ORIGINAL ARTICLE

UTILITY OF PLEURAL FLUID PROTEIN TO DIFFERENTIATE MALIGNANCY FROM TUBERCULOSIS

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Background: Pleural effusion, a significant clinical problem, often poses diagnostic challenges. Tuberculosis and malignancy are the leading causes of exudative pleural effusion globally and in Pakistan. Differentiating between these two causes is essential for effective treatment, yet difficult due to overlapping clinical and biochemical profiles. **Methods:** This cross-sectional study was conducted at Jinnah Postgraduate Medical Center from February 2017 to May 2023, involving 603 patients with pleural effusion. It focused on exudative effusions, excluding transudative effusions, other causes, and patients with specific comorbidities. Procedures included diagnostic thoracenteses, pleural ultrasounds, biopsies, and various laboratory tests. The study aimed to assess the diagnostic utility of pleural fluid protein levels in distinguishing tuberculous from malignant effusions. **Results:** Out of 603 cases, 582 were analyzed. The study found significant age differences between patients with tuberculosis and malignancy. Tuberculosis was more common in younger patients, with no marked gender difference. The mean pleural fluid protein level was higher in tuberculosis (5.02±1.07 g/dL) than in malignancy (4.48±1.10 g/dL, p=0.004). A cut-off value of 5.08 g/dL for pleural fluid protein was identified as effective in differentiating between the two conditions. **Conclusion:** The study suggests that pleural fluid protein levels can be a valuable diagnostic marker for distinguishing between tuberculous and malignant pleural effusions. This is particularly relevant in settings where advanced diagnostic options are limited, highlighting the importance of pleural fluid analysis in clinical diagnosis.

Keywords: Pleural Effusion; Tuberculosis; Malignancy; Diagnostic Methods; Pleural Fluid Protein

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INTRODUCTION

Pleural effusion is a very common problem and poses a diagnostic challenge to physicians. Worldwide, tuberculous and malignant are the most common aetiologies of exudative pleural effusion.[1–5] This is similarly seen in Pakistan, where more than 50% of the exudative pleural effusions are diagnosed as tuberculosis.[6–11] It is crucial to differentiate between tuberculosis and malignancy as delayed or incorrect treatment of both diseases has grave consequences. Though, differentiating between malignant and non-malignant pleural effusions is difficult due to their similar clinical and biochemical profiles.[3,12]

The gold standard for diagnosis of pleural tuberculosis is the detection of Mycobacterium tuberculosis in pleural fluid or pleural tissue.[13] The ability to diagnose tuberculosis using this is limited because tuberculous pleural effusions primarily result from an immunological response, which typically contains only a minimal number of mycobacteria. [14] Additionally, the outcomes of microbiological tests are often delayed, and the clinical decision to initiate anti-tuberculous treatment is usually made before receiving confirmation. While conducting a pleural biopsy and acid-fast bacilli culture together with the pleural biopsy enhances the diagnostic yield to 90%, these methods are more invasive, time-consuming, and costly.[15]

The diagnosis of malignant pleural effusion relies on detecting malignant cells in the pleural fluid or tissue. Cytology of pleural fluid, with a diagnostic yield ranging from 40 to 87%, is more effective than closed biopsy, which has a yield of 35–65%.[16,17] Research indicates that combining pleural fluid adenosine deaminase (ADA) levels with differential leukocyte counts is useful in distinguishing between tuberculous and malignant pleural effusions [18,19]

However, ADA testing in pleural fluid is not generally accessible, and elevated ADA levels do not effectively differentiate between tuberculous effusions and those caused by lymphoma.[20,21]

In this context, the objective of this study was to assess the diagnostic performance of pleural fluid protein in differentiating tuberculous from malignant pleural effusion.

MATERIAL AND METHODS

This is a cross-sectional study in which 603 patients with pleural effusion were recruited from the chest ward at the Jinnah Postgraduate Medical Center from February 2017 to May 2023. The study was approved by the institutional ethics review board (Reference No. F.2-81/2014-GENL/8132/JPMC). The study included patients who had exudative pleural effusion, confirmed by Light's criteria[22], and who consented to diagnostic tests including thoracentesis and pleural fluid analysis for tuberculosis or malignancy. The study excluded several cases: those with transudative pleural effusion as defined by Light's criteria[22], exudative effusions caused by factors other than tuberculosis or malignancy, patients with comorbid illnesses like diabetes mellitus, hypertension, liver disease, or renal disease, and known cases of human immunodeficiency virus (HIV) positivity. Patients were enrolled after informed consent, and data related to age and gender was recorded.

Diagnostic thoracenteses were done and patients with exudative pleural effusion as per Light's criteria were included for the study. Pleural ultrasound was done in patients with exudative effusion, and they underwent pleural biopsy (Abrahms for simple and thoracoscopic for complicated effusion on ultrasound). Pleural fluid samples taken during biopsy procedures were sent for tests like AFB smear, mycobacterial culture, Xpert assay and cytology where clinically indicated. Pleural biopsy specimens were sent for histopathology, mycobacterial culture and Xpert assay.

The diagnostic criteria for tuberculosis in this study included either the detection of Mycobacterium tuberculosis in pleural fluid or tissue, or the presence of granulomatous inflammation on histopathology, accompanied by a compatible clinical history and radiological examination. These criteria were specifically applied to patients with a lymphocytic exudate who showed a favourable clinical response to anti-tuberculous treatment, such as resolution of fever and weight gain. For malignancy, the diagnosis was based on the detection of malignant cells in pleural fluid cytology or in tissues obtained through pleural biopsy.

Statistical analysis was done using SPSS version 23. Mean and standard deviation were calculated for pleural fluid protein level. For better understanding of the difference pleural fluid protein was grouped into 4: Group I had protein levels of 2.5–2.9 g/dL, Group II 3–4 g/dL, Group III 4–5 g/dL and Group IV >5 g/dL. Mann-Whitney U test was used for analyzing continuous variables (for data that were not normally distributed). Categorical variables were compared using the chi-square (X^2) test. A *p*-value of less than 0.05 for a two-tailed test was considered statistically significant.

RESULTS

Out of 603 cases, 582 were included in the final analysis. Study flow diagram is given in Figure 1. The demographic distribution of study population is given in table 1, which shows a significant difference in the age of malignancy and tuberculosis populations. With respect to pleural fluid protein, protein concentrations were significantly greater (p=0.004) in tuberculosis group (5.02±1.07 g/dL) as compared to malignant effusion (4.48±1.10 g/dL). Group-wise breakdown of protein analysis showed that higher pleural fluid protein levels related to higher chances of tuberculosis diagnosis as shown in table-2. When plotted in ROC curve (Figure-2) in tuberculosis versus malignancy, the best cut-off value for pleural fluid proteins was 5.08 g/dL (p<0.05).

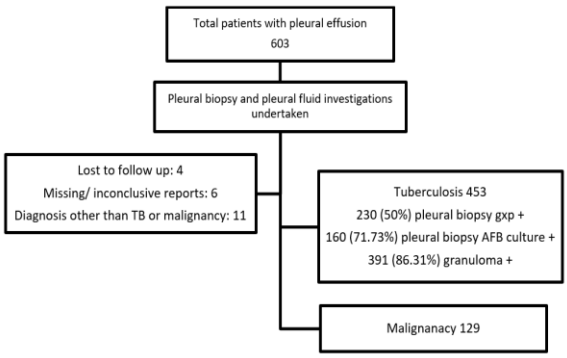

Figure 1: Study Flow Diagram

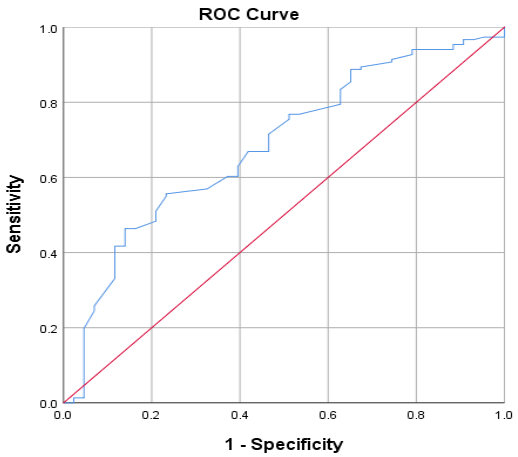

Figure-2: ROC curve showing sensitivity and specificity of pleural fluid

Table-1: Demographic distribution of the study population.

	Tuberculosis	Malignancy	*p*-value
Mean age±SD (years)	36.81±16.11	49.63±18.23	<0.05
Gender (%)			
Male (%)	303 (66.89%)	90 (69.77%)	0.85
Female (%)	150 (33.11%)	39 (30.23%)	

Table-2: Group-wise breakdown of pleural fluid protein analysis.

Groups (pleural fluid protein content)	Tuberculosis	Malignancy	*p*-value
I (2.5 – 2.9 g/dL)	12	6	0.009
II (3 – 3.9 g/dL)	54	39	
III (4 – 4.9 g/dL)	129	42	
IV (5 g/dL)	258	42	

DISCUSSION

Tuberculosis and malignancy continue to be the leading causes of exudative pleural effusion, both in Pakistan and worldwide. This observation is corroborated by numerous studies conducted over past years.[1–11] An accurate method is needed for assessing pleural effusion and pinpointing its various possible causes, particularly tuberculosis and malignancy, which often mimic each other. The diagnostic process should begin with a thorough clinical history and physical examination to gather indicative signs of the underlying condition, prior to proceeding with laboratory investigations.

In our study, we found that tuberculosis is more prevalent among younger participants. These findings align with what is documented in the literature.[15] While malignancy typically presents in older individuals, in areas with high tuberculosis rates, pleural tuberculosis also remains a significant issue among adults.[23]

Thoracentesis is the easiest and fastest first test in cases of pleural effusion. Although the cause of pleural effusion remains uncertain in about 20% of cases, detailed biochemical, microbiological, and cytological analysis of pleural fluid should be done to avoid more invasive and time-consuming tests. In our study, we first segregated exudates from transudates by Light's criteria[22] and then subjected patients with exudative pleural effusion to further analysis.

In our study, we observed that elevated pleural fluid protein levels not only assist in differentiating exudative from transudative effusions, but also hint at the potential cause of the effusion. Specifically, a high total protein content in the pleural fluid, particularly values exceeding 5.0 g/dL, typically indicates tuberculosis.[24] Indeed, more than half of our study participants with tuberculous pleural effusions had pleural fluid protein greater than 5 g/dL. Mean pleural fluid protein in tuberculous pleural effusion was significantly higher at 5.02±1.07 g/dL as compared to 4.48±1.10 g/dL in malignant pleural effusion which is in concordance with results from a study which found that pleural fluid protein content was notably lower in malignant effusions (4.2±1.0 g/dL) compared to tuberculosis (5.3±0.8 g/dL).

We found the optimal cut-off value to be 5.08 g/dL (AUC 0.685) in differentiating tuberculous versus malignant pleural effusion. A study from Spain[25] done on 392 subjects found that tuberculous fluids were protein-rich and 74% had total protein contents greater than 5 g/dL. They also devised two scoring models to diagnose pleural tuberculosis. The second model included pleural fluid protein ≥5 g/dL along with 5 other parameters. This score-based model had an area under the ROC curve of 0.982 (95% CI 0.968–0.995) and correctly classified 75% of the fluids. Another study showed median protein level of 5.1 g/dL in the tuberculous group.[26]

One of the main limitations of the study is that it is a single center study. Hence, the results cannot be generalized. Further studies can be done on the subject including multiple centers to increase the validity.

CONCLUSION

The optimal pleural fluid protein cut-off value of 5.08 g/dL for distinguishing tuberculosis from malignancy in pleural effusions, as identified in our study, offers a practical diagnostic marker that is both accessible and cost-effective. This advancement enriches the medical literature by providing a reliable, non-invasive method that can be especially useful in resource-limited settings. Clinically, it holds the potential to improve patient management by allowing for prompt and accurate treatment decisions, thereby improving patient outcomes, and informing public health policies.

Conflict of interest

The authors declare they have no conflict of interest.

AUTHORS' CONTRIBUTION

KKS: Literature search, conceptualization of study design, data interpretation, write up and proof reading. NA: Conceptualization of study design, write up, data collection, data analysis and interpretation. DC: Data collection, data interpretation, write up. NAR: Write up and proof reading.

REFERENCES

1. Reddy SL, Varaprasad K, Narahari N, Bhaskar K, Varma GR, Paramjyothi GK. Clinical and etiological profile of an exudative pleural effusion in a tertiary care center. Indian J Respir Care 2019;8(1):22–6.
2. Hussein M, Thomas M, Al-Tikrity M, Elarabi A, Hameed M, Al-Adab A, Ibrahim W, *et al*. Etiology of exudative pleural effusion among adults: differentiating between tuberculous and other causes, a multicenter prospective cohort study. IJID Reg 2024;12:100425.
3. Gao S, Wang C, Yu X, Teng T, Shang Y, Jia J, *et al*. Xpert MTB/RIF Ultra enhanced tuberculous pleurisy diagnosis for patients with unexplained exudative pleural effusion who underwent a pleural biopsy via thoracoscopy: A prospective cohort study. Int J Infect Dis 2021;106:370–5.
4. Gong L, Huang G, Huang Y, Liu D, Tang X. Medical Thoracoscopy for the Management of Exudative Pleural Effusion: A Retrospective Study. Risk Manag Healthc Policy 2020;13:2845–55.
5. Petborom P, Dechates B, Muangnoi P. Differentiating tuberculous pleuritis from other exudative lymphocytic pleural effusions. Ann Palliat Med 2020;9:2508–15.
6. Ali S, Abbas M. Diagnostic evaluation of patients presenting with pleural effusion to Mardan Medical Complex, Khyber Pakhtunkhwa. Pak J Chest Med 2021;27(3):140–5.
7. Sadaf S, Noor U, Kazmi S, Noor A, Yasin M, Kanwal N. The utility of pleural biopsy in differentiating between different types of lymphocytic exudative pleural effusions. Pak J Chest Med 2021;27(1):32–6.
8. Waheed SA, Nisar A, Lail A, Lail G, Imran M, Ali J, *et al*. Pleural fluid alkaline phosphate levels to differentiate between tuberculosis and malignant pleural effusion a tertiary care experience. J Tuberc Res 2023;11(2):86–93.
9. Qureshi AR, Irfan M, Ashraf Z. Diagnostic Accuracy of Sonographic Septations in Tuberculous and Malignant Pleural Effusions. J Islamabad Med Dental Coll 2020;9(2):95–102.
10. Muhammad N, Saeedullah SU, Khan ZU, Ayaz M, Nabi A, Khan MW. Incidence of Pleural Effusion and its causes in Chronic Kidney Disease Patients. Pak J Chest Med 2023;29(1):25–9.
11. Sumalani KK, Akhter N, Chawla D, Rizvi NA. Visual Diagnosis of Pleural Tuberculosis and its Association with Tissue Biopsy, Culture and Xpert Assay. Pneumologie 2022;76(2):92–7.
12. Zhang W, Liu Z, Duan X, Li Y, Shen C, Guo Y, *et al*. Differentiating malignant and benign pleural effusion in patients with lung cancer: an ^{18}F-FDG PET/CT retrospectively study. Front Oncol 2023;13:1192870.
13. McNally E, Ross C, Gleeson LE. The tuberculous pleural effusion. Breathe (Sheff) 2023;19(4):230143.
14. Lo Cascio CM, Kaul V, Dhooria S, Agrawal A, Chaddha U. Diagnosis of tuberculous pleural effusions: A review. Respir Med 2021;188:106607.
15. Sood S, Arya R, Dutta N, Paul A, Behera RK, Nanda RK, *et al*. Current Methods and Future of Tuberculosis (TB) Diagnosis. In: Dutta G, Biswas A, Chakrabarti A, editors. Modern Techniques in Biosensors. Studies in Systems, Decision and Control. Springer, Singapore: 2021; p.327.
16. Kassirian S, Hinton SN, Cuninghame S, Chaudhary R, Iansavitchene A, Amjadi K, *et al*. Diagnostic sensitivity of pleural fluid cytology in malignant pleural effusions: systematic review and meta-analysis. Thorax 2023;78(1):32–40.
17. Durgeshwar G, Mohapatra PR, Bal SK, Mishra P, Bhuniya S, Panigrahi MK, *et al*. Comparison of diagnostic yield and complications in ultrasound-guided closed pleural biopsy versus thoracoscopic pleural biopsy in undiagnosed exudative pleural effusion. Cureus 2022;14(4):e23809.
18. Aggarwal A, Kumar S, Jethani V, Khanduri S, Khanduri RS, Sharma A. Pleural fluid adenosine deaminase, c -reactive protein levels and lymphocyte/ neutrophil count ratio in differentiating tubercular and non-tubercular pleural effusion. J Cardiothorac Med 2022;10(3):1017–24.
19. Shimoda M, Hirata A, Tanaka Y, Morimoto K, Yoshiyama T, Yoshimori K, *et al*. Characteristics of pleural effusion with a high adenosine deaminase level: a case–control study. BMC Pulm Med 2022;22(1):359.
20. Mittal N, Das B. Role of adenosine deaminase (ADA) in etiological classification of exudative pleural effusion. Int J Res Rev 2020;7(1):401–6.
21. Choe J, Shin SH, Jeon K, Huh HJ, Park HD, Jeong BH. Features which discriminate between tuberculosis and haematologic malignancy as the cause of pleural effusions with high adenosine deaminase. Respir Res 2024;25(1):17.
22. Light RW, Macgregor MI, Luchsinger PC, Ball WC Jr. Pleural effusions: the diagnostic separation of transudates and exudates. Ann Intern Med 1972;77(4):507–13.
23. Olmo-Fontánez AM, Turner J. Tuberculosis in an Aging World. Pathogens 2022;11(10):1101.
24. Vyas Y. Pleural Tuberculosis. In: Strumfa I, Uljanovs R, Strumfs B, editors. Challenges in Pleural Pathology - Diagnostics, Treatment and Research [Internet]. IntechOpen; 2024 [cited 2025 Jan]. Available from: http://dx.doi.org/10.5772/intechopen.114244.
25. Porcel JM, Vives M. Differentiating tuberculous from malignant pleural effusions: a scoring model. Med Sci Monit 2003;9(5):175–80.
26. González A, Fielli M, Ceccato A, Luna C. Score for Differentiating Pleural Tuberculosis from Malignant Effusion. Med Sci (Basel) 2019;7(3):36.

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