JPSIM Journal of Pakistan Society of Internal Medicine

Original Article

Diagnostic Accuracy of Pleural Fluid Protein in Differentiating Tuberculous and Malignant Pleural Effusion

Karishma Rehman, Mohammad Younas, Rukhsana Javed Farooqi, Rabia Saeed, Sheema Sajjad, Saadia Ashraf

MTI Khyber Teaching Hospital Peshawar

Abstract

Objective: The utility of pleural fluid protein in differentiating between malignant and tuberculous conditions in patients with pleural effusions, with histology serving as the gold standard for diagnosis.

Methods: Cross-sectional (validation) study. Patients were referred from in- and out-of-door patient departments. Patients fulfilling the inclusion criteria underwent Abrams needle biopsies according to routine and following the obtaining of informed written consent, and the pleural tissue was examined by a single histopathologist. A pleural fluid protein cut-off value of 5 g/dl for tuberculosis was marked.

Results: In this study, we identified 209 patients with suspected tuberculous or malignant pleural effusions. Mean age was 42.7 + 10.8 SD. In the diagnosis of cancer, pleural fluid protein has a positive predictive value of 35.9%, a negative predictive value of 98.82%, and sensitivity and specificity of 87.5% and 87.05%, respectively. The overall diagnostic performance of pleural fluid protein for cancer was 87.08%.

Conclusion: When combined with a suitable clinical setting, the pleural fluid total protein level is a useful diagnostic tool for suspected tuberculous or malignant pleural effusions.

Key words: tuberculous pleural effusion, malignant pleural effusion, exudates, pleural biopsy, pleural fluid protein.

How to cite this:

Rehman K, Younas M, Farooqi RJ, Saeed R, Sajjad S, Ashraf S. Diagnostic Accuracy of Pleural Fluid Protein in Differentiating Tuberculous and Malignant Pleural Effusion. J Pak Soc Intern Med. 2026;7(2): 141-145

Corresponding Author: Dr. Rukhsana Javed Farooqi, **Email:** rukhsanafarooqi1995@gmail.com

Received: 16-12-2025 **Revised:** 13-04-2026 **Accepted:** 04-05-2026 **DOI:** https://doi.org/10.70302/jpsim.v7i2.2628

Introduction

Pleural effusion defines the abnormal accumulation of fluid within the pleural space and is a common clinical presentation in patients with pulmonary or systemic diseases. Among exudative effusions, the two most frequent causes worldwide are tuberculous pleural effusion (TPE) and malignant pleural effusion (MPE).[1] It is very important to make a differential diagnosis between them because their management strategies, prognosis, and follow-up differ significantly.[2] The definitive diagnosis often depends on pleural biopsy and histopathological examination, though accurate, they are invasive and time-consuming and not always feasible in resource-limited settings.[3]

In such scenarios, biochemical analysis of pleural fluid is a relatively rapid and least invasive diagnostic approach. Pleural fluid protein concentration has traditionally been applied to the differentiation of effusions into transudates or exudates, but recently some studies have also investigated its role in differentiating TPE from MPE.[4,5] A few authors have documented that proteins are usually higher in TPE, owing to the severe inflammation accompanying the infection with Mycobacterium tuberculosis.[6]

On the other hand, the counter-argument is raised that it is very nonspecific because its levels can be affected by increased vascular permeability, tumor-induced inflammation, and systemic hypoalbuminemia.[7,8] This debate serves as a background for the present study, which will try to establish whether pleural fluid protein alone can distinguish tuberculous from malignant effusion with good enough diagnostic accuracy to be clinically acceptable, with histopathology being the gold standard. The research is necessitated by the fact that studies have persistently claimed pleural fluid protein as diagnostically unhelpful, and seeks to establish the actual clinical value of this analyte. Hopefully, it would prove to be a good marker that is quick, inexpensive, and easily accessi-

ble; above all, it would be of immense utility in poor resource settings where invasive procedures are not possible. In case it proves to be a poor discriminator, the results would still be useful as they would unequivocally establish its inadequacy and underscore the use of multi-marker or composite diagnostic approaches.[9–12]

This research is important for developing improved early clinical decision-making, reducing invasive procedures, and assisting in timely treatment in tuberculosis-endemic regions like Pakistan.

Methods

This hospital-based validation-cross-sectional study was conducted at the pulmonology department of MTI Khyber Teaching Hospital, Peshawar, between September 16, 2023 and March 15, 2024, after approval by the hospital's ethics committee. Sample size was calculated using the following parameters: 50% sensitivity,[6] 57.5% specificity,[6] 46.1% incidence of pleural effusion,[11] 95% confidence level, and 10% margin of error. All patients who came to the pulmonology department from the emergency room or outpatient department (OPD) with a suspicion of tuberculosis or malignant pleural effusion were evaluated. This has been confirmed by an X-ray of the chest.

After written informed consent, the patient with exudative pleural effusion underwent a fluid protein level and, if indicated, an Abrams needle biopsy. The complete medical history of the patient and biopsy results were also collected. The biopsy sample was submitted for histopathology analysis. A structured proforma designed to employ the study was used to collect and record the biopsy report. The sensitivity, specificity, positive predictive value, and negative predictive value of pleural fluid protein in the identification of the causative agent of cancer or tuberculosis are evidence of diagnostic accuracy. A cutoff of 3 g/dl was used for the differentiation of malignant fluid (that is, less than 3 g/l) and tuberculous pleural effusion (that is, more than 3 g/dl). Biopsy showed malignant pleural effusion or the presence of neoplastic cells in the pleural tissue along with caseating granulomas typical of tuberculosis.

The pleural fluid was analysed in a standard laboratory, the pleural tissue by one histopathologist, and the pleural biopsy was performed with a standard Abrams needle, and all the materials were transported in standard tubes or bottles containing standard chemicals to prevent bias in the study outcomes. Patients with transudative pleural effusion, polymorphic exudative pleural effusion/empyema, and those with ambiguous pleural biopsy results were excluded to control for confounders and confirm the study results.

Baseline clinical data, including age, sex, and pleural fluid protein level, were filled in the proforma. Data were entered and analyzed using version 10.0 of Statistical Program for Social Sciences (SPSS).

Results

Table 1 presents the demographic characteristics of the 209 patients included in the study. The mean age of participants was 42.7 ± 10.8 years. Most patients (33.5%) were between 41 and 50 years of age, followed by 27.8% aged 51 years and above. The study population consisted of 139 males (66.5%) and 70 females (33.5%).

Table 1: *Demographic Distribution of the Patients (n = 209)*

Variables	Categories	Frequency (n)	Percentage (%)	Mean ± SD
Age (years)	≤ 30	26	12.4	42.7 ± 10.8
	31 – 40	55	26.3	
	41 – 50	70	33.5	
	≥ 51	58	27.8	
	Total	209	100.0	
Gender	Male	139	66.5	-
	Female	70	33.5	
	Total	209	100.0	

Table 2 shows that the diagnostic utility of pleural fluid protein was assessed in different age groups. When using the test in a population of age 30, sensitivity was 100%, specificity was 92.31%, positive predictive value (PPV) of 33.3%, negative predictive value (NPV) of 66.7%, and overall accuracy was 92%. sensitivity and specificity were 100% and 83.64% for the 31–40 age group, PPV 35.5%, NPV 64.3%, and accuracy 82% for the 31–40 age group. The sensitivity was decreased by 66.7%, PPV 22.2%, NPV 77.8% and accuracy 89.5% among participants over the age of 41-50. For the 51-year-old group, pleural fluid protein had a sensitivity of 85.71%, a specificity of 86.21%, a PPV of 46.2%, an NPV of 53.8%, and an overall accuracy of 86.27%. Overall, pleural fluid protein diagnostic accuracy was consistently high across all age categories, slightly better for younger patients (>40 years) than for older patients.

Table 3 shows the diagnostic performance of pleural fluid protein analysis across gender and BMI categories. Males were more likely to take the test because their sensitivity was 87.5%, specificity was 87.05%, positive predictive value (PPV) was 29.2%, and negative predictive value (NPV) was 70.8%. The overall accuracy was 87.02%. In females, they were sensitivity and specificity 87.5%, 887.14%, PPV 46.7%, NPV 53.3% and total accuracy of 87.1%.

When BMI was steered by BMI, patients with BMI under 28 kg/m2 were sensitive to 100% accuracy, speci-

ficity, PPV 35.3%, NPV 64.7%, and accuracy was 88.89%. The sensitivity and specificity of BMI 29 kg/m^2 were 80% and 844.62%, respectively, with a PPV of 36.4%, NPV of 63.6%, and overall accuracy of 85.11%.

Table 2: *Age-Wise Stratification of Accuracy of Pleural Fluid Protein*

Age (in years)	Category	Histopathology: Malignant	Histopathology: Tuberculosis	Sen. Spec. PPV NPV	Accuracy
<= 30.00	Malignant	1	2	100%	92.31%
		33.3%	66.7%	92%	
	Tuberculosis	0	23	33.3%	
		0.0%	100.0%	100%	
31–40	Malignant	5	9	100%	83.64%
		35.5%	64.3%	82%	
	Tuberculosis	0	41	35.71%	
		0.0%	100.0%	100%	
41–50	Malignant	2	7	66.7%	88.57%
		22.2%	77.8%	89.5%	
	Tuberculosis	1	60	22.2%	
		1.6%	98.4%	98.6%	
51.00+	Malignant	6	7	85.71%	86.21%
		46.2%	53.8%	86.27%	
	Tuberculosis	1	44	46.15%	
		2.2%	97.8%	97.78%	

Table 3: *Gender and BMI-wise stratification of the accuracy of pleural fluid protein*

Variable		Pleural Fluid Protein	Histopathology: Malignant	Histopathology: Tuberculosis	Sen. Spec. PPV NPV	Accuracy
Gender	Male	Malignant	7	17	87.5%	87.05 %
			29.2%	70.8%	87.02%	
		Tuberculosis	1	114	29.17%	
			.9%	99.1%	99.13%	
	Female	Malignant	7	8	87.5%	87.14 %
			46.7%	53.3%	87.1%	
		Tuberculosis	1	54	46.67%	
			1.8%	98.2%	98.18%	
BMI (Kg/m)	<= 28.00	Malignant	6	11	100%	89.52 %
			35.3%	64.7%	88.89%	
		Tuberculosis	0	88	35.29%	
			.0%	100.0%	100%	
	29.00+	Malignant	8	14	80%	84.62 %
			36.4%	63.6%	85.11%	
		Tuberculosis	2	80	36.36%	
			2.4%	97.6%	97.56%	

Overall, pleural fluid protein was highly sensitive to distinguish malignant versus tuberculous pleural effusions among genders and BMIs, with slightly less accuracy in males and patients with low BMI.

Table 4 describes the pleural fluid protein diagnostic utility for the diagnosis of malignant versus tuberculous pleural effusion using histopathology as a reference standard. Of the 209 cases, 14 true positives, 25 false positives, 2 false negatives, and 168 false negatives were found.

The calculated diagnostic parameters were as follows:

- Sensitivity: 87.5% (14/16)
- Specificity: 87.05% (168/193)
- Positive Predictive Value (PPV): 35.9% (14/39)
- Negative Predictive Value (NPV): 98.8% (168/170)
- Overall Accuracy: 87.08%

These results indicate that pleural fluid protein demonstrates high sensitivity, specificity, and overall accuracy, making it a reliable screening tool for differentiating tuberculous from malignant pleural effusion.

Table 4: *Diagnostic Accuracy of Pleural Fluid Protein*

Variable outcomes		Histopathology: Positive	Histopathology: Negative	Histopathology: Total
Pleural Fluid Protein	Positive	14	25	39
	Negative	2	168	170
Total		16	193	209

Discussion

The physician faces a diagnostic dilemma when attempting to differentiate between malignant and tuberculous pleural effusions. This is mostly because microbiological techniques are unable to confirm a pleural tuberculosis diagnosis in a significant number of cases, and cytological investigations' sensitivity for malignancy is insufficient.[12]

A malignant cause, such as lung cancer, is the most common cause of lymphocytic exudative pleural effusion. The figure varies between developed and developing nations, however. In non-TB endemic areas, MPE is more common than TPE.

A 2003 study of 392 patients in Spain found that MPE was present in 73% of cases, and 27% had TPE13. Another recent study on lymphocytic exudative pleural effusion conducted in Thailand showed that nonspecific pleuritis, TPE and MPE consisted of 22.3%, 37.2% and 40.6% of cases, respectively.[14] TB pericarditis (TPE) is more common than malignant pericardial effusion (MPE) in areas where tuberculosis is endemic conducted on 326 patients in Brazil. TPE cases were 55.9% while MPE cases were 44.1% of total cases.[15]

In our country, malignant empyema is second only to

tuberculosis as the most common cause of lymphocytic exudative pleural effusion, Javaid A. et al., in collaboration with Pakistan Medical Research Council. Done a study on those patients who had lymphocytic exudative pleural effusion.[16]

Another Peshawar-based study of 74 patients who had percutaneous pleural biopsies revealed that 18.91% of the patients had MPE and 52.71% had TPE. 71.62% 8 was the pleural biopsy yield. Similarly, in Rizwan M's study, the most frequent cause of lymphocytic exudative PE was tuberculous pleural effusion (75%), which was followed by MPE (22.5%).[17] Our analysis revealed that TPE accounted for 92.34% of all instances, making it more prevalent than MPE. The remaining 7.66% of cases had malignant PE.

When choosing between malignant or tuberculous PE, age has also been a significant supplementary factor. TPE was more prevalent in the younger age group of our study than MPE, which was more prevalent in the older age group. Our results were similar to those of the worldwide research. According to Porcel JM et al. (2003), the average age of MPE cases was 68 years old (range: 58–76 years), but the average age of TPE cases was 30 years old (range: 22–40).[13]

In their study, Antonangelo et al. found that patients with MPE were considerably older than those with tuberculous PE. The average age for malignant PE was 58 years, whereas the average age for tuberculous PE was 36 years.[14]

Although the incidence of cancer in women has been rising over the past few decades, it is known that men are more likely than women to contract lung cancer and tuberculosis.[17]

Our research revealed that female patients were more prevalent in MPE. Global epidemiology statistics show a different outcome. It is easy to understand this prejudice given our institution's tertiary status as a referral centre for pleural involvement cancer, particularly breast cancer.

The primary diagnostic method for exudative pleural effusion in our nation is closed pleural biopsy with an Abram needle; in this context, national and international research is available that provides varying diagnostic yields for malignant and tuberculous PE. In Javaid et al.'s study, the diagnostic yield showed 69%. 45% cases were tuberculous and 24% malignant PE. A study by Magsi JA et al, 60% diagnostic yield was reported. According to Fishman AP et al,[19] the diagnostic yield in their patients was 40%. Heidri et al reported a diagnostic yield of 70% for TPE and 54% for MPE[1,16,20]

A variety of parameters have been applied to differentiate tuberculous from malignant PE and to assist in this task, including PV, CRP, CEA, IL, IFN, VEGF, TNF, and pleural fluid T-cells in developed centers. But no national study has examined any of these factors, presumably because they are not easily available or affordable. In light of these limitations, the current investigation utilized the total pleural fluid protein. It is commonly executed in PE cases, easily accessible, and cheaper. To the best of our knowledge, this study is the first of its kind in the country exploring the role of total pleural fluid protein in differentiating malignant and tuberculous PE. 73% of TPE had pleural fluid protein level ≥5g/dl reported by Porcel-Perez JM et al (2004)[21]. This was the threshold beyond which tuberculous etiology of the lymphocytic exudative PE was considered[15].

According to another study in Spain that involved 105 TPE patients found that 57% of them had pleural fluid protein levels higher than 5g/dl.[20] TPE has a greater protein level than MPE, according to Antonangelo et al. (2007)[22]. The protein level in MPE was 4.2±1, but in tuberculous PE it was 5.3±0.8g/dl. Statistical significance was achieved by the difference.[15]

The combination of protein level with other laboratory markers separates tuberculous from malignant PE. A study conducted by Liam et al also found similar outcomes. (2000) in patients with tuberculous or malignant PE.[22] Melo et al. proposed that a TPE diagnosis could be assumed if at least three parameters were ≥4.5g/dl.[23]

Two scoring models were suggested by the study to distinguish between malignant and tuberculous PE. Additionally, it showed that the pleural fluid total protein level, which is employed in one scoring model without ADA, can be used to distinguish between tuberculous and malignant PE in places without ADA facilities. The pleural fluid protein demonstrated 80% specificity and 77% sensitivity. These findings are similar to those of our investigation, which demonstrated 90.60% specificity and 73.30% sensitivity at a pleural fluid protein level of ≥5g/dl.[17-19]

Conclusion

Even in rich countries where complex investigative strategies are well developed, it has been challenging to identify tuberculous or malignant PE. These two aetiologies are still the most common causes of undiagnosed lymphocytic exudative PE.

Although closed pleural biopsy remains the principal method of diagnosis in our country, the yield is often poor owing to the unavailability of specialised and costly tests. Due to these limitations, total pleural fluid protein is used to differentiate between malignant and tuberculous effusions, apart from an adequate clinical picture.

Ethical Approval: The IRB/EC approved this study via letter no. 224/DME/KMC dated April 13, 2023.

Conflict of Interest: None

Funding Source: None

Authors' Contribution

KR: Conception.

MY, SA: Design of the work.

RJF, RS, SS: Data acquisition, analysis, or interpretation.

MY, RJF, RS, SS: Draft the work.

KR, SA: Review critically for important intellectual content.

All authors approve the version to be published.

All authors agree to be accountable for all aspects of the work.

References

1. Koegelenberg CFN, Shaw JA, Irusen EM, Lee YCG. Contemporary best practice in the management of malignant pleural effusion. Ther Adv Respir Dis. 2018; 12:1753466618785098
2. Ping Luo, Kaimin Mao, Juanjuan Xu, Feng Wu, Xuan Wang, Sufei Wang, et al. Metabolic characteristics of large and small extracellular vesicles from pleural effusion reveal biomarker candidates for the diagnosis of tuberculosis and malignancy. J Extracellular Vesicles. 2020; doi: 10.1080/20013078.2020.1790158
3. Kaul V, McCracken DJ, Rahman NM, Epelbaum O. Contemporary Approach to the Diagnosis of Malignant Pleural Effusion. Ann Am Thorac Soc. 2019; 16(9): 1099-106
4. Zhang X, Duan H, Yu Y, Ma C, Ren Z, Lei Y, et al Zhang M. Differential diagnosis between benign and malignant pleural effusion with dual-energy spectral CT. PLoS One. 2018;13(4):e0193714
5. Kim CH, Oh HG, Lee SY, Lim JK, Lee YH, Seo H, et al. Differential diagnosis between lymphoma-associated malignant pleural effusion and tuberculous pleural effusion. Ann Transl Med. 2019 Aug;7(16):373 doi: 10.21037/atm.2019.07.17
6. Petborom P, Dechates B, Muangnoi P. Differentiating tuberculous pleuritis from other exudative lymphocytic pleural effusions. Ann Palliat Med 2020; 9(5): 2508-15.
7. Yang MF, Tong ZH, Wang Z, Zhang YY, Xu LL, Wang XJ, et al, Jiang T, Shi HZ. Development and validation of the PET-CT score for diagnosis of malignant pleural effusion. Eur J Nucl Med Mol Imaging. 2019; 46(7): 1457-67
8. Mercer RM, Corcoran JP, Porcel JM, Rahman NM, Psallidas I. Interpreting pleural fluid results. Clin Med (Lond). 2019;19(3):213-7
9. Takeuchi E, Okano Y, Machida H, Atagi K, Kondou Y, Kadota N, et al. Eosinophilic pleural effusion due to lung cancer has a better prognosis than non-eosinophilic malignant pleural effusion. Cancer Immunol Immunother. 2022;71(2):365-72
10. Schwalk AJ, Ost DE, Saltijeral SN, De La Garza H, Casal RF, Jimenez CA, et al. Risk Factors for and Time to Recurrence of Symptomatic Malignant Pleural Effusion in Patients With Metastatic Non-Small Cell Lung Cancer with EGFR or ALK Mutations. Chest. 2021; 159(3):1256-64
11. Farraga M, El-Masrya A, Shoukria AM, ElSayedb M. Prevalence, causes, and clinical implications of pleural effusion in pulmonary ICU and correlation with patient outcomes. Egypt J Bronchol. 2018;12(2):247–52.
12. Ferrer J. Tuberculous pleural effusion and tuberculous empyema. Crit Care Med 2001;22(6):637-46.
13. Porcel JM, Vives M. Differentiating tuberculous from malignant pleural effusion: A scoring model. Med Sci Monit 2003;9(2):175-80.
14. Chierakul N, Kanitsap A, Chaiprasert A, Virivataveekul R. A simple C- C-reactive protein measurement for the differentiation between tuberculous and malignant pleural effusion. Respirol. 2004;9(1):66-9.
15. Antonangelo L, Vargas FS, Seiscento M, Bombarda S, Teixera L, Sales RK. Clinical and laboratory parameters in the differential diagnosis of pleural effusion secondary to tuberculosis or cancer. Clin 2007;62:585-90.
16. Javaid A, Amjad M, Shah N, Samad A, Ullah Z. Diagnostic evaluation of exudative pleural effusion, the value of pleural biopsy. Pak J Chest Med 2001;7(1):12-20.
17. Khaliq MR. Pleural biopsy by Abrams punch needle pattern and frequency of histopathological lesions encountered in patients with exudative pleural effusion. Ann Abbasi Shaheed Hosp Karachi Med Dent Coll 2003;8(1):6-11.
18. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. Cancer J Clin 2005;55(1):4-108.
19. Fishman AP. Disorders of the pleural space. In: Elias JA, Fishman JA, Grippi MA, Kaiser LR, Senior RM, (edi). Fishman's pulmonary diseases and disorders. 3rd ed. Washington, DC: McGraw-Hill; 1997:p.1389-452.
20. Heidari B, Bijani K, Eissazadeh M, Heidari P. Exudative pleural effusion: effectiveness of pleural fluid analysis and pleural biopsy. East Meditter Health J 2007; 13(3):765-73.
21. Haro M, Ruiz-Manzano J, Gallego M, Abad J, Manterola JM, Morera J. Pleural tuberculosis: analysis of 105 cases. Enferm Infecc Microbiol Clin 1996;14(2):285-9.
22. Liam CK, Lim KH, Wong CM. Differences in pleural fluid characteristics, white cell count, and biochemistry of tuberculous and malignant pleural effusions. Med J Malaysia 2000;55(1):21-8.
23. Melo AF, Santos ML. Diagnóstico da tuberculose pleural pela ada, isolada ou combinada a outras variáveis, inclusive em HIV positivos. Folha Med 2000; 119 (1): 19-21.