

FUNCTIONAL SEQUELAE OF TUBERCULOUS PLEURAL EFFUSION

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ABSTRACT

BACKGROUND

In patients with pleural effusion, irrespective of aetiology, the alterations in physiological states leading to restrictive lung functions and hypoxemia. In this study, we have aimed to study the effects of tuberculous pleural effusion on the pulmonary function and the predictive value of the initial severity of pleural effusion on chest x-ray and the residual pleural thickening in the severity of the restrictive abnormality. Also, we have compared the various pleural fluid characteristics in predicting the restrictive abnormality in tuberculous pleural effusion.

MATERIALS AND METHODS

The patients selected for the study, were initially subjected to diagnostic and therapeutic pleural tap on admission. They were then put on standard DOTS therapy. Their PFT was done on admission, then at one month, then two months and at the end of therapy at six months. Their chest X-ray was taken at monthly intervals and the residual pleural thickening was estimated. The resultant data was analysed statistically by ANOVA test, paired-t test and by Pearson's correlation.

RESULTS

In our study, we have found a significant restrictive abnormality in lung function testing in our selected patients of tuberculous pleural effusion. They had a FVC% value of less than 80%. An interesting finding in our study was that, there was an element of small airway disease in our patients. This was manifested as an abnormal FET 25-75%. Also, we have found no relationship of the initial severity of pleural effusion with the final restrictive abnormality.

Also, we found no correlation between the pleural fluid characteristics and the RPT. We had compared the protein concentration, ADA and lymphocyte counts with the RPT. There was no statistical difference in the group with RPT and the group without any RPT as far as these parameters is applied. So, the finding from our study does support the theory of increased hypersensitivity as the origin of RPT.

In our patients, we have done therapeutic thoracentesis on admission. PFT done immediately after this found a significant restrictive abnormality though the patients had a subjective relief of dyspnoea. On follow-up, subsequent PFTs revealed that there was significant improvement in all the parameters of PFT.

All values showed statistically significant improvement after six months of treatment.

The small airway obstruction is a significant finding in our study. This compels us to speculate about its pathogenesis. So far in literature no clear-cut explanation has been offered. However, endobronchial fibrosis in small airways as a result of tubercular parenchymal disease may be responsible for this. This suggests that tuberculous pleural effusion is no more a compartmentalized affection of the pleura, but also has some parenchymal component difficult to demonstrate clinically and radiologically.

CONCLUSION

- Tuberculous pleural effusion causes a restrictive abnormality and small airway obstruction.
- These abnormalities improve gradually over a period of six months when the patient is on AKT.
- These abnormalities have no relation with the pleural fluid cytochemical and biochemical characteristics.
- These abnormalities also have no relationship with the initial severity of the pleural effusion or the RPT.

As we can see that, one of the highlights of this study was small airway obstruction, shown uniformly in all the thirty study subjects. The mechanism of which is difficult to explain and definitely needs undertaking of further long-term and large-scale studies.

KEYWORDS

Residual Pleural Thickening, Tuberculous Pleural Effusion, Restrictive abnormality, Small Airway Disease.

HOW TO CITE THIS ARTICLE: Menon SV, Abbas R, Padmini S, et al. Functional sequelae of tuberculous pleural effusion. J. Evid. Based Med. Healthc. 2017; 4(14), 763-777. DOI: 10.18410/jebmh/2017/149

BACKGROUND

In patients with pleural effusion, irrespective of aetiology, the alterations in physiological states leading to restrictive

lung functions and hypoxemia have been seen. Normally, 10 to 20 mL of fluid is spread thinly over the visceral and parietal pleurae.

*Financial or Other, Competing Interest: None.
Submission 02-01-2017, Peer Review 14-01-2017,
Acceptance 01-02-2017, Published 14-02-2017.*

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DOI: 10.18410/jebmh/2017/149



The fluid is similar in composition to plasma except that it is lower in protein (<1.5 g/dL). Pleural fluid enters from the pleural capillaries and exits via parietal pleural stomas and the lymphatics.

Eight million people developed tuberculosis in 1990 worldwide; with 95% occurring in developed countries.¹ The frequency of pleural effusion varies from country to country. In United States, tuberculous pleural effusions represent 4% of all cases of tuberculosis.² while in Spain it represents 23%.³

Tuberculous pleurisy is thought to be the result of a delayed hypersensitivity reaction in response to the presence of mycobacterial antigens in the pleural space.⁴ This immunologic reaction causes the stimulation and differentiation of lymphocytes, which release lymphokines, which in turn activate macrophages for an enhanced bactericidal effect.⁴

While new therapeutic regimens can control tuberculous pleural effusion, residual pleural thickening (RPT) has been found in about half of the patients treated in a number of studies.^{5,6,7}

To help reduce the incidence of RPT and to facilitate recovery, therapeutic thoracentesis or early complete drainage has been tried to obtain symptomatic improvement.

The levels of adenosine deaminase (ADA), an enzyme found in most cells, are increased in tuberculous pleural effusions, and this determination has acquired popularity as a diagnostic test in high-incidence areas for tuberculous pleural effusion because it is not invasive, the assay is not expensive, and it is readily accessible. They release ADA when stimulated in the presence of live intracellular microorganisms.⁸

Since the first description of the spirometer by John Hutchinson in the late 1800s, pulmonary function tests (PFT) have expanded to include spirometric lung volumes; Carbon monoxide-diffusing capacity (DLCO); Respiratory muscle performance; and exercise and functional testing, such as the 6-minute walk test (6MWT) and cardiopulmonary exercise testing (CPET).

Indications for PFT has widened substantially, ranging from screening smokers for early pulmonary disease or screening patients for drug induced toxicity to determining the diagnosis and prognosis of pulmonary conditions.

Pulmonary function tests (PFT) in pleural effusion show moderate restrictive abnormalities with mildly reduced diffusion capacity with mild hypoxemia and hypocapnia and

mild respiratory alkalosis. The derangements in PFT are proportional to the severity of pleural effusion, after institution of anti-tuberculosis therapy, radiological improvements occur much earlier but the lung functions continue improve up to six months after treatment is over. Even at the end of six months of therapy, some residual restrictive abnormalities are left which are directly proportional to the severity of pleural effusion prior to the start of treatment.⁹

The aetiology of pleural effusion in a country like India, in most of the cases is tuberculosis. Tuberculosis also causes a pleural fibrosis, which adds to the restrictive abnormality. In this study, we have assessed the predictive value of PFT in the prognosis of patients with tuberculous pleural effusion, and the severity of the restrictive abnormality to the severity of pleural effusion assessed by chest X-rays and PFTs and also the relationship of the restrictive defect with the biochemical and microscopic characteristics of the pleural fluid.

AIMS AND OBJECTIVES

1. To study the lung function abnormalities in cases of tuberculous pleural effusion.
2. To correlate the abnormalities if detected with the severity of the pleural effusion.
3. To correlate such abnormalities if detected with the radiological and cytochemical parameters, duration of disease and the treatment.
4. To correlate the residual defects (both radiological and PFT-wise) with various pleural fluid characteristics.

MATERIALS AND METHODS

Study Population-

Thirty patients, diagnosed as tuberculous pleural effusion meeting the inclusion and exclusion criteria over a period of six months, were followed up for a period of six months of DOTS therapy.

Inclusion Criteria

- Age >12 years.
- A diagnosis of tuberculous pleural effusion based on clinical data, pleural fluid characteristics and radiological findings.
- Parenchymal tuberculous process ruled out as given in exclusion criteria.

Exclusion Criteria

- Age < 12 years
- Patients already on AKT
- Seropositive for HIV
- Smokers
- Occupation posing risk to lung function
- History of prior lung diseases like bronchial asthma, COPD and bronchiectasis
- Lung parenchymal involvement as detected by clinical examination, X-ray/USG, Sputum AFB positivity.
- Patients with hypertension, congestive cardiac failure and diabetes mellitus.

Study Protocol

The patients selected for the study, were initially subjected to diagnostic and therapeutic pleural tap on admission. They were then started on 4 drugs AKT for 2 months (comprising Isoniazid, Rifampicin, Ethambutol and Pyrazinamide). After this intensive phase of therapy, they were put on 2-drug therapy for 4 more months (comprising of Isoniazid and Rifampicin). The patients were, followed up with serial monthly chest x-rays for 6 months when they were on AKT. RPT was calculated and monitored. The patients were also subjected to PFTs on admission and thereafter at first, second and sixth months.

Radiology and Interventions

Chest X-rays were taken on admission and then at every monthly interval to follow up the amount of fluid. The effusion was graded as follows-

1. Mild : Just above the costophrenic angle till Lower border of fifth rib.
2. Moderate : up to lower border of third rib.
3. Severe : above the third rib.

Maximal pleural thickening was measured at the costal margin of the affected hemi thorax in a postero-anterior radiograph. A residual pleural thickening (RPT) of >2 mm was considered to be radiologically abnormal.

Diagnostic thoracentesis was done on the day of admission with the patient in the sitting position, using a standard 18-gauge needle and the pleural fluid sent for routine microscopy and Adenosine deaminase (ADA) tests. Patients were diagnosed as tuberculous pleural effusion on the basis of a lymphocytic predominance, high proteins and an ADA level more than 40 IU/l on the pleural fluid analysis. Following this, patients having moderate to severe pleural effusion were tapped till the fluid was less than at least 1/3rd of the hemi thorax or till there was no more free flow of fluid.

Pulmonary Function Tests-

The following pulmonary function tests were performed:

1. Forced Vital Capacity (FVC)
2. FVC %
3. Forced Expiratory Volume in one second (FEV1)
4. FEV1
5. FEV1/FVC %
6. Peak Expiratory flow rate (PEF)
7. FEF 25-75 %
8. Maximal Ventilatory Volume (MVV %)
9. FEF 75-85%
10. FEF 200-1200
11. Inspiratory Capacity (IC)
12. Tidal Volume (TV)
13. Resistance (R)

Each pulmonary function test was expressed as a percentage of the predicted values based on age, sex, height, weight and body surface area as per the Indian community reference values.^{10,11}

Follow-up of each patient was done at monthly intervals where serial chest x-rays were done and PFT was done at one, two and six months. During this period the patients were on DOTS regimen of AKT.

Statistical Analysis

For comparison of data, the following statistical tests were applied-

1. ANOVA Test

This test was applied to compare the severity of pleural effusion and the residual pleural thickening with the restrictive abnormality i.e., with the FVC %.

2. Paired t Test

This test was used to compare the severity of the PFT parameters over a period of six months with the initial values on admission.

3. Pearson's Correlation

This test was used to compare the pleural fluid characteristics namely, protein concentration, ADA and lymphocyte count with the FVC% i.e., the restrictive abnormality on admission and subsequently at the 1st, 2nd and 6th follow-ups.

Review of Literature

Pulmonary function testing includes both simple spirometry and sophisticated physiologic testing.

Static Lung Volumes and Capacities.^{12,13}

Static lung volumes (see Figure 1) reflect the elastic properties lungs and chest wall.

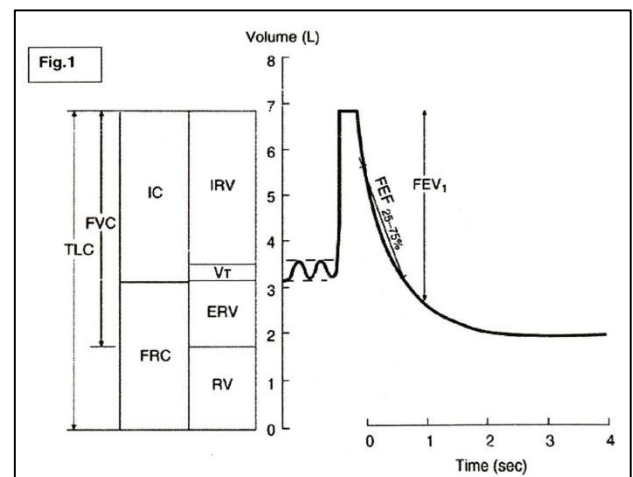


Figure 1

Vital Capacity (VC or "slow VC") is the maximum volume of air that can be expired slowly after a full inspiratory effort. Simple to perform, it is one of the most valuable measurements of pulmonary function. Because VC decreases as a restrictive lung disorder (e.g., pulmonary oedema, interstitial fibrosis) worsens, it can be used along with the diffusing capacity to follow the course of such a disorder and its response to therapy. The VC also reflects

the strength of the respiratory muscles and is often used to monitor the course of neuromuscular disorders.

Forced Vital Capacity (FVC), similar to VC, is the volume of air expired with maximal force. It is usually measured along with expiratory flow rates in simple spirometry (see Dynamic Lung Volumes and Flow Rates, below). The VC can be considerably greater than the FVC in patients with airway obstruction. During the FVC manoeuvre, terminal airways can close prematurely (i.e., before the true residual volume is reached), trapping gas distally and preventing its measurement by the spirometer.

Dynamic Lung Volumes and Flow Rates.^{12,13}

Dynamic lung volumes reflect the caliber and integrity of the airways. Spirometry (see Figure. 1) records lung volume against time during an FVC manoeuvre.

Forced Expiratory Volume in 1 Sec (FEV1) is the volume of air forcefully expired during the first second after a full breath and normally accounts for >75% of the FVC. This value is recorded both as an absolute value and as a percentage of the FVC (FEV₁/FVC). The mean forced expiratory flow during the middle half of the FVC (FEF_{25-75%}) is the slope of the line that intersects the Spirographic tracing at 25% and 75% of the FVC. The FEF_{25-75%} is less effort-dependent than the FEV1 and is a more sensitive indicator of early airway obstruction.

In restrictive lung disorders, increased tissue elastic recoil tends to maintain the caliber of the larger airways so that at comparable lung volumes, flow rates are often higher than normal. (Tests of small airways function, however, may be abnormal)

Maximal Voluntary Ventilation (MVV) is determined by encouraging the patient to breathe at maximal tidal volume and respiratory rate for 12 sec; the volume of air expired is expressed in L/min. The MVV generally parallels the FEV₁ and can be used to test internal consistency and estimate patient cooperation.

When the MVV is disproportionately low in a patient who seems to be cooperating, neuromuscular weakness should be suspected. Except in advanced neuromuscular disease, most patients can generate fairly good single-breath efforts (e.g., FVC). Because the MVV is much more demanding, it can reveal the diminished reserves of weak respiratory muscles. The MVV decreases progressively with increasing weakness of the respiratory muscles and, along with maximum inspiratory and expiratory pressures (see below), may be the only demonstrable pulmonary function abnormality in patients with moderately severe neuromuscular disease.

Airway Resistance (R) can be directly measured with a body plethysmograph, which determines the pressure required to produce a given flow.

Small Airways Studies.^{12,13}

In the normal lung, bronchi <2 mm in diameter constitute <10% of the total airway resistance, but their aggregate surface area is large. Disease affecting primarily the small (peripheral) airways can be extensive yet not affect the R or

any tests dependent on it (e.g., FEV₁). This is true of early obstructive lung disease and interstitial granulomatous, fibrotic, or inflammatory disorders.

The status of the small airways is reflected by the FEF 25-75% and by expiratory flow rates in the last 25 to 50% of the FVC, determined from the flow-volume loop (see Figure. 2A).

- (A) Normal. Inspiratory limb of loop is symmetric and convex. Expiratory limb is linear. Flow rates at midpoint of VC are often measured. MIF 50% FVC is >MEF 50% FVC because of dynamic compression of the airways. Peak expiratory flow is sometimes used to estimate degree of airway obstruction but is very dependent on patient effort. Expiratory flow rates over lower 50% of FVC (i.e., approaching RV) are sensitive indicators of small airways status.¹⁴
- (B) Restrictive Disease (e.g., sarcoidosis, kyphoscoliosis). Configuration of loop is narrowed because of diminished lung volumes, but shape is basically as in (A). Flow rates are normal (actually greater than normal at comparable lung volumes because increased elastic recoil of lungs and/or chest wall holds airways open).¹⁴

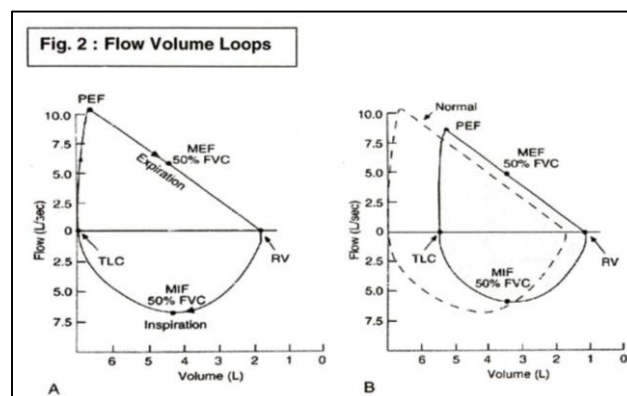


Figure 2. Flow Volume Loops

Volume	Flow sensing (Pneumotach)
Bellows	Fleisch
Rolling seal	Screen
Water	Hotwire
Dry	Turbine

Types of Spirometers.¹⁴

A spirometer, including the waterless, rolling seal type, and Stead-Wells water seal type is an instrument that directly measures the volume of air displaced or measures airflow by a sensing device, such as a pneumotachometer or a tube containing a fixed resistance to flow (Table 1).¹⁵ Today, most clinical pulmonary function testing laboratories use a microprocessor-driven pneumotachometer to measure air flow and then to mathematically derive volume.

Acceptability Criteria.¹⁵

- Individual spirometrys are "acceptable" if:
 - They are free from artefacts

- Cough or glottis closure during the first second of exhalation
- Early termination or cut-off
- Variable effort
- Leak
- Obstructed mouthpiece
- Have good starts
 - Extrapolated volume less than 5% of FVC or 0.15 L, whichever is greater;
 - OR
 - Time-to-PEF of less than 120 ms (optional until further information is available)
- Have a satisfactory exhalation
 - 6 s of exhalation and/or a plateau in the volume-time curve;
 - Reasonable duration or a plateau in the volume-time curve;
 - OR
 - If the subject cannot or should not continue to exhale.

Reproducibility Criteria.¹⁵

- After 3 acceptable spiromograms have been obtained, apply the following tests:
 - Are the two largest FVC within 0.2 L of each other?
 - Are the two largest FEV1 within 0.2 L of each other?
- If both of these criteria are met, the test session may be concluded.
- If both of these criteria are not met, continue testing until:
 - Both of the criteria are met with analysis of additional acceptable spiromograms; OR
 - A total of eight tests have been performed; OR
 - The patient /subject cannot or should not continue
- Save at a minimum the three best manoeuvres.

Interpretation of PFTs is usually based on comparisons of data measured in an individual patient or subject with reference (predicted) values based on healthy subjects. Predicted values should be obtained from studies of "normal" or "healthy" subjects with the same anthropometric (e.g. sex, age and height) and, where relevant, ethnic characteristics of the patient being tested. Ideally, reference values are calculated with equations derived from measurements observed in a representative sample of healthy subjects in a general population. Reference equations can also be derived from large groups of volunteers, provided that criteria for normal selection and proper distribution of anthropometric characteristics are satisfied.¹⁶ Criteria to define subjects as normal or healthy have been discussed in previous ATS and European Respiratory Society (ERS) statements.^{17,18,19}

Criteria for Assessing the Severity of Abnormalities on PFT.¹⁹

A. Obstructive Abnormality

This is interpreted when the FEV₁/FVC ratio is below the normal range. The severity of the abnormality might be graded as follows:

"May be a physiological variant"	% Pred FEV ₁ >100
"Mild"	% Pred FEV ₁ <100 and >70
"Moderate"	% Pred FEV ₁ <70 and >60
"Moderately severe"	% Pred FEV ₁ <60 and >50
"Severe"	% Pred FEV ₁ <50 and >34

B. Restrictive Abnormality

This is most reliably interpreted on the basis of TLC. If this is not available, one may interpret a reduction in the VC without a reduction of the FEV₁/FVC ratio as a "restriction of the volume excursion of the lung." The severity of the abnormality might be graded as follows:

Based on spirometry

"Mild"	% Pred FVC < LLN but > 70
"Moderate"	% Pred FVC < 70 and > 60
"Moderately severe"	% Pred FVC < 60 and > 50
"Severe"	% Pred FVC < 50 and > 34
"Very severe"	% Pred FVC < 34

Tuberculous pleurisy is thought to be the result of a delayed hypersensitivity reaction in response to the presence of mycobacterial antigens in the pleural space.⁴

Radiographs of patients with tuberculous pleural effusion typically show small-to-moderate, unilateral effusions, although massive effusions are seen in 14 to 29% of those with primary disease.^{3,9,20,21}

While new therapeutic regimens can control tuberculous pleural effusion, residual pleural thickening (RPT) has been found in about half of the patients treated in a number of studies.^{5,6,7}

Tuberculous pleural effusions resolve spontaneously within 2 to 4 months in most healthy individuals: however, if untreated, 65% of patients will develop pulmonary or extra pulmonary tuberculosis within 5 years.³

To help reduce the incidence of RPT and to facilitate recovery, therapeutic thoracocentesis or early complete drainage has been tried to obtain symptomatic improvement.

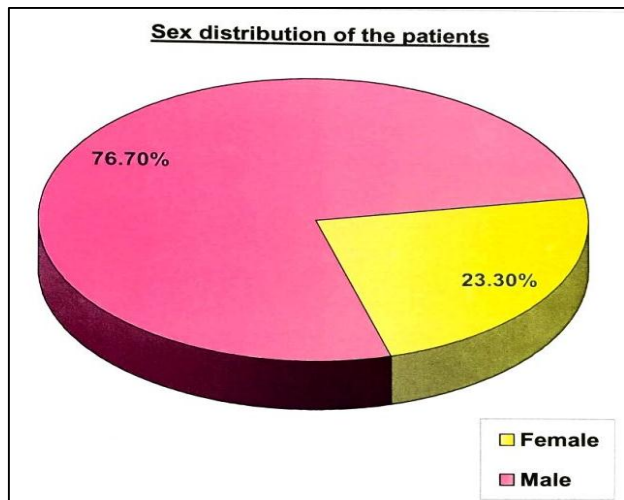
The levels of adenosine deaminase (ADA), an enzyme found in most cells, are increased in tuberculous pleural effusions, and this determination has acquired popularity as a diagnostic test in high-incidence areas for TPE because it is not invasive, the assay is not expensive, and it is readily accessible. They release ADA when stimulated in the presence of live intracellular microorganisms.⁸ For this reason, ADA has been looked on as a marker of cell-mediated immunity and, in particular, as a marker of the activation of T lymphocytes.²²

Statistics and Data Analysis

Sex	Number	Percentage
Female	7	23.30%
Male	23	76.70%
Total	30	100.00%

Table 1. Sex Distribution of the Patients

The above table shows the sex distribution of patients included in this study. Out of 30 patients in the study, 7 were Females while 23 were males. All the patients were followed up for 6 months over a period of one year.



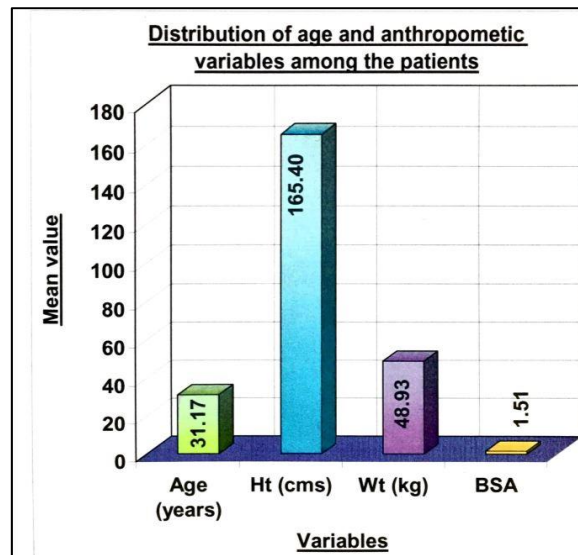
Graph 1. Sex Distribution of the Patients

This pie chart shows the sex distribution of the study population.

Variables	Mean (n=30)	SD	Minimum	Maximum
Age (years)	31.17	9.97	15.00	48.00
Ht (cms)	165.40	7.31	153.00	180.00
Wt (kg)	48.93	7.14	40.00	70.00
BSA	1.51	0.11	1.36	1.73

Table 2. Distribution of Age and Anthropometric Variables

This table shows the age and anthropometric distribution of the population chosen for the study. The mean age of the study population was 31.17, with a minimum age of 15 years and maximum age of 48 years. The average height of the population was 165.40 cms, with a minimum height of 153 cms and a maximum height of 180 cms. The mean weight of the study population was 48.93 kg, with a minimum weight of 40 kg and a maximum weight of 70 kg. These anthropometric criteria were used to calculate the Body surface area (BSA), which in turn was the basis for calculating the reference values for pulmonary function tests for this study population, using the accepted standards for the Indian population.



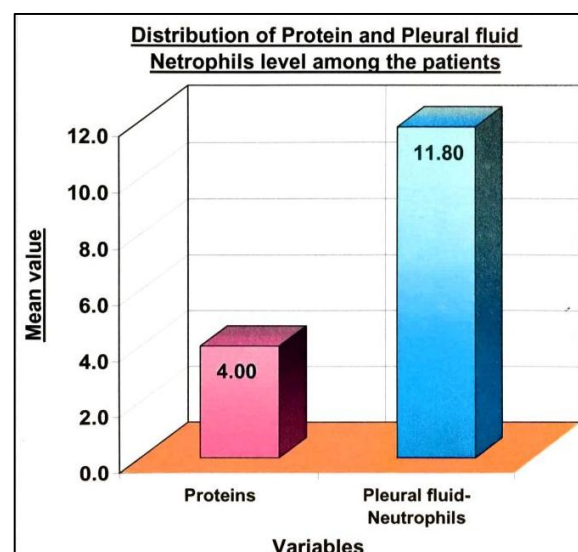
Graph 2. Distribution of Age and Anthropometric Variables

This graph shows the anthropometric variables in the study population.

Variables	Mean (n=30)	SD	Minimum	Maximum
ESR	73.33	26.66	34.00	123.00
Pleural fluid-Total Cells /mm ³	804.60	370.04	120.00	1600.00
Pleural fluid-Lymphocytes %	88.53	11.29	60.00	99.00
Pleural fluid-Neutrophils %	11.80	11.92	1.00	40.00
RBCs/mmm ³	419.67	492.79	0.00	2000.00
Proteins Gm%	4.00	1.39	1.80	6.20
ADA IU	82.35	31.86	9.40	47.00

Table 3. Distribution of Hematological and Pleural Fluid Variables in the Study Population

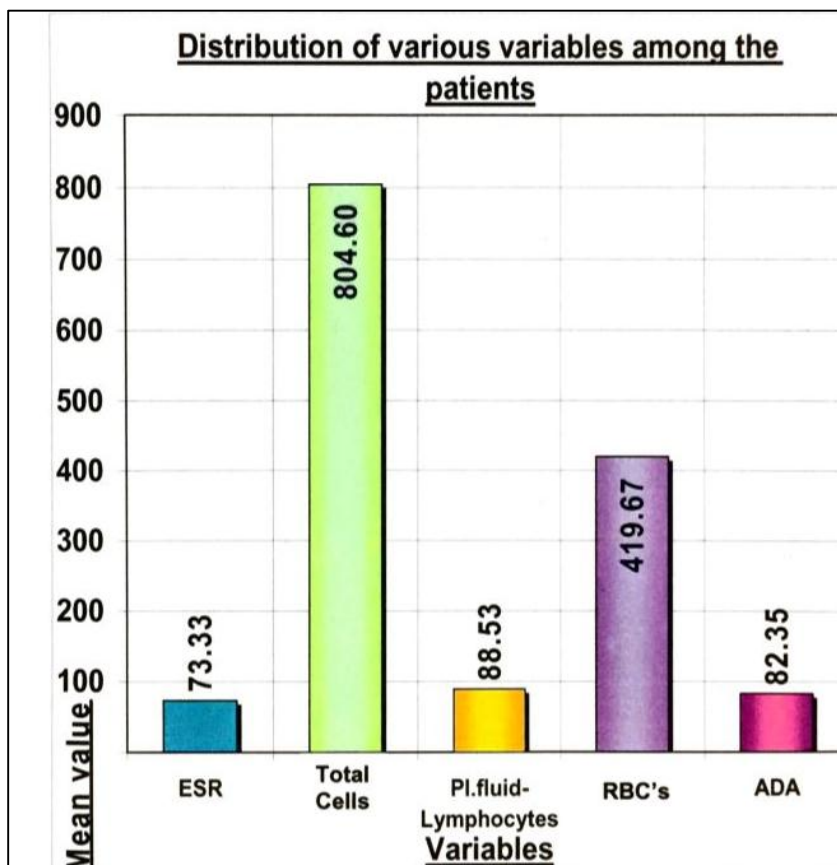
This table shows the ESR and pleural fluid characteristics of the study population.



Graph 3A. Distribution of Pleural Variables in the Study Population

This graph shows the distribution of BSA and the pleural fluid proteins and neutrophil levels in the study population.

Distribution of Various Variables among the Patients



Graph 3B. Distribution of Haematological and Pleural Fluid Variables in the Study Population

The above graph shows the distribution of ESR and pleural fluid variables in the study population.

Effusion

RPT*

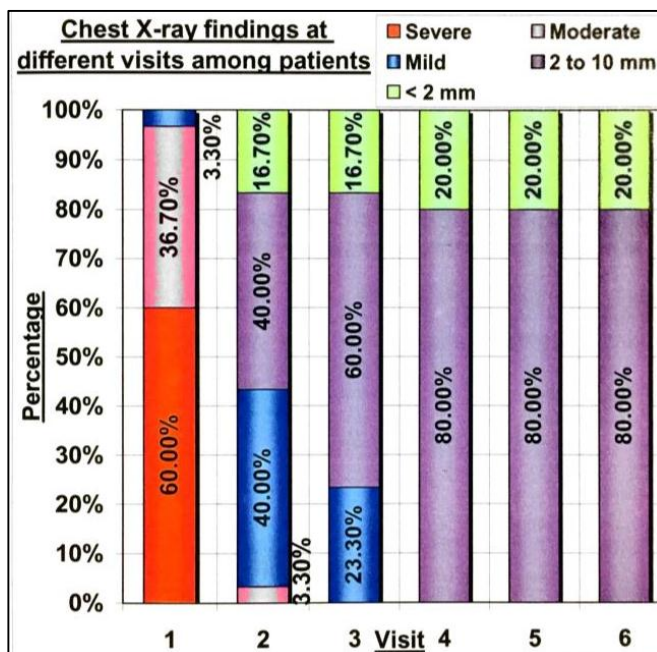
Chest X-ray P-A view		Severe	Moderate	Mild	2to 10 mm	<2 mm	Total
Visit 1	No.	18	11	1			30
	%	60.00%	36.70%	3.30%			100.00%
Visit 2	No.		1	12	12	5	30
	%		3.30%	40.00%	40.00%	16.70%	100.00%
Visit 3	No.			7	18	5	30
	%			23.30%	60.00%	16.70%	100.00%
Visit 4	No.				24	6	30
	%				80.00%	20.00%	100.00%
Visit 5	No.				24	6	30
	%				80.00%	20.00%	100.00%
Visit 6	No.				24	6	30
	%				80.00%	20.00%	100.00%

Table 4. Chest X-ray findings at follow-up visits

RPT: Residual pleural thickening

The above table summarizes the severity of pleural effusion and the residual pleural thickening, which was seen in the study group. 18 of the patients had a severe pleural effusion on admission, while 11 and 1 had moderate and mild pleural effusion respectively. Following the diagnostic tap and AKT initiation, the patients were followed up for a period of six months. The serial chest x-rays show that the RPT was radiologically significant in:4 of the 30 patients.

Chest X-ray findings at different Visits among Patients



Graph 4. Chest X-ray findings at follow-up visits

The above graph shows the chest x-ray findings at each follow-up of the patients and the subsequent recovery or PT during the follow-up period of one year.

Visits	FVC	FVC%	FEV1	FEV1%	FEV1/FVC%	FEF25-75%
0	1.87	56.87	1.58	59.21	85.32	2.06
1	2.11	64.36	1.86	69.56	88.03	2.47
2	2.39	73.16	2.16	81.30	90.68	2.79
6	2.65	81.55	2.44	91.68	92.27	3.18

Table 5. Improvement in PFT Parameters Over Time

This table shows the gradual improvement in the mean PFT parameters over a period of six months of follow-up. It shows a gradual improvement in the restrictive abnormality and the all airway disease.

Variables	Mean (n=30)	SD	Minimum	Maximum
0-FVC	1.87	0.55	1.01	2.96
1-FVC	2.11	0.51	1.23	3.13
2-FVC	2.39	0.51	1.40	3.45
6-FVC	2.65	0.53	1.72	3.56

Table 6. Distribution of FVC at various intervals

This table shows the distribution of FVC in the study population on all the follow-ups.

Variables	Mean (n=30)	SD	Minimum	Maximum
0-FVC (%)	56.87	12.12	36.90	80.50
1-FVC (%)	64.36	9.52	48.00	81.00
2-FVC (%)	73.16	8.57	53.00	88.00
6-FVC (%)	81.55	7.23	55.90	90.00

Table 7. Distribution of FVC (%) at Various Intervals

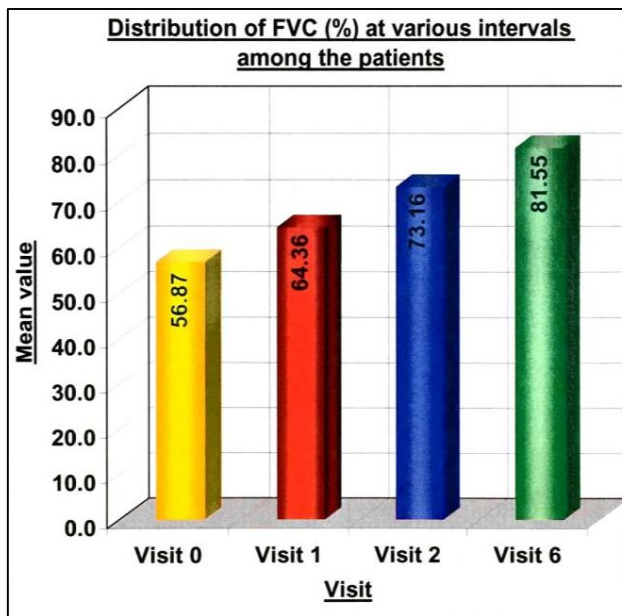
This table shows the correlation of FVC (%) in at each follow-up of the patients. The 0-FVC% i.e., the FVC% at first visit is showing severe restrictive abnormality. This shows an improvement over a period of six months i.e., on 1st, 2nd and 3rd follow-up at 1, 2 and 6 months.

		Mean	SD	t-value	p-value
Comparison between	0-FVC (%)	56.87	12.12	-9.258	3.69E-10
	1-FVC (%)	64.36	9.52		Difference is significant
Comparison between	0-FVC (%)	56.87	12.12	-10.993	7.39E-12
	2-FVC (%)	73.16	8.57		Difference is significant
Comparison between	0-FVC (%)	56.87	12.12	-13.232	8.13E-14
	6-FVC (%)	81.55	7.23		Difference is significant

Table 8. Comparison of FVC (%) at visit 1, 2 & 6 with that at visit 0

(Paired t-test Applied) The above table shows the comparison of the restrictive abnormality of the study population and the subsequent significant improvement in the restriction after 6 months of AKT.

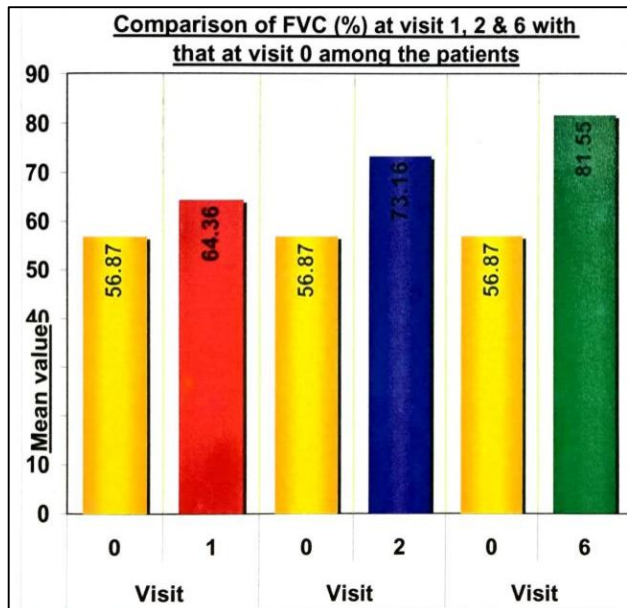
Distribution of FVC (%) at Various Intervals among the Patients



Graph 5. Distribution of FVC (%) at Various Intervals

This graph shows the distribution of the FVC (%) i.e. the restrictive abnormality in the study population.

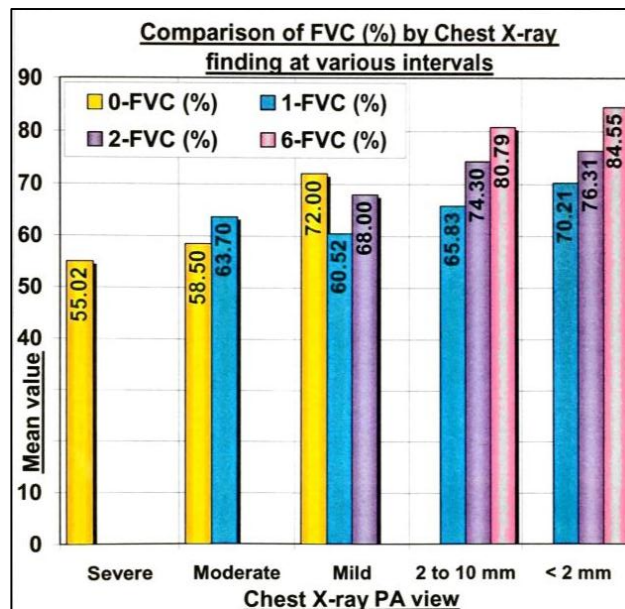
Comparison of FVC (%) at visit 1, 2 & 6 with that at visit 0 among the patients



Graph No. 6. Comparison of FVC (%) at visit 1, 2 & 6 with that at visit 0

This graph shows the comparison of the restrictive abnormality at each visit compared with that at visit 0. It shows a significant improvement over a period of six months.

Comparison of FVC (%) by Chest X-ray finding at Various Intervals



Graph 7. Comparison of FVC (%) by Chest X-ray finding at Various Intervals among the Patients

This graph shows the graphical representation of the significance of the restrictive abnormality with the severity of effusion and the RPT.

Variable	Mean (n=30)	SD	Minimum	Maximum
0-FEV1	1.58	0.45	0.88	2.43
1-FEV1	1.86	0.46	0.98	2.66
2-FEV1	2.16	0.45	1.31	2.93
6-FEV1	2.44	0.48	1.63	3.28

Table 10. Distribution of FEV1 at various intervals

This table shows the distribution of FEV1 in the study group on all the follow-ups.

Variables	Mean (n=30)	SD	Minimum	Maximum
0-FEV1 (%)	59.21	11.92	41.00	81.00
1-FEV1 (%)	69.56	10.41	52.00	90.00
2-FEV1 (%)	81.30	9.49	62.00	98.00
6-FEV1 (%)	91.68	7.49	65.00	99.00

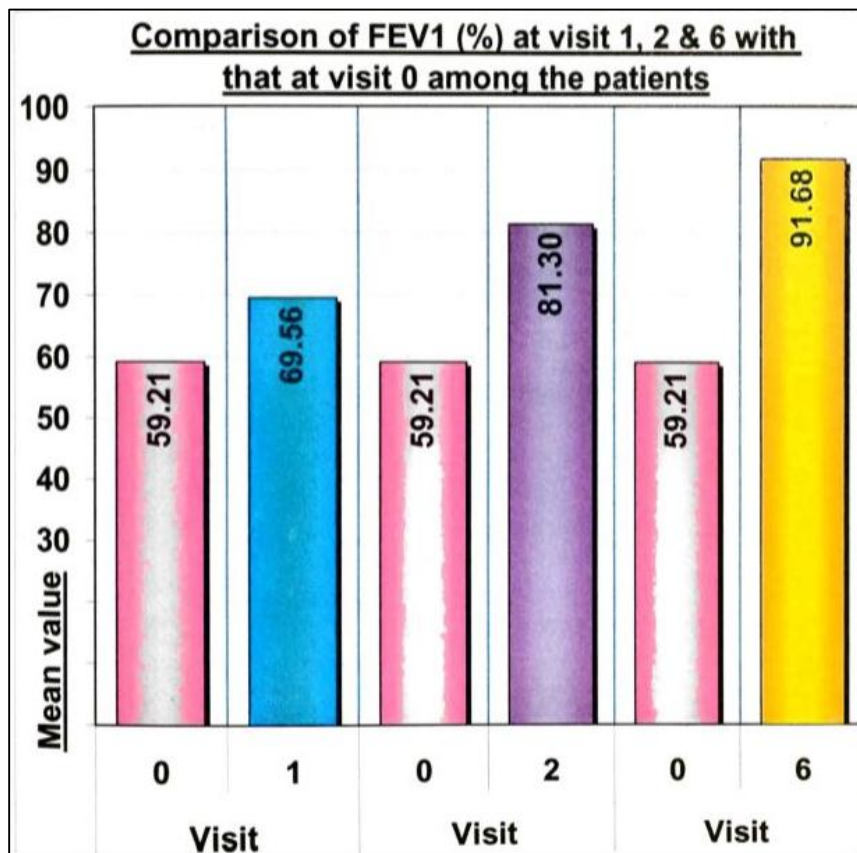
Table 11. Distribution of FEV1 (%) at various intervals

This table shows the correlation of FEV1 % at each follow-up of the patients. It shows a gradual improvement at each follow-up.

		Mean	SD	t-value	p-value
Comparison between	0-FEV1 (%)	59.21	11.92	-13.576	4.27E-14
	1-FEV1 (%)	69.56	10.41	Difference is significant	
Comparison between	0-FEV1 (%)	59.21	11.92	-13.285	7.36E-14
	2-FEV1 (%)	81.30	9.49	Difference is significant	
Comparison between	0-FEV1 (%)	59.21	11.92	-15.476	1.50E-15
	6-FEV1 (%)	91.68	7.49	Difference is significant	

Table 12. Comparison of FEV1 (%) at visit 1, 2 & 6 with that at visit 0

(Paired t-test applied) This table shows significant improvement in FEV1 in the population over a period of 6 months on AKT.



Graph 8. Comparison of FEV1 (%) at visit 1, 2 & 6 with that at visit 0

This graph compares the FEV1 (%) at visit 0 with FEV1 (%) at visit 1, 2 and 6. It shows an improvement in FEV1 in the study population over a period of 6 months on AKT.

Variables	Mean (n=30)	SD	Minimum	Maximum
0-FEV1/FVC (%)	85.32	5.43	65.50	93.50
1-FEV1/FVC (%)	88.03	4.40	74.00	94.50
2-FEV1/FVC (%)	90.68	3.71	82.00	95.00
6-FEV1/FVC (%)	92.27	3.45	84.00	97.00

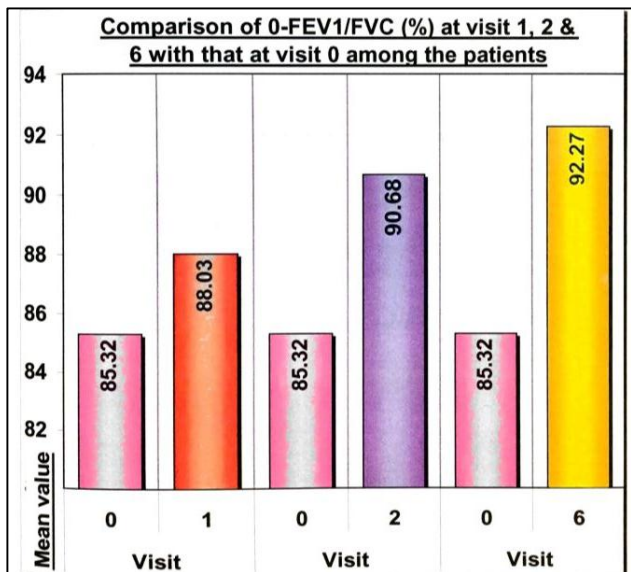
Table 13. Distribution of FEV1/FVC (%) at various intervals

The above table shows the distribution of FEV1/FVC (%) in the study population.

		Mean	SD	t-value	p-value
Comparison between-	0-FEV1/FVC (%)	85.32	5.43	-5.847	2.43E-06
	1-FEV1/FVC (%)	88.03	4.40	Difference is significant	
Comparison between-	0-FEV1/FVC (%)	85.32	5.43	-8.031	7.40E-09
	2-FEV1/FVC (%)	90.68	3.71	Difference is significant	
Comparison between-	0-FEV1/FVC (%)	85.32	5.43	-8.899	8.69E-10
	6-FEV1/FVC (%)	92.27	3.45	Difference is significant	

Table 14. Comparison of FEV1/FVC (%) at visit 1, 2 & 6 with that at visit 0

(Paired t-test applied) This table shows significant improvement in FEV1/FVC (%) over a period of 6 months when compared to the same at admission.



Graph 9. Comparison of FEV1/FVC (%) at visit 1, 2 & 6 with that at visit 0

This graph shows the comparison of FEV1/FVC (%) at visit 0 with that at visit 1,2 and 6.

Variables	Mean (n=30)	SD	Minimum	Maximum
0-FEF-25-75 (%)	2.06	0.66	0.64	3.12
1-FEF-25-75 (%)	2.47	0.74	1.34	3.91
2-FEF-25-75 (%)	2.79	0.73	1.58	4.11
6-FEF-25-75 (%)	3.18	0.71	1.78	4.24

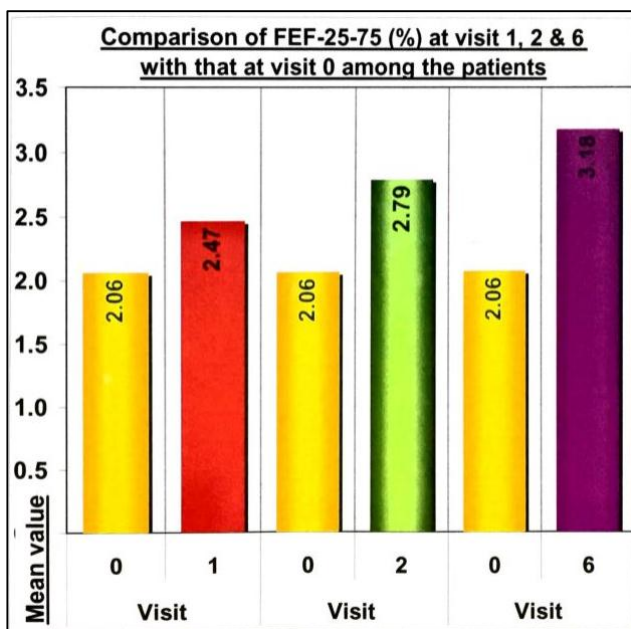
Table 15. Distribution of FEF-25-75 (%) at various intervals

The above table shows the distribution of FEF 25-75(%) in the study population. This shows that there is an element of small airway disease also associated with TB pleural effusion.

Comparison between-		Mean	SD	t-value	p-value
Comparison between-	0-FEF-25-75 (%)	2.06	0.66	-6.760	2.03E-07
	1-FEF-25-75 (%)	2.47	0.74	Difference is significant	
Comparison between-	0-FEF-25-75 (%)	2.06	0.66	-8.031	7.40E-09
	2-FEF-25-75 (%)	2.79	0.73	Difference is significant	
Comparison between-	0-FEF-25-75 (%)	2.06	0.66	-8.899	
	6-FEF-25-75 (%)	3.18	0.71	Difference is significant	

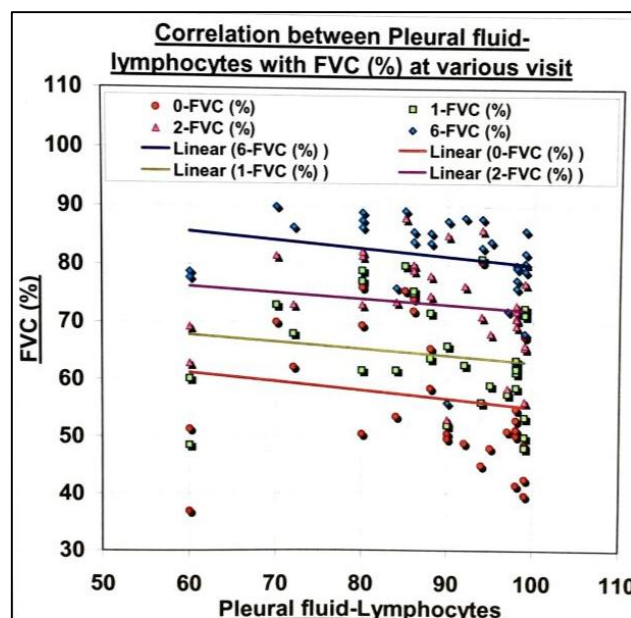
Table 16. Comparison of FEF-25-75 (%) at visit 1, 2 & 6 with that at visit 0

(Paired t-test applied) This table shows the improvement in small airway disease over a period of 6 months when compared to the same on admission.



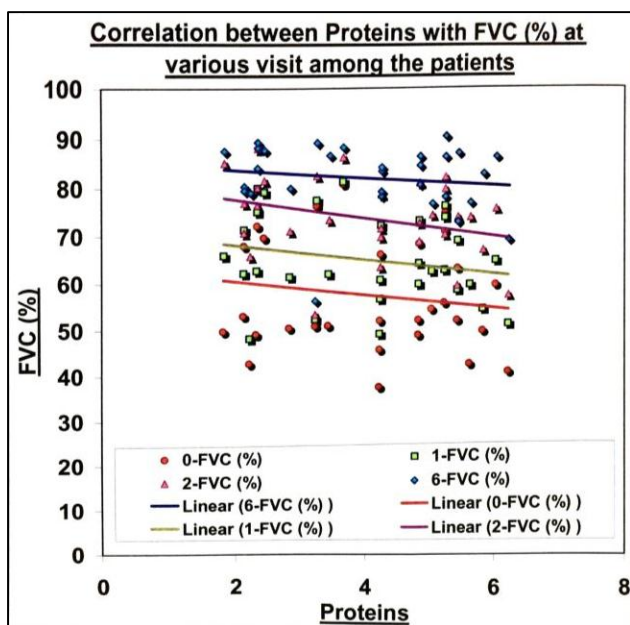
Graph 10. Comparison of FEF-25-75 (%) at visit 1, 2 & 6 with that at visit 0

This graph shows the comparison of the defects in small airway disease and the improvement in them over a period of six months.



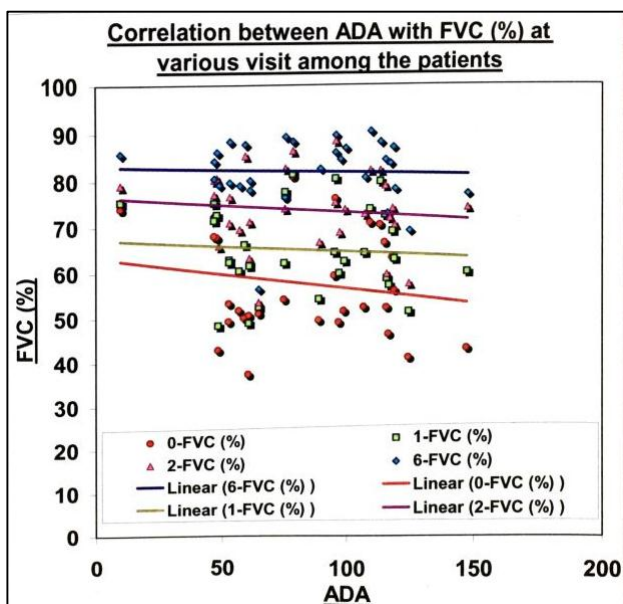
Graph 11. Correlation between Pleural fluid-lymphocytes with FVC (%) at various visit

This graph shows the negative correlation of pleural fluid lymphocytes with FVC (%) at each visit.



Graph 12. Correlation between pleural fluid Proteins with FVC (%) at various visit

This graph shows a negative correlation of pleural fluid proteins with FVC (%) at each visit.



Graph 13. Correlation between Pleural Fluid ADA with FVC (%) at various visit

This graph shows the negative correlation of pleural fluid ADA with the restrictive abnormality.

DISCUSSION

In this study, we have compared the pleural fluid characteristics i.e; lymphocyte counts, ADA and proteins with the restrictive abnormality i.e; FVC% and the RPT in diagnosed cases of tuberculous pleural effusion.

The pertinent aim wise discussion is as follows-

Aim 1) To study the lung function abnormalities in cases of tuberculous pleural effusion-

In patients with pleural effusion, the alterations on physiological states leading to restrictive lung functions and hypoxemia have been recognized.^{23,24,25} Studies have been done regarding acute changes in pulmonary functions within 24 hours or so after thoracentesis. But very few studies are available about the course of recovery of lung functions over time after institution of therapy. These studies have limitations either due to very small number of patients or lack of periodic follow up, over time. Yoo et al²⁴ studied only 3 patients; Altschule et al¹⁶ studied 8 patients and Estenne.²⁶ studied 9 patients.

In our study we have found a significant restrictive abnormality in lung function testing in our selected patients of tuberculous pleural effusion. All the selected patients had an initial restrictive abnormality. They had a FVC% value of less than 80 % (See Table No. 6,7 & 8 and Graph No 5,6) An interesting finding in our study was that, there was an element of small airway disease in our patients. This was manifested as an abnormal FET_{25-75%} (See Table No 16 and Graph No. 10). Also, we have found no relationship of the initial severity of pleural effusion with the final restrictive abnormality. (See Table No. 9 and Graph No.7)

Aim 2) To correlate the PFT abnormalities if detected with the severity of the pleural effusion.

Aim 3) To correlate such abnormalities if detected with the radiological and cytochemical parameters, duration of disease and the treatment.

Aim 4) To correlate the residual defects (Both radiological and PFT-wise) with various pleural fluid characteristics.

The incidence of RPT after AKT varies from one study to another. Lee et al²⁹ in his study had found a 10% incidence, while Soler et al²⁷ had 72%. Barbas et al⁷ and Moudgil et al²⁸ had 52% and 66% respectively. We found an incidence of 80% i.e., 24 of 30 patients had radiologically significant RPT.

As we can see that there is a wide variation in the incidence of RPT in all the above studies conducted worldwide. These variations can be attributed to the lack of a uniform concept of RPT. Some define RPT as a pleural thickness of >2 mm as abnormal, while others require a thickness of >10 mm. We had decided on a RPT of more than 2 mm as radiologically significant for our study. (See Table No.4 and Graph No.4)

A study done by Soler et al²⁷ had concluded that RPT is a consequence of an inflammatory mechanism. Study by Barbas et al⁷ has found that patients with RPT have a higher LDH levels or a hypersensitivity reaction and also that there is a higher incidence of positive tuberculin test and fewer positive Lowenstein cultures of pleural fluid. These findings are not corroborated by all the studies.²⁹ In tuberculous pleural effusion, the pleural fluid concentrations of biological parameters such as ADA are increased as a result of

inflammation produced by tuberculosis.³⁰ Barbas et al⁷ has also demonstrated that the presence of RPT was not related to the chemotherapeutic regimen or the performance of a therapeutic thoracocentesis. Also, it was seen in the same study that approximately fifty percent of patients with tuberculous pleural effusion will have RPT when their therapy is completed, but one cannot predict which of the patients will have RPT from either their clinical profile or their pleural fluid findings.⁷ This has been refuted in a related study by Morrone et al³¹ done at Sao Paulo where they had found that the pleural thickening was prevented through complete aspiration of tuberculous pleural effusion.

In our study we too found no correlation between the pleural fluid characteristics and the RPT. We had compared the protein concentration, ADA and lymphocyte counts with the RPT. They were compared using the Pearson's correlation. There was no statistical difference in the group with RPT and the group without any RPT as far as these parameters is applied. So the finding from our study does support the theory of increased hypersensitivity as the origin of RPT. In our study we did not have any patient with RPT more than 10 mm. (See Table No. 9, 17, 18 and Graph No.7, 11, 12, and 13)

Studies by Estenne et al²⁶ have found that thoracocentesis resulted in only small changes in pulmonary mechanics. These changes were inconsistent and could not explain the immediate and remarkable relief of dyspnoea noted by the patients. By contrast, thoracocentesis invariably resulted in a shift of the minimal (inspiratory) pleural pressure-volume curve so that the pressures generated by the inspiratory muscles were markedly more negative at any comparable lung volume. This shift was entirely due to the decrease in the thoracic cage volume. They had suggested that the relief of dyspnoea following thoracocentesis was primarily due to reduction in size of the thoracic cage, which allows the inspiratory muscles to operate on a more advantageous portion of their length-tension curve. The above phenomenon is reflected in our observations given below.

In our study we have done therapeutic thoracocentesis on admission. PFT done immediately after this found a significant restrictive abnormality though the patients had a subjective relief of dyspnoea as described above. On follow-up subsequent PFTs revealed that there was significant improvement in all the parameters of PFT. As we can see that compared to the initial PFT on admission, there was a significant improvement in the PFT parameters namely FVC, FVC%, FEV1, FEV1%, FEV1/FVC% and FEF_{25-75%} at the subsequent follow-ups at one, two and six months. (See Table No. 5) A study by Bhatia et al³² has shown that pleural effusion has a ventilatory restrictive and small airway obstructive pattern on spirometry, as mean pretreatment FVC, FEV1, FEV1, and FEF_{25-75%}. The derangements in spirometry were proportional to the severity of pleural effusion. All values showed statistically significant improvement after six months of treatment. This finding of improvement in PFT parameters has also been seen in our study. All of our patients had an element of small airway

disease as seen by the abnormal FEF_{25-75%}, which gradually improves over the period of six months of treatment. The study by Bhatia et al³² had found that the small airway disease improves while the restrictive abnormality persists and the restriction has a relation with the severity of pleural effusion. Our study however differs from that of Bhatia et al in that the finding that there was no relationship between severity of pleural effusion and restrictive abnormality. (See Table No.9 and Graph No. 6).

Also the small airway obstruction is a significant finding in the quoted study of Bhatia et al. The same observation done by us in the present study compels us to speculate about its pathogenesis. So far in literature no clear-cut explanation has been offered. However, endobronchial fibrosis in small airways as a result of tubercular parenchymal disease may be responsible for this. This suggests that tuberculous pleural effusion is no more a compartmentalized affection of the pleura, but also has some parenchymal component difficult to demonstrate clinically and radiologically. Thus, we can see from this study of thirty patients of tuberculous pleural effusion followed up for a period of six months, that tuberculous pleural effusion causes a restrictive abnormality and small airway obstruction. These abnormalities have no relationship with the initial severity of pleural effusion or the RPT. Also, there is no relationship between these abnormalities and the pleural fluid characteristics, namely the lymphocyte count, proteins and the ADA and on treatment there is progressive improvement in the same.

CONCLUSIONS

This study comprising of thirty tuberculous pleural effusion cases was done progressively for six months, to observe the residual restrictive defects in the pulmonary function and its relationship with the pleural fluid characteristics and the initial severity of the effusion. The obvious conclusions which could be drawn from this study were as follows-

1. Tuberculous pleural effusion causes a restrictive abnormality and small airway obstruction.
2. These abnormalities improve gradually over a period of six months when the patient is on AKT.
3. These abnormalities have no relation with the pleural fluid cytochemical and biochemical characteristics.
4. These abnormalities also have no relationship with the initial severity of the pleural effusion or the RPT.

As we can see that, one of the highlights of this study was small airway obstruction, shown uniformly in all the thirty study subjects. The mechanism of which is difficult to explain and definitely needs undertaking of further long-term and large-scale studies.

ABBREVIATIONS

1. RPT : Residual pleural thickening
2. ADA : Adenosine deaminase
3. PFT : Pulmonary function test
4. DLCO : Carbon monoxide-diffusing capacity
5. CPET : Cardiopulmonary exercise testing

6. AKT : Anti-Koch's treatment
7. HIV : Human Immunodeficiency virus
8. COPD : Chronic obstructive pulmonary disease
9. USG : Ultrasonography
10. AFB : Acid fast bacillus
11. FVC : Forced Vital Capacity
12. FEV1 : Forced Expiratory Volume in one second
13. PEF : Peak Expiratory flow rate
14. MVV : Maximal Ventilatory Volume
15. IC : Inspiratory capacity
16. TV : Tidal volume
17. R : Resistance
18. VC : Vital capacity
19. ATS : American Thoracic Society
20. BSA : Body Surface Area
21. IU : International units.

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