**ORIGINAL ARTICLE**

# DIAGNOSTIC OUTCOME OF LARGE AND MASSIVE PLUERAL EFFUSION.

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## ABSTRACT

**Objective**: The primary objective of this study was to report the diagnostic outcome of all pleural effusions and compare the etiology of large and massive effusions. The secondary objective was to compare the biochemical characteristics of different sizes of effusions, in relation to diagnostic outcome.

**Design:** Retrospective chart review of all patients undergoing thoracentesis at Saidu teaching Hospital Saidu Sharif, during five years period.

**Methods:** The size of the effusion was assessed on the postero anterior radiograph by visually estimating the area of the hemithorax occupied by pleural fluid. Diagnostic thoracentesis report was available on all the cases that included RBC count, leukocyte count, percentage of neutrophils, lymphocytes and cytology. Biochemical tests included, glucose level, protein level, lactate dehydrogenase (LDH) level, pH, fluid/serum protein ratio, and fluid/serum LDH ratio. Pleural biopsies were performed on selected cases.

**Results:** Among 388 screened cases of pleural effusion 108 had either large or massive effusion and 280 cases had non- large effusion. Large pleural effusions (two thirds or more of the hemi thorax) were found in 68 cases and massive effusions (entire hemi thorax) in 40 cases.
There was a similar etiological spectrum between large and massive pleural effusion. The most frequent cause of these pleural effusions was tuberculosis; in 40 patients (37%) followed by malignancy in 31 (29%), and complicated parapneumonic effusion in 19 patients (18%). Among massive effusions, malignancy was most frequent (15 patients: 38%). Compared with non-malignant pleural effusions, patients with large or massive malignant pleural effusions were more likely to have pleural fluids with higher RBC counts (18.0 $10^9$cells/L vs. 2.7 $10^9$cells/L, respectively; $p < 0.001$). Compared with non-large effusions, large and massive malignant pleural effusions showed higher median RBC counts ($18.0\times10^9$cells/L vs. $4.3\times10^9$cells/L, respectively; $p < 0.001$), higher lactate dehydrogenase levels (641 vs. 409 U/L, respectively; p 0.001), lower pH (7.39 vs. 7.42, respectively; p 0.006)

***Conclusions:***
The presence of a large or massive pleural effusion enables the clinician to narrow the differential diagnosis of pleurisy, since most effusions are secondary to malignancy or infections (either bacterial or mycobacterial). Bloody pleural fluid are likely to favor malignancy.



**Key words:** Pleural effusion, Large, Massive, Malignant, Non-Malignant. Tuberculosis.

## INTRODUCTION

Pleural effusion is a very common clinical condition that is encountered almost every day in a general medical ward or outpatient department. A pleural effusion is an abnormal accumulation of fluid in the normal pleural space. This is broadly classified to an exudate and transudate based upon the underlying pathophysiological mechanism of pleural fluid accumulation and partly on the laboratory examination of pleural fluid.[1] Diagnosing underlying etiology of pleural effusion may be straightforward in some clinical conditions but will need extensive investigations in other cases. The history and physical examination are critical in guiding the evaluation of pleural effusion.[2] This is likely to provide useful clue to the underlying pathology and a plan for further investigations. Apart from routine investigations, the first step in the evaluation is to determine whether an effusion is transudative or exudative by performing a diagnostic thoracocentesis[3, 4]. If it is exudative, more diagnostic tests are required in order to determine the cause of the local disease, whereas if it is transudative, the physician must establish or rule out a diagnosis of congestive heart failure, cirrhosis, or pulmonary embolism [1.] For the past several decades, transudates have been differentiated from exudates according to Light's criteria, [5] by measurement of the levels of protein and lactate dehydrogenase in the pleural fluid and in the serum. Since these criteria were originally published, several alternative measurements have been proposed for making this distinction.[4,6,7] Light's criteria is the most sensitive for identifying exudates but have lower specificity than other criteria.[8] It has been noted in some studies that the size of a pleural effusion may also help in diagnosing the underlying cause besides checking for pleural fluid characteristics,[6-9] The aim of our study was to evaluate the etiological factors of large and massive pleural effusions as well as to compare their biochemical characteristics correlating with the final diagnostic outcome.

### Materials and Methods

The study was carried out at Department of Medicine, Saidu Teaching Hospital affiliated to Saidu Medical College, Saidu Sharif. This is a 500 bedded hospital with a 104 bedded Medical Unit. The hospital catchment area extends from Malakand Agency up to the hilly top of Kohistan and covering districts of Swat, Shangla and lower Dir.

We reviewed the medical records of all patients who had an underlying diagnosis of a pleural effusion due to any cause and had been admitted and investigated in our unit during the study period. Inclusion criteria were all the cases of either sex whose proper record was available particularly a standard postero-anterior chest radiograph and diagnostic thoracentesis, with result of pleural fluid analysis obtained from a standard reference laboratory. Clinical, radiological and pleural fluid data were recorded on to the study protocol. The size of effusion was assessed on the postero-anterior chest radiograph by visually estimating the area of the hemi thorax occupied by pleural fluid. Pleural effusions were considered to be *Non large* if they were small or medium size. They were classified as *large* if they affected two thirds or more of the hemi thorax without reaching its complete length, and similarly classified as Massive *if* they opacified the entire hemithorax. Only the measurement of the predominant side was considered in patients with bilateral effusions.

We examined the following pleural fluid analytes:

RBC count; leukocyte count; percentage of neutrophils, and lymphocytes; glucose level; protein level; lactate dehydrogenase (LDH) level; pH; fluid/serum protein ratio; and fluid/serum LDH ratio. The causes of pleural effusions were determined by well-established criteria.[8] Specifically, the criteria for pleural effusions of tuberculous origin were as follows: (1). An exudative lymphocytic effusion while excluding all other potential causes of pleurisy. (2) the presence of a granuloma in a pleural biopsy specimen after excluding other causes of granulomatous pleuritis; or (3) positive results of pleural fluid or sputum for Acid fast bacilli (AFB) or a positive culture. A pleural effusion was categorized as *malignant* if pleural fluid cytology or pleural biopsy findings were positive for malignancy (*i.e.*, *true malignant*), or if the patient had a known cancer with no other explanation for the effusion (*i.e.*, *paramalignant*).[11,12] The term *complicated parapneumonic effusions* (PPEs) referred to those non-purulent-appearing effusions in association with radiographic sign of pneumonia, whereas *empyema* described the presence of pus within the pleural space.[13,14] The terms *transudate* or *exudates* were based on the cause of the effusion.[15] Thus, the category *transudates* encompass those effusions that were clearly due to congestive heart failure, cirrhosis, or nephrosis or hypoprotinemia. Exudative effusions not associated with neoplasm, tuberculosis, or pneumonia were classified as *other exudates*.[15]

### *Statistical Analysis*

Results are reported as medians (quartiles). Comparisons between groups used the Fisher exact tests for categoric variables, and the non parametric Kruskal-Wallis and Mann-Whitney tests were used for continuous variables. Demographic and pleural fluid data that distinguished malignant from nonmalignant large/massive effusions in the bivariate analysis were entered into a stepwise logistic regression model. All statistical comparisons were two sided and were carried out at the 0.05 significance level. Data were analyzed with a statistical software package SPSS version 10.0

## RESULTS

During the study period, from January 2003 to December 2007, the record revealed 423 cases of pleural effusion admitted to our unit. Out of these, 35 cases were excluded from the study as either the radiological data were unavailable or other investigations were missing and incomplete. Of the remaining 388 patients, a poster anterior upright chest radiograph and all other laboratory data were obtained for review. Among this study group, 117 patients had tuberculous effusions, 122 patients had Parapneumonic effusions (uncomplicated effusion, 76 patients; complicated pleural effusion or empyema, 46 patients), 56 patients had malignant effusions, 56 patients had transudative pleural effusions and 37 patients had other exudative pleural effusions. Sixty eight patients (18%) exhibited large pleural effusions, and 40 patients (10%) exhibited massive pleural effusions. In this group of large and massive effusions (n=108) most of these pleural effusions were unilateral (104 out of 108 pleural effusions; 96%). There were 65 men and 43 women, with a median age of 60 years (quartiles, 48 to 75 years). Their underlying diseases are shown in Table1.

The most common and important cause of large and massive effusion was Tuberculosis. Somewhat less than a half of large or massive pleural effusions (40 out of 108 pleural effusions; 47 %) were related to this common infectious disease of the region.

The second most common cause of large and massive effusions was related to malignancies, representing a fifth of the total number of etiologies (31out of 108; 29%). The group of patients with large/massive malignant pleural effusions as a whole encompassed 25 patients with true malignant effusions and 6 cases with para-malignant effusions. The following primary tumors were found: lung: 15 tumors, breast: 5 tumors, unknown: 5 tumors, gynecologic: 2 tumors, hematologic: 2 tumors, GI: 1 tumor and mesothelioma: 1tumor.

The third most common and important group emerging here is para pneumonic effusions. (PPEs) i.e., 19 out of 108). Of note, all patients in this subgroup had complicated PPEs or empyema, whereas none of the uncomplicated PPEs extended to two thirds or more of the hemithorax. Overall, 62% of malignant effusions, 69% of tuberculous effusions and 36% of complicated PPEs and empyema affected two thirds or more of the hemithorax. These percentages changed to 38%, 25%, and 20%, respectively, if only a subgroup analysis of massive effusions was considered. There were significant differences between the groups of patients with large/massive and non-large effusions regarding the following pleural fluid parameters: RBC count; pH; glucose level; LDH level; pleural fluid/serum protein ratio; and pleural fluid/serum LDH ratio (Table 2).

When the 31 patients having large or massive malignant effusions were compared to the remaining 25 patients in the malignant effusion population, the former had fluids with higher median levels of RBCs ($18.0 \times 10^9$ cells/L vs. $4.3\times 10^9$cells/L, respectively; p=0.001), higher median levels of LDH (641U/L vs. 409 U/L respectively; p=0.001), and lower pH (7.39 vs. 7.42, respectively; p0.006), yet only the subgroup with massive effusions differed in terms of glucose fluid concentrations (5.55 mmol/L vs. 6.27 mmol/L, respectively; p=0.006). Similar results were obtained when only true malignant patients were considered for comparisons. However, the sensitivity of cytologic examination did not differ between the large/massive and non-large

malignant pleural effusion groups. On the other hand, the 19 patients with large or massive PPEs showed higher median leukocyte counts ($13.38\times10^9$cells/L vs. $2.72\times10^9$cells/L, respectively; p=0.001), higher median LDH levels (2,438 U/L vs. 996 U/L respectively; p 0.002), lower pH (6.97 vs. 7.34, respectively; p=0.001), and lower glucose levels (0.28 mmol/L vs. 5.00 mmol/ respectively p=0.001) than the 103 patients with PPEs of smaller size. Finally, the leukocyte count was significantly higher in the pleural fluid of the 77 patients whose tuberculous effusions occupied less than two thirds of the hemithorax (2.35 cells/L) than that of patients with large or massive tuberculous pleurisy ($0.92\times10^9$cells/L; p=0.001).

In comparison to the patients with non-malignant etiologies, those with malignant pleural effusions belonging to the large/ massive group were older, and their pleural fluids exhibited significantly higher values of RBC, glucose, and pH, but lower leukocyte count, LDH level, and pleural fluid/serum LDH ratio (Table 3).

**DISCUSSION:**

Several studies were found in the literature on the subject of quantifying pleural effusion relating to the underlying diagnosis. In 1972, Maher and Berger[9] reported on 46 patients with pleural effusions, occupying the entire hemithorax, of whom 31 (67%) had malignant diseases and 15 (33%) had nonmalignant conditions. Later on, Pedro de Lelis and colleagues[11] reviewed 84 cases of massive pleural effusions, and recognized that most (60 effusions; 71%) were of neoplastic origin. The largest study on the subject has been from Jose Manuel Parcel et al [16]who reported on 766 patients with pleural effusion. Of these 163 cases had large or massive pleural effusion. In this group they found malignancy in 55% cases, parapneumonic effusions in 22% and only 12 % due to

tuberculosis. An excellent review of this subject has been published recently by Light R.W.[17] The data in our study differs from most of these western studies as tuberculosis is a very common condition in this part of the world. In one American study Tuberculosis was found only in 4% cases of massive effusion[9] and overall western literature does not quote more than 10% figure.[17] Only a Spanish study has reported tuberculosis as the leading etiology of the non-malignant category (13 of 24, 54%)[10] . This is probably due to the still high incidence of tuberculosis in Spain. Interestingly, two [18,19] series from Spain involving 642 and 1,000 consecutive patients respectively, with pleural effusions found that tuberculosis was the most frequent etiology (25%) [18] and the second most frequent etiology (15.5%)[19] In our study we found Tuberculosis as the most common cause (30%) of pleural effusion in the whole study population. This also accounted for 25% of cases when large and massive effusion was considered. Malignancy emerged as very important cause of large and massive effusion This does highlight the fact that although tuberculosis is very common in our country and should be considered in differential diagnosis of every sized effusion but when large and massive effusion are encountered , malignancy should be on the top of the list. PPEs and empyema represented the main non-malignant etiology (49%) and

the top most common overall etiology (31%) in our series. The absence of patients with typical or non complicated PPEs extending into two thirds or more of the hemithorax supports the inclusion of large effusions as a risk of poor outcome in patients with PPEs that deserve drainage of the pleural space. As in study of Valde‘s et al, [12] our study also showed that bout 20% of tuberculous effusion affected two thirds or more of the hemithorax. Overall when we look into the etiologic spectrum of large and massive pleural effusions, it becomes clear that they have the same clinical significance. However it is also important to remember that large and massive pleural effusions occur occasionally as a complication of cirrhosis (hepatic hydrothorax),[20]congestive heart failure,[21]Trauma,[22] chronic pancreatitis,[23] dialysis,[24] connective tissue diseases and vasculitis,[25,26]ovarian hyper stimulation syndrome,[27]chylothorax,[28] or subarachnoid pleural fistulas,[29]among others.

Finally a brief discussion on the pleural fluid examination. Overall, the examination of pleural fluid in large/massive pleural effusions revealed the presence of biological markers of both inflammation (*i.e.*, high LDH levels) and metabolic activity (*i.e.*, low pH and glucose content) compared with smaller pleural effusions, which may be in the genesis of an increased pleural fluid formation. In addition to pleural inflammation, increased vascular permeability and leakage play a key role in the development of exudative pleural effusions. As expected older age and hemorrhagic fluids were more likely to be associated with malignancy.

**CONCLUSION:**

In conclusion, Tuberculosis remains the commonest cause of an exudative pleural effusion in this part of the world regardless of the size of effusion. The malignancy is a strong consideration in the diagnosis of any massive hemorrhagic pleural effusion. however, a significant proportion of benign etiologies, complicated PPEs, empyema and other less common causes of exudates should be kept in mind.

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**Table 1:**
**Etiology of Non-large, large and Massive pleural effusion.**
**Number and percentages. Total patients: 388**

| | Non-large 280 (72%) | Large 68(18%) | Massive 40 (10%) | Total:388 |
|---|---|---|---|---|
| Tuberculosis | 77 (28%) | 30 (44%) | 10 (25% | 117 (30%) |
| Malignancy | 25 (9%) | 16 (24%) | 15 (38%) | 56 (14%) |
| PPEs | 103 (37%) | 11 (16%) | 8 (20%) | 122 (31%) |
| Tansudates | 45 (16%) | 8 (12%) | 3 (8%) | 56 (14%) |
| Other Exudates | 30 (11%) | 3 (4%) | 4 (10%) | 37(10%) |

**Table 2—Comparison of Demographics and Pleural Fluid Data Among Nonlarge, Large, and Massive Pleural Effusions***

| Characteristics | Nonlarge Effusions (n=280) | Large Effusions (n=68) | Massive Effusions (n=40) | p Value |
|---|---|---|---|---|
| Male gender | 152(54%) | 36 (53%) | 26 (65%) | 0.040 |
| Age, yr | 56 (30–75) | 62 (40–72) | 67 (50–77) | 0.067 |
| RBC count, $10^9$cells/L | 2.8 (0.76–13.63)† | 4.75 (1.32–47.20) | 5.48 (1.26–43.20) | 0.001 |
| Leukocytes, $10^9$cells/L | 1.05 (0.40–2.80) | 0.96 (0.34–2.67) | 0.97 (0.40–2.20) | 0.889 |
| Lymphocytes, % | 72 (30–91) | 71 (28–90) | 69 (33–92) | 0.823 |
| Neutrophils, % | 26 (8–69) | 35 (10–70) | 30 (8–67) | 0.647 |
| pH | 7.42 (7.36–7.49)† | 7.37 (7.26–7.43) | 7.37 (7.27–7.42) | 0.001 |
| Glucose, mmol/L | 6.11 (4.77–7.94)† | 5.61 (4.16–7.05) | 5.00 (3.39–6.88) | 0.001 |
| Protein, g/L | 42.0 (30.1–50.4) | 43.4 (37.1–51.9) | 43.1 (36.7–48.5) | 0.114 |
| LDH, U/L | 420 (238–933)† | 726 (389–1,430) | 676 (393–1,534) | 0.001 |
| PF/S protein ratio | 0.64 (0.48–0.74)† | 0.70 (0.61–0.78) | .70 (0.62–0.76) | 0.001 |
| PF/S LDH ratio | 1.09 (0.65–2.62)† | 1.7 (0.98–3.24) | 1.74 (1.09–3.37) | 0.001 |

*Values given as median (25th–75thpercentiles), unless otherwise indicated

† significantly different by test with analysis of adjusted residuals.

**Table 3—Comparison of Demographics and Pleural Fluid Data Between Patients With Malignant and Nonmalignant Effusions of Large/Massive Size***

| Characteristics | Malignant (n=33) | Nonmalignant (n=77) | p Value |
|---|---|---|---|
| Male gender | 20(60%) | 55(71%) | 0.006 |
| Age, yr | 65 (55–77) | 52 (36–75) | 0.001 |
| RBC count, $10^9$ cells/L | 18.00 (3.37–80.00) | 2.70 (0.40–6.40) | 0.001 |
| Leukocytes, $10^9$ cells/L | 0.66 (0.28–1.47) | 1.40 (0.58–10.60) | 0.001 |
| Lymphocytes, % | 78 (47–91) | 56 (10–90) | 0.011 |
| pH | 7.39 (7.33–7.44) | 7.31 (7.06–7.41) | 0.001 |
| Glucose, mmol/L | 5.99 (4.72–7.11) | 4.22 (0.28–6.49) | 0.001 |
| Protein, g/L | 43.4 (38.1–48.7) | 42.4 (32.9–50.9) | 0.783 |
| LDH, U/L | 641 (381–1,026) | 1,061 (492–2,438) | 0.005 |
| P/S protein ratio | 0.69 (0.62–0.75) | 0.72 (0.55–0.81) | 0.578 |
| P/S LDH ratio | 1.46 (0.94–2.21) | 3.18 (1.48–5.28) | 0.001 |

*Values given as median ($25^{th}$-75th percentiles), unless otherwise indicated.