Efficacy and Safety of Diagnostic Thoracoscopy in Undiagnosed Pleural Effusions

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Introduction

Pleural effusions are a common clinical problem with more than 60 recognized etiologies including diseases local to the pleura or underlying lung, organ dysfunction, systemic conditions, and drugs. It is estimated that about 1.5 million people suffer from a pleural effusion in the United States [1]. The etiology of pleural effusions varies depending on the population studied; however, the most common exudative pleural effusions include malignant and tuberculous pleural effusions [2]. The differential diagnosis of pleural effusions can present a considerable challenge. After thoracocentesis and/or blind pleural biopsy, about 25–40% of the pleural effusions remain undiagnosed [3, 4].

Conclusions: MT is an effective and safe procedure for diagnosing pleural effusions of undetermined causes. In areas with high tuberculosis prevalence, MT should be particularly helpful in the differential diagnosis of tuberculous pleural effusion.

Key Words
Medical thoracoscopy · Pleural biopsy · Pleural effusion
Medical thoracoscopy (MT) refers to the examination of the pleural space in a nonintubated patient under conscious sedation, and this procedure has been well documented to be highly sensitive for detecting malignant pleural effusion with negative pleural fluid cytology and for diagnosing tuberculous pleural effusion [5, 6]. A recent meta-analysis [7] revealed that the overall sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of MT was 91%, 100%, 4.92, and 0.08, respectively; the area under the curve for the summary receiver operating characteristic curve was 0.93. Therefore, MT is an efficacious procedure in the diagnosis of undiagnosed exudative pleural effusions.

In the present study of patients having undergone at least one MT over a 9-year period in a 1,600-bed general hospital in China, we analyzed the diagnostic efficiency of MT, together with its safety and complications, in the differential diagnosis of pleural effusions performed by chest physicians.

**Patients and Methods**

The study protocol was approved by the Institutional Review Boards for Human Studies of Beijing Chaoyang Hospital, Beijing, China. All patients with undiagnosed pleural effusions who underwent at least one MT in our Institute between July 2005 and June 2014 were included in the present study. The detailed medical history, clinical presentation, laboratory examination results, and image data of all patients who underwent MT were recorded and analyzed. The characteristics of the study population are presented in table 1.

All patients have had a thoracic computed tomography (CT) scan first before undergoing MT. The size of a pleural effusion was estimated as small, moderate, or large according to CT features with anteroposterior quartile and maximum anteroposterior depth measured at the midclavicular line, as described by Moy et al. [8]: first anteroposterior-quartile effusions are small, second anteroposterior-quartile effusions are moderate, and third or fourth anteroposterior-quartile effusions are large.

Thoracoscopic procedures have been described in our previous publication [9]. The diagnosis of idiopathic or nonspecific pleural effusion was accepted after at least 12 months of follow-up when no other definitive diagnosis was made during that time.

Descriptive statistical methods were used for data analysis (mean ± SD, range, or/and 95% CI).

**Results**

Between July 2005 and June 2014, 833 patients with undiagnosed pleural effusions successfully underwent MT, and satisfactory biopsy samples were obtained for diagnostic evaluation.

As shown in table 1, the age of the patients was 57.8 ± 14.5 years (range 17–90). There were 503 males and 330 females. In 294 (35.3%) patients, pleural effusion occurred only on the left side, in 403 (48.4%) only on the right, and in 136 (16.3%) both sides were affected. In either unilateral or bilateral effusion, the proportions of small, moderate, and large size of pleural effusions were 21.1, 15.8, and 63.1%, respectively. We also noted that the size of transudative effusions showed no preference for small, moderate, or large. Overall, in 306 (36.7%) patients, the appearance of pleural effusions was blood-stained, in 522 (62.7%) it was yellow, and in 5 (0.6%) it was chylous.

<table>
<thead>
<tr>
<th>Table 1. Characteristics of the study population (n = 833)</th>
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<tbody>
<tr>
<td>Male/female</td>
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<tr>
<td>Age, years</td>
</tr>
<tr>
<td>Smoking status</td>
</tr>
<tr>
<td>Current or previous smoker</td>
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<tr>
<td>Non-smoker</td>
</tr>
<tr>
<td>Not clear</td>
</tr>
<tr>
<td>Past history</td>
</tr>
<tr>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Malignancy</td>
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<tr>
<td>Previous thoracentesis</td>
</tr>
<tr>
<td>Protein, g/l</td>
</tr>
<tr>
<td>Lactate dehydrogenase, IU/l</td>
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<tr>
<td>Side of effusion</td>
</tr>
<tr>
<td>Left</td>
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<tr>
<td>Right</td>
</tr>
<tr>
<td>Bilateral</td>
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<tr>
<td>Size of effusion</td>
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<tr>
<td>Small</td>
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<tr>
<td>Moderate</td>
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<tr>
<td>Large</td>
</tr>
<tr>
<td>Effusion appearance</td>
</tr>
<tr>
<td>Blood-stained</td>
</tr>
<tr>
<td>Yellow</td>
</tr>
<tr>
<td>Chylous</td>
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<tr>
<td>Length of stay in hospital, days</td>
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</table>

Values are expressed as n (%) or mean ± SD.

After MT, 342 (41.1%) patients were confirmed to have malignant pleural effusion, 429 (51.5%) patients had benign pleural effusions, and 62 (7.4%) patients did not achieve definite diagnoses (table 2). We noted that the most frequent cause of malignant pleural effusion was lung cancer (67.8%), followed by mesothelioma (10.2%), lymphoma (2.9%), etc. The original malignancies in 25 patients (7.3%) with malignant pleural effusion could not be identified.
The most common form of benign pleural diseases was tuberculous pleural effusion (77.6%), followed by bacterial infection (8.4%), chylothorax (1.4%), chemical pleurisy (0.9%), and other exudates (5.1%). In addition, 17 (4.0%) patients with transudative pleural effusion were included in this benign group.

Since malignancy and tuberculosis were the two leading causes of pleural effusion, we explored the age-wise distributions of malignant and tuberculous pleural effusion. As shown in figure 1, the numbers of patients with malignant pleural effusion increased steadily to a peak in the sixth decade. Surprisingly, the number of tuberculous pleural effusion did not show significant fluctuation in our study.

We also noted that in 62 (7.4%) patients, no definite diagnoses of pleural effusion could be obtained even after MT. All of these patients were followed up for at least 12 months and did not complain about a new pleural effusion. No diagnosis other than benign pleural effusion was found in these 62 patients.

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### Table 2. Cause distribution of pleural effusions (n = 833)

<table>
<thead>
<tr>
<th>Cause</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>Malignancies</td>
<td>342 (41.1)</td>
</tr>
<tr>
<td>Metastatic cancers</td>
<td>272 (32.5)</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>35 (4.2)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>10 (1.2)</td>
</tr>
<tr>
<td>Undetermined</td>
<td>25 (3.0)</td>
</tr>
<tr>
<td>Benign diseases</td>
<td>429 (51.5)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>333 (77.6)</td>
</tr>
<tr>
<td>Bacterial infection</td>
<td>36 (8.4)</td>
</tr>
<tr>
<td>Chylothorax</td>
<td>6 (1.4)</td>
</tr>
<tr>
<td>Chemical pleurisy</td>
<td>4 (0.9)</td>
</tr>
<tr>
<td>Other exudates</td>
<td>33 (7.7)</td>
</tr>
<tr>
<td>Transudates</td>
<td>17 (4.0)</td>
</tr>
<tr>
<td>Undiagnosed</td>
<td>62 (7.4)</td>
</tr>
</tbody>
</table>

### Table 3. Complications of thoracoscopy (n = 833)

<table>
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<tr>
<th>Complication</th>
<th>n (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain*</td>
<td>367 (44.1)</td>
<td>40.7 to 47.5</td>
</tr>
<tr>
<td>Subcutaneous emphysema</td>
<td>67 (8.0)</td>
<td>6.2 to 9.8</td>
</tr>
<tr>
<td>Fever</td>
<td>44 (5.3)</td>
<td>3.8 to 6.8</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>38 (4.6)</td>
<td>3.2 to 6.0</td>
</tr>
<tr>
<td>Hypotension</td>
<td>4 (0.5)</td>
<td>0.02 to 1.0</td>
</tr>
<tr>
<td>Empyema</td>
<td>3 (0.4)</td>
<td>-0.03 to 0.8</td>
</tr>
</tbody>
</table>

* Pain requiring additional analgesic.

As shown in table 3, during this 9-year study, 0.4% of the patients had empyema caused by methicillin-sensitive *Staphylococcus aureus* but recovered after chest tube drainage and antibiotic treatment. Among the minor adverse events were 367 (44.1%) patients with local pain requiring additional analgesic. Eight percent of the patients had subcutaneous emphysema but recovered after chest tube drainage, and 5.3% of the patients had transient self-limited fever (38 °C or more). No major bleeding was found, and minor bleeding was seen in 4.6% of the patients.

### Discussion

In this study, our data showed that the overall diagnostic efficiency of MT was 92.6% in a Chinese population. Our current results were consistent with our and others’ previously published data demonstrating that MT appears to be an efficacious procedure in the diagnosis of pleural effusions [9–15].

Blind pleural biopsy has been recommended as the first choice for the management of pleural effusion in resource-poor areas with a high incidence of tuberculosis by the current guideline due to its reasonably high sensitivity [16]. CT- or ultrasound-guided pleural biopsies are quite sensitive and safe, with the only reported complications being local hematoma and minor hemoptysis [17, 18]. Image-guided pleural biopsies have been shown to be superior to blind pleural biopsies in the diagnostic effi-
cacy for malignant pleural effusion [16]. As a matter of fact, neither blind pleural biopsies nor image-guided biopsies have been used widely in many hospitals in China, including our hospital. Actually, the etiological diagnostic rate of pleural effusions, especially tuberculous pleural effusion, had been really low before MT was introduced in China.

Malignant pleural effusion is always the main diagnosis detectable on MT in patients with exudative pleural effusions. In the present study, we also found that malignant pleural effusion is much more common than the other exudates, such as tuberculous and infectious effusions, etc. We further found that the most frequent cause of malignant pleural effusion was lung cancer, followed by mesothelioma and lymphoma. Malignant pleural effusion was diagnosed by MT and was found in older patients rather than in younger ones.

Tuberculous pleural effusion is the second most common form of extrapulmonary tuberculosis after lymph node tuberculosis [19, 20]. On the other hand, tuberculosis is always the leading etiology of pleural effusions in the developing countries [20]. As a developing country, China is a country with a high tuberculosis burden that still had an estimated 1 million new tuberculosis cases in 2010, accounting for 11% of the global tuberculosis incidence [21]. In the current study, the diagnosis of tuberculous pleural effusion was established by the presence of Mycobacterium tuberculosis in pleural biopsy specimen, or by demonstration of caseating granulomas and/or epithelioid cell granulomas in pleural tissue with no evidence of other granulomatous diseases. As expected, in the present study, we observed that 40.0% (333/833) of the patients who underwent MT were confirmed to suffer from tuberculous pleural effusion, which was much higher than the 5.9% reported in the study from New Zealand [12], the 5.6% from the United Kingdom [14], the 3.2% from Spain [22], the 2.7% from France [13], the 2.0% from Denmark [23], and even the 0% from the United States [24].

After a complete work-up including MT biopsies, 771 patients with pleural effusions were diagnosed definitely, indicating that our overall diagnostic efficiency of MT was as high as 92.6%, which was similar to those reported by the others [12–15]. On the other hand, we also noted that no definite diagnoses of pleural effusions could be obtained in 62 (7.4%) patients even after MT. One limitation of our current study was that the follow-up was only 1 year, which was insufficient to draw any concrete conclusions of undiagnosed pleural effusions. We could only state here that these patients were followed up for 12 months, and no diagnosis other than benign pleural effusion was found in these patients. Several studies suggest that among the patients with a histological diagnosis of nonspecific pleurisy made after MT, 8.3−18% were eventually diagnosed with malignant pleural effusion, usually malignant pleural mesothelioma, during long-term follow-up [25–27]. Therefore, in most of these cases, a wait-and-see approach should be justified after nondiagnostic MT, unless repeated thoracocentesis suggests a progressive pleural disease.

The fact that MT is a safe procedure in the diagnosis of pleural effusion has been elucidated in almost all related clinical studies, and the meta-analysis [7] further revealed that there was no mortality with the procedure, and that the rates of major and minor complications are 1.5 and 10.5%, respectively. Our data also showed that MT is a very safe procedure for the investigation of undiagnosed pleural effusions with a low level of complications in general terms.

In conclusion, MT is an efficacious procedure in the diagnosis of undiagnosed exudative pleural effusions with excellent safety. In the developing countries (i.e., China) with high tuberculosis prevalence, MT should be particularly helpful for patients with clinically suspected tuberculous pleural effusion.

Acknowledgements

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Disclosure Statement

The authors have declared that no conflict of interest exists.
References