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Pleural Fluid Alkaline Phosphate Levels to Differentiate between Tuberculosis and Malignant Pleural Effusion a Tertiary Care Experience

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Abstract

Introduction: Pleural effusion (PF) is a common clinical presentation in several diseases. Tuberculosis is one of the most frequent causes of exudative pleural effusions in immunocompetent patients. Tuberculosis is the leading cause of morbidity and mortality from an infectious disease in developing countries. Pakistan is ranked fifth in the world in terms of tuberculosis high-burden countries. Various pleural fluid parameters have been used to identify the cause of pleural effusion. It has been discovered that tuberculous pleural effusions had a greater alkaline phosphatase (ALP) concentration than transudative effusions. This study used pleural fluid alkaline phosphatase levels to distinguish between tuberculous pleural effusion and malignant pleural effusion because there is little information from tuberculosis-high burden nations like Pakistan. **Study Design:** A descriptive cross-sectional study conducted at the Jinnah Postgraduate Medical Center in Karachi between October 2016 and October 2017. **Material and Methods:** The study comprised all patients who were admitted to the department of chest medicine at Jinnah post graduate medical centre (JPMC) of either gender between the ages of 18 and 70 who had exudative lymphocytic pleural effusions lasting two weeks or more included in the study. Non probability consecutive sampling was used to collect data. Patients who have tonsillitis, pharyngitis, pneumonia, asthma, Chronic obstructive pulmonary disease (COPD), or a history of hemoptysis, Bleeding disorders like, platelet function disorder, thrombocytopenia, Liver

cirrhosis and Pregnant women were excluded. Parents' informed consent was obtained after being informed of the study's protocol, hazards, and advantages. Each patient had their level of pleural fluid alkaline phosphate (PALP) assessed. In order to evaluate the patient's pleural effusion, a pre-made questionnaire was used. All the collected data were entered into the SPSS 20. An independent sample t-test was used to recognize alkaline phosphate levels association with pleural fluid secondary to tuberculosis or malignancy. **Results:** In this Descriptive Cross-Sectional Study, the total of 156 patients with age Mean ± SD of was 41.96 ± 17.05 years. The majority of patients 110 (70.5%) were male and 46 (29.5%) were female. Advanced age was associated with raised pleural fluid alkaline phosphatase. The difference of pleural fluid alkaline phosphate level between tuberculous v/s malignant group was found to be (38.03 ± 45.97) v/s (82.77 ± 61.80) respectively with P-value (P = 0.0001). **Conclusion:** Malignant pleural effusions had elevated PALP when compared to tuberculous pleural effusions in exudative lymphocytic pleural effusions; better differences are seen in older ages and shorter disease durations.

Keywords

Pleural Fluid (PF), Alkaline Phosphatase (ALP), Tuberculosis, Malignant

1. Introduction

Globally, tuberculosis has a significant negative influence on public health; nevertheless, Pakistan has the highest prevalence of tuberculosis cases. The primary infectious illness responsible for morbidity and mortality, primarily in developing and underdeveloped nations, is tuberculosis [1]. In 2010, there were reportedly 12 million reported cases of TB. This translates to 178 cases per 100,000 people. There were an estimated 650,000 cases of multi drug resistant tuberculosis among the world's prevalent 12 million cases of tuberculosis [2].

The clinically confident etiological diagnosis of pleural effusions (PF) is a challenging task for doctors. To pinpoint the reason, various pleural fluid biochemical markers have been used. Pleural effusions have been divided into transudates and exudates by Light *et al.* [3] using pleural fluid protein and LDH concentrations. Pleural fluid cholesterol [4], PF bilirubin [5], PF amylase [6], PF adenosine deaminase (ADA) [7] [8], and PF gamma interferon [9] are additional variables that were examined. Biochemical indicators such ADA, lysozyme, and gamma interferon [8] [9] [10] have been used to try and separate tuberculous pleural effusions from non-tuberculous effusions. These levels have been reported to be higher in pleural effusions caused by tuberculosis. In contrast to congestive heart failure transudates, tuberculous pleural effusions have been observed to have greater alkaline phosphatase levels 10. Patients with pleural effusion often have a mean ALP level of 95.792 +/− 51.394, which is substantially higher in patients with tuberculous pleural effusion than in those with nontuberculous pleural effusion ($P < 0.0001$) [11].

Exudative effusions had pleural fluid alkaline phosphatase levels greater than 75 mg/dl, while transudative effusions had levels less than 75 mg/dl. However, it failed to distinguish between tubercular pleural effusions and other exudative conditions, such as malignancy [12].

According to a study by El-Habashy MM *et al.*, the average alkaline phosphate level in tuberculosis was 258.8695.44 and in malignant pleural effusion, it was 278.5574.68. Given the high prevalence of tuberculosis in our nation, we sought to evaluate the usefulness of pleural fluid alkaline phosphatase level for separating tuberculous from malignant pleural effusion. Considering that this test is easily accessible and little intrusive.

2. Material and Methods

From October 2016 to October 2017, this cross-sectional study was conducted on inpatients at the Jinnah Postgraduate Medical Center's (JPMC) Department of Chest Medicine in Karachi. The calculated sample size was n = 156 using the WHO calculator and the following data: Mean SD of alkaline phosphate level 258.8695.44 [13] in patients with tuberculosis pleural effusion, margin of error (d) = 15%, confidence level = 95%. According to non-probability consecutive sampling, patients between the ages of 18 and 70 who had exudative lymphocytic pleural effusions lasting two weeks or more were included. Individuals with pharyngitis, tonsillitis, pneumonia, asthma, COPD, a history of hemoptysis, bleeding disorders such thrombocytopenia and platelet function problems were also eliminated. After the institutional ethical review board gave its clearance, **dated June 17, 2017, IRB no. 2-81/2017-GENL/22503/JPMC.** All patients who met the inclusion criteria gave their written informed consent. Every patient had their pleural fluid's alkaline phosphate level checked. After taking the necessary aseptic precautions, an ultrasound-guided diagnostic pleural tap was performed, and 20 cc of pleural fluid were submitted to the lab. The researcher himself filled out a structured Performa to gather data. SPSS 20 was used to enter and evaluate the data. For each gender and pleural effusion type, frequency and percentages were calculated. In patients with TB pleural effusion and malignant pleural effusion, the mean and standard deviation (SD) for age, P.E. duration, and alkaline phosphate level were calculated. The alkaline phosphate level in the two groups was compared using an independent sample t-test. Using an independent sample t-test, the alkaline phosphate level was compared by age, the length of the pleural effusion, and gender to evaluate how these factors affected the outcome variable. P 0.05 was considered significant.

3. Results

To determine the mean alkaline phosphate level in patients with various types of pleural effusion and to compare the mean alkaline phosphate level in biopsy-proven tuberculosis v/s malignant pleural effusion, a total of 156 patients with pleural effusion were included in this descriptive cross-sectional study. The re-

sults were analyzed. Our study population was predominantly male *i.e.* 110 (70.5%), Mean ± SD of age was 41.96 ± 17.05 with C.I (39.26 - 44.66) years, Baseline characteristics are shown in Table 1.

Duration of pleural effusion in Mean ± SD was 14.51 ± 4.99 days, Mean ± SD of alkaline phosphate level was 49.21 ± 53.81 with C.I (40.70 - 57.72) U/l, while distribution for type of pleural effusion; tuberculosis was noted in 117(75.0%) while malignant was found in 39 (25.0%).

Age (Mean ± SD in years) of biopsy proven tuberculosis v/s malignant pleural effusion was 38 ± 16 and 55 ± 14 years respectively.

In group wise distribution of gender 84 (53.8%) men and 33 (21.2%) women were enrolled in biopsy proven tuberculous group and 26 (16.7%) men and 13 (8.3%) women were included in malignant pleural effusion group as shown in Figure 1.

In comparison of Mean ± SD of alkaline phosphate level between biopsy proven tuberculosis v/s malignant pleural effusion was found to be (38.03 ± 45.97) v/s (82.77 ± 61.80) with C.I [(−63.13 - (−26.35)] and very significant P value was discovered *i.e.* (P = 0.0001) as shown in Table 2. In stratification of age group (18 - 41), (>41) years, gender and duration of pleural effusion (7 - 14), (>14) days with respect to mean alkaline phosphate level in both groups *i.e.* (biopsy proven tuberculosis v/s malignant pleural effusion) were done from Table 2.

Table 1. Baseline characteristics and laboratory parameters of the study population, N = 156.

Total number of study population, n = 156	
Male, n (%)	110 (70.5%)
Females, n (%)	46 (29.5%)
Age, Mean ± SD in years	41.96 ± 17.05
≥41 Years, n (%)	76 (48.7%)
<41 years, n (%)	80 (51.3%)
Duration of pleural effusion, Total study population, Mean ± SD in days	14.51 ± 4.99
Pleural effusion due to tuberculosis (n = 117) Mean ± SD in days	13 ± 4
Malignant pleural effusion (n = 39) Mean ± SD in days	19 ± 4
Pleural fluid Alkaline phosphatase, Mean ± SD (U/l)	49.21 ± 53.81
Type of pleural effusion	
Tuberculous effusion, n (%)	117 (75.0%)
Malignant effusion, n (%)	39 (25.0%)

SD = Standard deviation, n = number of patients, U/l = units per liter.

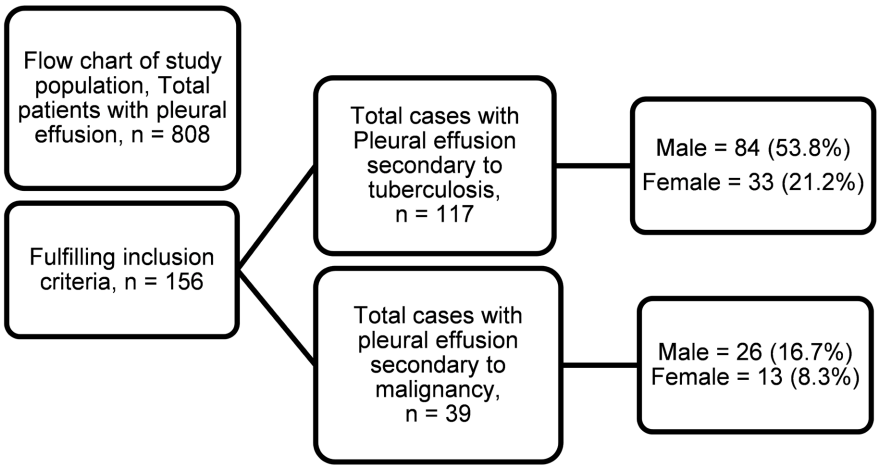

Figure 1. Flow chart of the study population.

Table 2. Stratification of pleural fluid alkaline phosphate level (Mean ± SD) in U/L with respect to Age, gender and duration of effusion in both groups (n = 156).

Characteristics with total numbers	Biopsy proven tuberculosis effusion	Biopsy proven malignant pleural effusion	P-Value
Age			
≤41 years, (76)	41.19 ± 56.82 (n = 72)	33.00 ± 17.32 (n = 4)	0.536
>41 years, (80)	32.96 ± 17.85 (n = 45)	88.46 ± 62.59 (n = 35)	**0.0001***
Gender			
Male, (88)	34.65 ± 51.18 (n = 84)	84.62 ± 75.39 (n = 26)	**0.0001***
Female (92)	46.61 ± 27.58 (n = 33)	79.08 ± 15.19 (n = 13)	**0.0001***
Duration of pleural effusion			
7 - 14 days (107)	31.76 ± 23.27 (n = 92)	73.33 ± 39.61 (n = 15)	**0.0001***
>14 days (49)	61.08 ± 86.36 (n = 25)	88.67 ± 72.53 (n = 24)	0.233

Independent sample t-test applied. P-value of <0.05 was taken significant; *indicate significant p-value; SD = Standard deviation.

4. Discussion

By attempting to evaluate the significance of alkaline phosphatase in TB effusion in our investigation, we took a risk. Although other studies [12] [14], and [15] tried to use ALP to separate tuberculous pleural effusion from other kinds of pleural effusion, none of them were able to do so with any degree of clarity.

Francisco Carrion and Miguel Perpina 15 discovered that compared to tuberculous, nontuberculous, and effusions from other origins, malignant pleural effusions had much greater levels of ALP. Moreover, Muzaffer Metintas [14] found that tuberculous pleural effusion had considerably greater P ALP and P/S ALP ratios than neoplastic effusion, other exudates, and transudates when exudates and transudates were separated. However, Mushtaq A. Lone 12 noted that when separating exudates from transudates, ALP did not distinguish between tuberculous and other causes of effusion, such as malignancy, parapneumonic effusion, and nonspecific. In light of the aforementioned disagreement, we evaluated the usefulness of ALP in differentiating tuberculous from non-tuberculous pleural effusion and found that ALP is a useful biochemical marker for such separation. In our study, the mean and standard deviation (SD) for the age of biopsy-proven tuberculosis vs. malignant pleural effusion were 3816 with C.I. (35.07 - 49.92) and 5514 with C.I. (5.04 - 59.53) years, respectively.

Mean ± SD for duration of pleural effusion in biopsy proven tuberculosis v/s malignant pleural effusion group was 13 ± 4 with C.I (12.26 - 13.73) and 19 ± 4 with C.I (17.70 - 20.29) days. In present study Mean ± SD alkaline phosphate level between biopsy proven tuberculosis v/s malignant pleural effusion was found to be (38.03 ± 45.97) v/s (82.77 ± 61.80) with C.I [(−63.13 - (−26.35)] and P value found to be highly significant *i.e.* (P = 0.0001).

Some of the studies are discussed here supporting the results of our study as Mushtaq A lone *et al.* [12] in his study on pleural effusions had obtained an ALP level of >75 in 72 exudates and <75 in 12 exudates studied. They had obtained a sensitivity of 100 & and specificity of 85.71% in diagnosis of exudates. Both the positive and negative predictive values were 58.62% and 100%, respectively. They believed that the ability of alkaline phosphatase levels to distinguish tuberculous effusions from other exudate-causing conditions was limited and that these levels were higher in exudative pleural effusions than in transudates. K.B. Gupta *et al.* [16] found a mean pleural fluid level of 88.53 ± 31.27 in exudates with a statistical significance of p 0.05 in their study on exudates of various etiologies. They achieved 85% and 75% sensitivity and specificity, respectively. The positive and negative predictive values were 92% and 63%, they had opined that the increased levels are seen in exudates when compared to transudates and can be used complimentarily with lights criteria in classification of exudates.

F Carion *et al.* [15] in their study on exudates of different etiology of which 72 cases were of tuberculous origin obtained a mean and standard deviation of 54.6 ± 34.3 in tuberculous effusions and 55.3 ± 31.6 in nontuberculous effusions. They did not find any significance in tuberculous pleural effusions.

However, the study done by Jadhav *et al.* [17] observed a mean and standard deviation of 140.36 ± 43.21 in the serum of tuberculous pleural effusions and 140.6 ± 32.80 in non-tuberculous groups. In pleural fluids of the two groups the mean and standard deviations were 124.66 ± 58.69 and 60.83 ± 56.51.

The mean and standard deviation of pleural and serum ratio were 0.906 ±

0.370 in tuberculous group and 0.390 ± 0.280 in non-tuberculous group. The p values were significant <0.0001 in pleural fluids and p/s ratio and <0.981 in serum. They came to the conclusion that pleural fluid ALP levels and the ratio of serum to pleural fluid can be utilized to distinguish between pleural effusions caused by tuberculosis and those that are not. However, the findings suggested additional research.

The strength of our study was that we used stringent inclusion and exclusion criteria and collected data using consecutive sampling, which was best suited for our study design. Bias was reduced in our study by using objective definitions for predictor and outcome variables. The use of a case series with poor study design, limited analysis, and weak evidence were the main limitations of our investigation. As a result, the study design did not call for any prior sample size calculations. The limited outcomes we selected also have an impact on the value of our study. Many variables and elements that were related to our predictor and outcome variables may have been examined in our study. Non-probability sampling restricts generalizability as well, although we Nevertheless, we only had a few patients, and there wasn't much time for follow-up.

This study does not accurately represent the prevalence and severity of the condition because single hospital-based study thus cannot be generalized.

5. Conclusions

A highly significant difference between biopsy-proven tuberculosis and malignant pleural effusion was detected in the mean pleural fluid alkaline phosphate level. In exudative lymphocytic pleural effusion raised PALP is found in malignancy, the better differences noted in the higher age, the less duration of disease is.

What is already known?

- The ability to distinguish between exudative and transudative pleural effusions using the alkaline phosphate level of pleural fluid.
- Pleural effusion due to pulmonary tuberculosis and malignancy is exudative pleural effusion.

What is new here?

- Pleural fluid alkaline phosphate level to differentiate between Malignant effusion and tuberculous effusion.
- Better results at relative higher-age group for pleural fluid alkaline phosphate in differentiating tubercluous and malignant pleural effusion.

Acknowledgments

Authors acknowledge their patients for participating in study by giving consent.

Conflict of Interest

No novel pharmacological agents were used in our experiment, and neither the authors nor we have any financial or other conflicts of interest. Informed written consent was obtained.

Authors' Contribution

Syed Abdul Waheed, AfshanNisar, GhulamullahLail, Concept of study, designed the work wrote the manuscript including the initial and draft.

Javid Ali, Muhammad Imran, MahboobAli, Interviewed the patients also collected the data and analysis.

Kaamrankhan, Amanullahlail, and Nadeemrizvi has contributed with expert knowledge, reviewed and critically revised the draft into final version. All authors have read and agreed to the final manuscript.

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