# The utility of pleural biopsy in differentiating between different types of lymphocytic exudative pleural effusions

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SS AJ conceived idea, SK AN drafted the study, SS UN NK collected data, SK AN did statistical analysis and interpretation of data MY NK critical review manuscript, All approved final version to be published.

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The authors declare that there is no conflict of interest.

**Abstract**

**Background:** A great majority of patients present to outpatient clinics with pleural effusion in Pakistan and throughout the world. Till date more than fifty causes of pleural effusion have been identified. Among 22% remained undiagnosed despite intensive investigations. The most common causes of lymphocytic exudative pleural effusion are tuberculosis and malignancy. Pleural biopsy examination is considered an important investigation for the diagnosis of exudative effusions. The aim of this study was to evaluate ability of pleural biopsy to differentiate between different exudative pleural effusions with lymphocytic predominance.

**Methodology:** This cross-sectional descriptive study was conducted in Pulmonology unit, Ayub Teaching Hospital, Abbottabad from 12th October, 2017 to 20th May, 2018. Patients 13-90 years of age group of both genders, who presented with lymphocytic exudative pleural effusion diagnosed on pleural aspiration, were included in the study. A total of 126 patients were included in the study. Consecutive non probability sampling was used. Patients with transudative pleural effusion, those on diuretic therapy, bleeding diathesis and patients unwilling for the procedure were excluded from the study.

**Results:** Out of 126 patients,71were males and 55 were females. In 114/126 (90.4%) patients an adequate pleural tissue were obtained. Out of those 76 (60.3%) were having granulomatous inflammatory changes presumptive of tuberculosis, 38 (30.2%) patients had malignancy and 12 (9.5%) had non-specific results. When pleural biopsy was stratified with age and gender, there was statistically significant association with age with p value of<0.02 but no statistically significant association with gender with p value>0.02.

**Conclusion:** The most common causes of lymphocytic exudative pleural effusion are tuberculosis and cancer. Tuberculosis is more common in children and adolescents, whereas cancer is more common in adults. In patients with unidentified exudative lymphocytic pleural effusion, pleural biopsy should be a regular diagnostic technique.

**Key words:** Lymphocytic exudative pleural effusion; Tuberculosis; Malignancy; Pleural biopsy; Gender; Age

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## Introduction

Pleural effusion is a commonly encountered clinical issue in outpatient clinics. It is also a reason for a vaste majority of in-hospital consultations.[1] There are many causes of pleural effusions and therefore it is necessary to make accurate diagnosis in order to treat it effectively.[2] An estimated 4% of all visits to general medical outpatient department are found to have pleural effusion and among these patients around 22% remain undiagnosed despite extensive investiga-

tions.[3] Pleural effusions are grossly divided into two groups namely transudative and exudative depending upon the amount of proteins content. Transudative effusions are mostly due to extra pulmonary causes while exudative effusions are due to pulmonary involvement. Tuberculosis and malignancy are the most common causes of exudative pleural effusions.[1,3,4] In around 15% of cases no diagnosis can be made despite detailed work up.[3]

Diagnostic work up include detailed history and examination, hematological and chemical laboratory investigations, radiography, ultrasonography, pleural fluid examination and pleural biopsy.[3,5]The latter, is the investigation of choice for making diagnosis of exudative pleural effusion with diagnostic yield of 60-80%.[1,3,6] Pleural tissues can be acquired using closed (blind), image-guided, or thoracoscopic pleural biopsy. The method of choosing is determined by a number of considerations, including the patient's health, diagnostic yield, instrument availability, competence, and lastly the cost. Although thoracoscopy had a higher diagnostic yield than closed pleural biopsy in the event of malignant pleural effusion, it does not contribute any significant yield above closed pleural biopsy in the case of tuberculous pleural effusion. Furthermore, thoracoscopy has a number of drawbacks, including limited availability, high expense, and the necessity for thoracic surgical support. All of these circumstances combine to make closed pleural biopsy is an important component of the initial examination for exudative pleural effusion in a developing country like Pakistan.[1]

There are many studies showing variable positive results of pleural biopsy in exudative pleural effusion.[1,3-11] The most recent study done in Pakistan showed positive result in 78.7% cases with pleural tuberculosis in 48.9% and malignancy in 29.8% cases.[1] Another study in Nepal concluded positive result of 59.57% with tuberculous granulomatous inflammation in 44.68% and malignancy in 21.28%.[3] Similarly a study in England diagnosed malignancy and tuberculosis in 59.2% and 77% respectively.[6]

The present study is designed with the aim to determine different kinds of diseases i.e. tuberculosis and malignancy by examining pleural biopsies. Being a more accurate method of diagnosis of pleural pathologies, the method will properly determine the frequency of different patterns. Results will be used by planners and caregivers and institute meaningful interventions.

## Methodology

It was a cross-sectional study conducted at Pulmonology Unit, Ayub Teaching Hospital, Abbottabad, Pakistan from 12th October, 2017 to 20th May, 2018. Sample size was 126, calculated by using the WHO software with assumptions of 95% confidence level, 29.8% anticipated proportion of malignancy and 8% absolute precision. Patients of both genders with age 13 to 90 years having lymphocytic exudative pleural effusion were included in study. The lymphocytic exudative pleural effusions were those with pleural fluid protein content equal to or 3.5 gm/dl and having cell count more than 50% lymphocytes. Patients with transudative pleural effusions, those on diuretic therapy, patients with bleeding diathesis and those unwilling to participate in the study were excluded. All patients visiting Pulmonology Department with signs and symptoms suggestive of effusion were enrolled in the study. After taking informed consent detailed clinical history and a thorough clinical examination of patients was performed. Radiological diagnostic tests including chest x-ray, ultrasound and where indicated CT scan of thorax were done. Routine and specific investigations were performed as part of diagnostic work up. Pleural fluid was aspirated and examined for its color, protein content, cells, lactate dehydrogenase (LDH), glucose, malignant cells. Pleural fluid aspiration was followed by obtaining specimen for pleural biopsy via Abrams pleural biopsy needle. Standard procedure was followed in obtaining biopsies in each case. A minimum of 4-6 specimens were taken from a single site in a single procedure which were kept in formalin containing container and were sent for histopathology examination to hospital laboratory on the same day. Pleural biopsies were examined by hospital pathologist having more than five years experience in his field. All the above mentioned information including name, age, gender, address and outcome variables were recorded on a predesigned proforma.

Data was analyzed via SPSS 16. Mean ± SD were calculated for continuous variable like age. Categorical variables like gender and outcome were expressed as frequencies and percentages. Chi square test was applied at a level of 5% significance.

## Results

A total of 126 patients of lymphocytic exudative pleural effusion were inducted in the study. Out of total 126 pleural biopsies, adequate tissue was obtained in 121 (96%) cases and confirmed diagnosis on histopathology was established. The remaining 5 (4%) had inadequate biopsy. The mean±SD age of study participants was 56.59 ± 11.69 yrs. with a range of 13-90 years. There were 71(56.3%) males and 55 (43.7%) females in the study population. A total of 76 (60.3%) patients had granulomatous inflammatory changes consistent with tuberculosis, 38 (30.2%) had malignancy and 12 (9.5%) had non-specific results.

When the outcome i.e., pleural biopsy result was stratified by age and gender, statistically significant association was noted with age showing increased frequency of malignant pleural effusion in older age and increased frequency of granulomatous inflammation in younger age (P-value <0.01). However, no statistically significant association was noted with gender. All results are being presnted as tables below.

## Discussion

Exudative pleural effusion is a common clinical problem encountered in clinical practice and so many times poses a great diagnostic challenge for the physician.[12] No diagnosis is ever established in 15% of the cases.[13] Though causes of effusion vary at different regions of the world but in our country majority of the pleural effusions are due to either tuberculosis or malignancy. In most of the cases histopathology examination of the pleural tissue is required to establish the exact diagnosis. Pleural biopsy is commonly performed for this purpose all over the world.[14] Closed pleural biopsy can diagnose up to 49.1% of undiagnosed exudative effusions.[15] Our study showed positive results in 114 (90.5%) cases. This is comparable to a research conducted in Pakistan by Shah D et al (90.5 percent vs 88.9%), but lower than Ihsanullah et al. (90.5 percent vs 95 percent) and higher than Hussain SF et al (90.5 percent vs 46 percent).[16,17,18] In comparison to other research, our findings were comparable on the one hand (90.5 percent vs 88 percent & 84.5 percent)[19,20] and higher with a significant difference on the other (90.5 percent vs 49.1 percent, 59.57 percent )[3,15]

Khadadah et al. suggested that taking 4 or more specimen increases the positive result of closed pleural biopsy.[21] Another study conducted by Chakarbarti et al. suggested that taking 4-6 pleural specimens increased the diagnostic yield to 80%. In our study we took a minimum of 4 and maximum of 06 specimens which may be the reason of higher positive result.[22]

We found Tuberculosis to be the most common cause of exudative pleural effusions diagnosed on histopathology as chronic granulomatous inflammation with a percentage of 60.3%. Our results are comparable to other results by Javaid et al. Shah D et al. and Maskell NA et al.[14,16,19] The diagnostic yield of needle biopsy in diagnosing malignancy is variable ranging from 40 to 60%. The low yield is due to so many reasons. These include the stage of disease, the level of invasion of the parietal pleura, the nature of malignancy and other coexisting conditions causing formation of pleural effusion.[23] Our study demonstrated malignancy in 30.2% of lymphocytic exudative pleural effusions. This is comparable to the results by Jawaid etal., Shah D et al., and Akhtar et al. showing malignancy in 25%, 24% and 40-50% cases respectively.[14,16,24] An investigator reported the diagnostic yield of pleural biopsy to be only 17% but it is important to mention that his study population consisted of only pleural fluid cytology negative patients.[25]

Maskell NA et al showed pleural biopsy positive for malignancy in 57% of cases. This is in contrast to our findings. The possible reason may be the inclusion of a very large number of patients.[19]

Table 1. Age of study participants

| Variable | Mean | Standard Deviation | Minimum | Maximum |
|---|---|---|---|---|
| Age | 56.59 | 11.79 | 13.00 | 90.00 |

In our study malignant pleural effusion is more common in older age group as out of total 38 (30.8%) diagnosed malignant cases, 26(20.63%) were in age group 3 (61-90 years), 10 (7.9%) were in age group 2 (41- 60 years) and only 2(1.58%) were in age group 1(13-40 years).

This is in line with the findings of a few other research.[9,26] Furthermore, in our study, the age difference was not statistically significant, underscoring the fact that age alone cannot reliably distinguish between Tuberculous pleural effusion (TPE) and malignant pleural effusion (MPE). Although MPE is more common in people over 60 years old, reactivation of tuberculosis can also manifest as TPE in this age group, according to reports.[27]

Our study has several limitations. Firstly, we used blind pleural biopsy for histopathology for the diagnosis of MPE and TPE which is not the diagnostic

Table 2. Gender distribution of study participants

| Gender | Frequency | Percent |
|---|---|---|
| Male | 71 | 56.3 |
| Female | 55 | 43.7 |
| Total | 126 | 100.0 |

Table 3. Frequency of pleural biopsy result in study participants

| Pleural biopsy result | Frequency | Percent |
|---|---|---|
| Malignancy | 38 | 30.2 |
| Granuloma | 76 | 60.3 |
| Nonspecific | 12 | 9.5 |
| Total | 126 | 100.0 |

modality of choice to diagnose pleural diseases. Secondly, this study comprised patients presented to a single centre only. Thirdly, the study population was small and hence the results cannot be generalized.

Table 4. Cross-tabulation of pleural biopsy with the age of study participants

| Pleural biopsy result | Age of Patients | | | Total | p-value |
|---|---|---|---|---|---|
| | 13-40 yrs. | 41-60 yrs. | 61-90 yrs | | |
| malignancy | 2 | 10 | 26 | 38 | 0.000 |
| Granulomatous inflammation | 6 | 42 | 28 | 76 | |
| Non specific | 5 | 5 | 2 | 12 | |
| Total | 13 | 57 | 56 | 126 | |

Table 5. Cross tabulation of pleural biopsy with gender of study participants

| Pleural biopsy | Gender | | Total | p-value |
|---|---|---|---|---|
| | 41-60 yrs. | 61-90 yrs | | |
| Malignancy | 27 | 11 | 38 | 0.075 |
| Granulomatous inflammation | 37 | 39 | 76 | |
| Non specific | 7 | 5 | 12 | |
| Total | 71 | 55 | 126 | |

## Conclusion

The most prevalent cause of lymphocytic exudative pleural effusion is tuberculosis, followed by malignancy. Tuberculosis is more common in children and adolescents, whereas cancer is more common in adults. Pleural biopsy, as a more precise approach of diagnosing pleural diseases, will be able to accurately assess the frequency of various disease patterns. Pleural biopsy is strongly recommended for accurate pleural effusion diagnosis, and it should be a standard diagnostic technique in patients with exudative lymphocytic pleural effusion. In order to attain better outcomes, newer methods such as thoracoscopic pleural biopsy may be widely used.

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