ORIGINAL ARTICLE

A Comparative Study of Clinico-biochemical and Thoracoscopic findings of Tubercular and Non-Tubercular Pleural Effusion Patients Undergoing Medical Thoracoscopy: A Hospital Based Prospective Cohort Study

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ABSTRACT

Extra pulmonary tuberculosis accounts for 15% of TB cases. Tubercular Pleural effusion is the second most common form of EPTB. The diagnosis of TB pleural effusion is quite challenging due to the paucibacillary nature of the disease and often delays. The definite diagnosis of tubercular pleurisy still largely depends primarily on the demonstration of positive *Mycobacterium tuberculosis* culture in the pleural fluid which not only lacks sensitivity but is also time-consuming, often leading to delayed diagnosis of pleural effusion cases.

Several pleural fluid markers including adenosine deaminase (ADA), lactate dehydrogenase (LDH), glucose, and differential count of white blood cells have been used to distinguish TPE from non-tubercular exudative effusions. Still, none of these is affirmative for tubercular pleurisy[2,3]. Thus, even after thorough clinical assessment and detailed pleural fluid analysis, the aetiology of many cases of exudative pleural effusions remains elusive and requires pleural biopsy for confirmation.

Medical thoracoscopy or pleuroscopy with semi-rigid thoracoscope is a minimally invasive procedure for diagnosing pleural diseases especially undiagnosed exudative pleural effusion and has gained a lot of interest in pulmonologists in recent years. It is safe and cost-effective. It allows the pulmonologist to enter the pleural space, inspect it and directly take pleural biopsies from suspicious areas. It is done usually with local anaesthesia.

In this study, we compare clinical-biochemical features and pleural fluid characteristics of patients with unexplained exudative pleural effusions in our resource-limited setup and compare it with medical thoracoscopy findings as a reference standard for diagnosis of tubercular pleurisy to see if they can aid in early diagnosis and obviate the need for invasive diagnostic work up in our set up.

Keywords: Extra pulmonary tuberculosis, adenosine deaminase (ADA), lactate dehydrogenase (LDH), Medical thoracoscopy.

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INTRODUCTION

Tubercular pleurisy (also called tubercular pleural effusion) is the most common form of extrapulmonary tuberculosis globally and remains one of the common causes of exudative pleural effusion[1]. Early diagnosis of tubercular pleural effusion is critical as it is a potentially curable disease and any delay in diagnosis is associated with an adverse prognosis. However, the diagnosis of tubercular pleural effusion is often challenging because of the paucibacillary nature of the pleural fluid. The definite diagnosis of tubercular pleurisy still largely depends primarily on the demonstration of positive Mycobacterium tuberculosis culture in the pleural fluid which not only lacks sensitivity but is also time-consuming, often leading to a missed or delayed diagnosis. Several pleural fluid markers including adenosine deaminase (ADA), lactate dehydrogenase (LDH), glucose, and differential count of white blood cells have been used to distinguish TPE from non-tubercular exudative effusions, but none of these is confirmatory for tubercular pleurisy[2,3]. Thus, even after

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thorough clinical assessment and detailed pleural fluid analysis, the aetiology of many cases of exudative pleural effusions remains elusive and requires pleural biopsy for confirmation.

The advent of semi-rigid thoracoscopy has been a major step forward in patients with exudative pleural effusion who remain undiagnosed after initial assessment. It not only allows direct visualization of the pleural cavity but also allows taking pleural biopsies for histopathological and microbiological analysis. However, it is an invasive procedure, requires expertise to perform the procedure and is not available at all the centres in developing countries.

We aimed to compare different clinics-biochemical pleural fluid characteristics of patients undergoing semirigid thoracoscopy for diagnosis of tuberculosis in unexplained exudative pleural effusions in our resource-limited setup and compare it with invasive methods for diagnosis of tubercular pleurisy by taking pleural biopsy obtained by semirigid thoracoscopy as a reference standard to see if they can aid in early diagnosis and prevent the need for invasive diagnostic work up in our set up.

MATERIALS AND METHODS

Study Design & Patient Selection

It was an observational prospective study, conducted at a leading tertiary care hospital in north India from January 2020 to December 2021. Approval to conduct the study was obtained from the Institute's ethical committee with protocol no (# RP 235/2021) and written informed consent was taken from each participant before enrollment.

All patients with undiagnosed exudative pleural effusion who were planned for medical thoracoscopy by the treating physicians/pulmonologists were included in the study. Undiagnosed pleural effusion was defined for this study as exudative effusion meeting light criteria where the diagnosis was not achieved by initial pleural fluid analysis including pleural fluid adenosine deaminase (ADA), CBNAAT, negative acid-fast bacilli (AFB) stain and negative cytology results for malignant cells. All the included patients underwent a detailed clinical and laboratory assessment before thoracoscopy. Information regarding age, gender, residence, signs, and symptoms at presentation, laboratory and imaging findings, and pleural fluid analysis was recorded on a preformed proforma. Patients who had a contraindication for medical thoracoscopy like bleeding diathesis, clinical instability, severe intractable cough, minimal pleural effusion on presentation, and elderly frail patients were excluded from the study.

Thoracoscopy was performed by a semi-rigid thoracoscopy after obtaining proper informed consent. The patient was kept in a lateral decubitus position with the affected side upwards and the pocket of maximum depth was marked with the help of ultrasonography. The procedure was done under conscious sedation by giving intravenous midazolam and injecting fentanyl, the patient was monitored throughout the procedure regarding vital parameters. Local anaesthesia was infiltrated at the marked entry point. Blunt dissection was done at the site and an 11 mm plastic trocar was inserted after dilation of the track. A thoracoscope was inserted through the trocar into the pleural cavity and the whole of the pleural cavity was examined. Thoracoscopic findings were noted. Under direct vision, abnormal or suspicious areas were biopsied. Multiple biopsy pieces were taken in each patient.

Around 4 to 6 pieces were collected in formalin solution for histopathological examination and Ziehl-Neelson staining. At least two pieces of pleural tissue were collected in two saline tubes for mycobacterial culture and the CBNAAT test.

Based on outcomes of the histopathological examination and CBNAAT testing of pleural biopsy, patients were categorized into the following groups:

Tuberculous Pleural Effusion: typical granulomatous inflammation with caseous necrosis regardless of outcomes of AFB staining, or granulomatous inflammation with positive AFB staining and/or positive CBNAAT

Non-Tuberculous Pleural effusion: all those cases do not meet the above-mentioned diagnostic criteria for tuberculous pleural effusion.

Statistical analysis

The data was recorded in a Microsoft Excel spreadsheet and then exported to SPSS 22.0. Continuous variables were summarized as (mean±SD) and categorical variables were listed as frequencies and percentages. Student's t-test, Chi-square tests, and exact tests, whichever were appropriate, were used for comparing different variables between

tubercular and non-tubercular pleural effusions. Chi-square tests were used to calculate the sensitivity and specificity of different pleural fluid markers using histopathological confirmation as the gold standard.

RESULTS

A total of 50 patients who underwent medical thoracoscopy as the aetiology of their pleural effusion remained obscure after initial assessment were included in the study. Out of these, 50% of patients were found to have tubercular pleurisy, 24% had malignancy and 26% had nonspecific pleuritis. Table 1 shows the baseline characteristics and demographic profiles of patients who were diagnosed with tubercular pleurisy. The mean age of patients with tubercular pleurisy was 47.36 years (±SD 19.84). The majority of patients had a rural background. Males constituted 76% of the total cohort of tubercular pleural effusion.

Table 1: Baseline characteristics of patients with Tubercular pleural effusion

Variable	Frequency/mean	Percentage/SD
Demographics		
Age (years)	47.36	19.84
Rural residence	23	92.0
Males	19	76.0
Females	6	24.0
Side of pleural effusion		
Right	14	56.0
Left	11	44.0
Quantity of Pleural Effusion		
Mild	2	8
Moderate	18	72
Severe	5	20

Table 2 shows a comparative analysis of CT findings and pleural fluid analysis of the patients with tubercular and non-tubercular pleural effusion. CT chest showed a passive collapse in 44% of patients with tubercular pleural effusion with parenchymal abnormality in the form of consolidation seen in only 12% of patients. As compared to patients with non-tubercular pleural effusion, only pleural thickening and/or pleural enhancement on CT was significantly more in patients with tubercular pleural effusion with a p-value of 0.02.

Diagnostic thoracentesis was performed on all patients with pleural effusion and it revealed that tubercular pleural effusion was moderate in quantity and straw in colour in the majority of patients as seen in Table 2. Tubercular pleural effusion had significantly higher mean ADA levels than non-tubercular pleural effusion with a p-value of <0.001 and had lower mean LDH levels(p-value of 0.007) and LDH/ADA ratio(p-value of <0.001). An ADA level of more than 40 was seen in 40% of patients with tubercular pleural effusion.

Visual inspection of the pleura during medical thoracoscopy revealed several abnormalities in the study patients as outlined in Table 3. Pleural adhesions were seen in 96% of patients with tubercular pleural effusion patients, but the finding of sago-grain nodules with edematous pleura was significantly more seen in patients with tubercular pleural effusion.

Out of the 25 patients who were diagnosed with tubercular pleurisy based on histopathology, 9 had CBNAAT positive. We compared the diagnostic utility of different pleural fluid markers in tubercular pleural effusion. The ROC curve (Fig. 1) for the LDH/ADA ratio in differentiating tubercular pleurisy from other causes of exudative pleural effusion had an area under the curve of 0.952 (95% CI 0.894-1.000, $p < 0.001$). A ratio of less than 14.71 was the cut-off value with the maximal combined sensitivity and specificity of 92%. It had a PPV of 92% and an NPV of 92%.

The ROC curve for the lymphocyte-neutrophil ratio (fig 1) had an area under the curve of 0.654 (95% CI 0.499-0.809, $p = 0.06$). A value of 1.98 had a sensitivity and specificity of 60%. An ADA level ≥40 U/L alone had a sensitivity of 40% only, but specificity and PPV of 92% and 83.3% respectively (table 4).

DISCUSSION

Exudative pleural effusions are commonly encountered in clinical practice, but in about one-fourth of cases, aetiology remains elusive after a thorough initial evaluation involving patients' clinical presentation, imaging studies including CT of the chest, and pleural fluid analysis[4]. These patients often undergo medical thoracoscopy with a semi-rigid thoracoscope which has been reported to have a high diagnostic yield for diagnosing pleural diseases, especially in undiagnosed exudative pleural effusions[5,6]. In tubercular endemic areas, often these effusions turn out to be tubercular[4-7]. This study provides important insights into the profile of these patients with tubercular pleurisy diagnosed only after undergoing medical thoracoscopy and helps to elucidate different parameters that may aid in

Table 2: Comparison of CT findings and pleural fluid characteristics in tuberculous vs non tuberculous patients

Variable	Tuberculous PE (n= 25)		Non-Tuberculous PE (n= 25)		P value
	No./mean	%age/SD	No./mean	%age/SD	
CT findings					
Loculations	8	32	5	20	0.33
Passive collapse	11	44	15	60	0.26
Pleural thickening and/or, pleural enhancement	7	28	1	4	**0.02***
Lung Mass	1	4	5	20	0.08
Pleural deposits	0	0	1	4	0.31
Mediastinal lymphadenopathy	4	16	5	20	0.71
Consolidation	3	12	3	12	1.00
Pleural fluid characteristics					
Colour					
Haemorrhagic	7	28	9	36	0.54
Straw	18	72	14	56	0.24
Serous	0	0	2	8	0.15
Quantity					
Mild	2	8	3	12	0.64
Moderate	18	72	11	44	**0.04***
Massive	5	20	11	44	0.07
Analysis					
Mean leucocyte count	1182.68	1524.12	673.44	775.887	0.14
Mean protein concentration	4.67	1.21	4.59	0.81	0.79
Mean LDH	364.12	148.96	648.60	490.23	**0.007***
Mean ADA	40.46	12.69	17.27	9.76	**<0.001***
Mean LDH/ADA ratio	9.44	4.63	47.14	36.54	**<0.001***
Mean L:N ratio	3.97	4.10	2.95	4.46	**0.04**
ADA = 40	10	40	2	8	**0.008***

Table 3: Comparison of thoracoscopic findings in tuberculous vs non tuberculous patients

variable	Tuberculous PE (n= 25)		Non-Tuberculous PE (n= 25)		P value
	No./mean	%age/SD	No./mean	%age/SD	
Thoracoscopic findings					
Inflamed and/or, oedematous pleura	10	40	6	24	0.22
Plaques/nodules on parietal pleura	19	76	18	72	0.74
Nodules on visceral pleura	2	8	1	4	0.55
Sago-grain nodules with oedematous pleura	8	32	1	4	**0.01***
Pleural thickening	8	32	6	24	0.53
Thin pleural adhesions	14	56	12	48	0.57
Thick pleural adhesions	10	40	7	28	0.37

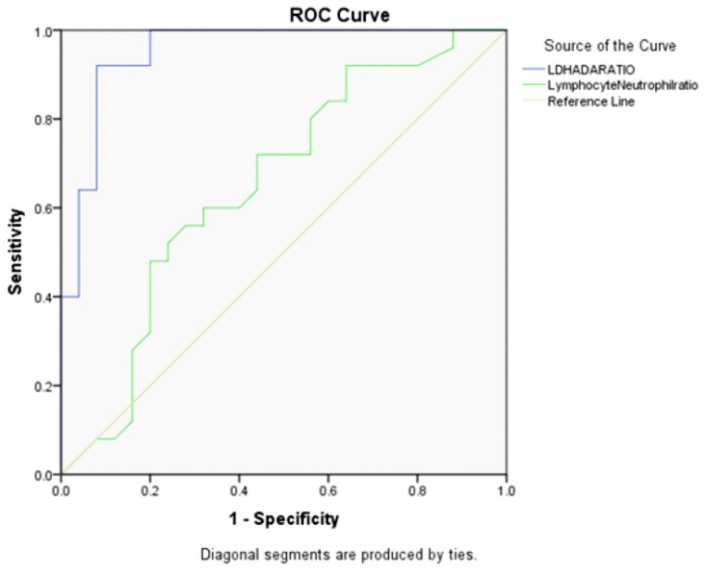


Fig. 1: ROC curve analysis of LDH/ADA and lymphocyte- neutrophil ratio (LNR) as a marker for differentiating tubercular and non-tubercular pleural effusion

Table 4: Comparison of different pleural fluid parameters for diagnosis of tubercular pleural effusion

Pleural fluid parameter	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
LDH/ADA ratio	92.00%	92.00%	92.00%	92.00%	92.00%
ADA >40	40.00%	92.00%	83.33%	60.53%	66.00%
Lymphocyte- Neutrophil-Ratio	60.00%	60.00%	60.00%	60.00%	60.00%

differentiating tubercular and non-tubercular exudative effusions. Also, the diagnostic utility of different pleural fluid markers in tubercular pleural effusion has been compared.

The mean age of patients diagnosed with tubercular pleurisy in this study was 47 years. In developing countries around the world, the incidence of tubercular pleurisy is higher in the younger population. This is in contrast with developed countries where patients tend to present at an older age as most cases are because of reactivation of disease rather than primary infection[8,9].

Tubercular pleural effusions are usually unilateral[10]. In our study, patients showed slight right predominance, though predisposition to either side has not been asserted. Tubercular pleural effusions vary significantly in size[10]. In our study, most cases were moderate occupying between one-third to two-thirds of hemithorax and it was statistically significant in comparison to non-tubercular exudative effusions where most cases were either mild or massive. This aligns with a previous study by Valdes et al. who reported that TB effusions are moderate in 47.2% of cases[11].

CT chest has an important role in the diagnostic workup of patients with exudative pleural effusion of unclear aetiology. It may help in differentiating benign from malignant causes. Though CT alone can't differentiate tubercular from non-tubercular aetiology, the presence of interlobular septal thickening and micronodules with peri-lymphatic distribution be associated more with pleural tuberculosis[12]. In our study, these findings were not profoundly seen possibly because of different patient inclusion criteria. We recruited only those patients who needed medical thoracoscopy for diagnosis and the patients

with these classical CT findings were empirically started on anti-tubercular therapy rather than being subjected to thoracoscopy. In our study, the presence of pleural thickening and/or enhancement on CT chest was seen as significantly more common in tubercular pleurisy.

Tuberculous pleural effusions are usually straw-coloured exudates, as ascertained in our study as well[9]. Generally, these effusions have lymphocyte predominance and a lymphocyte-to-neutrophil ratio of greater than 0.75[8]. In this study, though the mean L: N ratio of tubercular pleural effusion was greater than 0.75, there was a statistically significant difference between the two groups. Patients with tubercular pleurisy had lower LDH and more ADA levels than non-tubercular exudative pleural effusions. ADA, a purine-degrading enzyme found particularly in monocytes and lymphocytes, is present in high concentrations in tuberculous effusions and has been found to have good diagnostic utility. In the setting of lymphocytic exudative pleural effusion, an ADA level of >40 IU/L has been found to have a positive predictive value of 98% in TB-endemic areas. These findings also resonated in our study as we contemplated that a significantly higher proportion of patients with tubercular pleural effusion had an ADA level of > 40 IU/L than patients with non-tubercular pleural effusion[13,14].

Though the aetiology of pleural effusion is determined by clinical assessment and pleural fluid analysis in the majority of patients, 20% of patients remain undiagnosed[15]. Semi-rigid thoracoscopy has revolutionized the diagnostic work-up of these patients with undiagnosed pleural effusion. It not only enables taking specimens for histopathological examination but also allows direct visualization of the entire pleural surface. Certain characteristic patterns on pleuroscopic examination have been described previously with TB pleurisy including Sago grain-like nodules/micronodules, adhesions, and discrete distribution of lesions[16]. In our study, pleural adhesions and pleural plaques/nodules were the most common abnormalities in patients with tubercular pleurisy, but the presence of Sago grain-like micronodules was significantly associated with tuberculosis. These characteristic micronodules are thought to represent areas of granulomatous inflammation, the histological hallmark of tuberculosis. By identifying the characteristic features of TB pleurisy, a precise biopsy of the targeted lesion may increase the diagnostic yield rate and reduce the duration of the procedure.

Though medical thoracoscopy has overall improved the diagnosis of tubercular pleurisy, it has its limitations. It is an invasive procedure and requires expertise. It is not available at all the centres. This becomes a limiting step, especially in resource-poor countries. We analyzed the performance of the LDH/ADA ratio in differentiating tubercular and non-tubercular pleural effusions. At a cut-off level of 14.71 or less, this ratio had a sensitivity and specificity of 92%, which was found to be significantly higher than ADA levels of more than 40 and the lymphocyte-neutrophil ratio. The LDH/ADA ratio's accuracy in TB effusions can be explained physiologically, and it does so with some degree of plausibility. LDH levels rise proportionately more in malignant and parapneumonic effusions while ADA levels are more elevated in tubercular pleural effusions[17]. Similarly in a study done by Jinlin et al where he found that the LDH/ADA ratio at a cut-off value less than 16.2 has a sensitivity of 93.62%, a specificity of 93.06%, a PLR of 13.48, and a NLR of 0.068 for tubercular pleural effusions.

Thus, the ratio is significantly lower in TB effusions than in non-TB effusions. This finding may aid clinicians in early decision-making for the treatment of these patients. This helps in the better prognosis of these patients and avoidance of performing more invasive procedures on them for diagnosis.

Our study has its limitations. A small sample size precludes its use for the generalization of the results of this study. Many patients with lymphocytic exudative effusion with an ADA >40 IU/L are often empirically started on anti-tubercular therapy without subjecting them to pleural biopsy and that may be the reason for the low diagnostic utility of ADA levels in our study.

CONCLUSIONS

Tubercular pleurisy remains a common cause of undiagnosed exudative pleural effusions and poses a diagnostic challenge. Several clinical, biochemical and imaging findings may provide important clues towards the tubercular aetiology of exudative pleural effusions, which may help in obviating the need for further diagnostic workup. LDH/ADA ratio may be used as an important marker for differentiating tubercular from non-tubercular

effusions.

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