors confirm that the patient data in the text remained confidential and unidentified.

Conflict of interest

No competing interests exist in this study.

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