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Clinical Utility of Pleural Fluid Protein in Differentiating Tuberculous and Malignant Pleural Effusion in a Resource-Limited Setting

Bushra Arif, Sada Saeed, Hamid Nisar Khan, Sabeen Sajjad, Muhammad Mamoon, Fazal Mustan

Abstract

Objective: To evaluate the diagnostic performance of pleural fluid protein in differentiating tuberculous pleural effusion (TBPE) from malignant pleural effusion (MPE).

Study Design and Setting: This cross-sectional analytical study was conducted at the Department of Pulmonology, Ayub Teaching Hospital, Abbottabad, Pakistan, from October 2020 to March 2021.

Methodology: A total of 109 patients aged 20–75 years with pleural effusion were enrolled through consecutive non-probability sampling. Patients with end-stage renal, hepatic, or cardiac failure, terminal illness, or psychiatric disorders were excluded. Pleural biopsy with histopathological examination was used as the reference standard for diagnosing TBPE or MPE. Pleural fluid total protein was measured and categorized as <5 g/dL or =5 g/dL. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy were calculated.

Results: The mean age was 45.65 ± 15.34 years, with a near-equal gender distribution. Histopathology confirmed TBPE in 61 (56.0%) patients and MPE in 48 (44.0%). Pleural fluid protein levels =5 g/dL were observed in 46 (42.2%) patients, while 63 (57.8%) had levels <5 g/dL. Using a cutoff value of =5 g/dL, pleural fluid protein demonstrated a sensitivity of 81.97%, specificity of 72.92%, PPV of 79.37%, NPV of 76.09%, and diagnostic accuracy of 77.98% for identifying TBPE.

Conclusion: Pleural fluid protein estimation shows acceptable diagnostic performance in differentiating TBPE from MPE and may serve as a useful adjunct in resource-limited settings. Although histopathology remains the gold standard, pleural fluid protein measurement can support earlier clinical decision-making when interpreted with clinical and radiological findings.

Keywords: Diagnostic accuracy; Malignant pleural effusion; Pleural effusion; Pleural fluid protein

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INTRODUCTION

Pleural effusion is a common problem that doctors who treat breathing issues and other doctors see all the time everywhere. It happens a lot with people who have lung problems, heart problems, infections, inflammation and cancer. Pleural effusion uses up a lot of resources that hospitals and doctors have. People who have effusion might feel like they cannot breathe very well they might have chest pain and they might have a cough. They usually cannot do physical activity, which makes it really hard for them to do things they need to do every day and be comfortable[1].

Since pleural effusion can be caused by a lot of things it is very important for doctors to figure out what is causing the pleural effusion so they can treat it correctly and help people who have it feel better. When doctors check out an effusion the first thing they do is try to find out if the fluid, in the pleural effusion is transudative or exudative.[2]

Pleural fluid problems can be caused by diseases that affect how much fluid forms and gets absorbed. This includes things like heart failure, liver cirrhosis, nephrotic syndrome or hypoalbuminemia. In these cases the pleura itself is not the problem. We just need to treat the issue that is causing the trouble.[3] On the hand sometimes the pleura has local

problems. This can be due to vascular permeability, poor lymphatic drainage, inflammation or a disease that directly affects the pleura. Figuring out what caused these problems usually needs tests.

We can often tell when someone has an effusion just by looking at some clinical findings and lab tests. But working out what is behind an effusion is much harder. It is very important to make sure it is not tuberculosis or metastatic cancer. These are two of the causes of exudative effusions, in many parts of the world. We need to rule out effusions caused by tuberculosis and metastatic cancer because these diseases are big causes of exudative effusions.[3] Disease processes can cause pleural effusion in many parts of the body. This happens because of infections, cancer and problems with the system and also because of blockages in the lymphatic system blood clots in the lungs and other kinds of inflammation. Figuring out what caused the exudative pleural effusion is really tough because there are many things that can cause it. Doctors need to use their experience and knowledge. They also need to use tests like imaging tests and they need to look at the fluid from the pleura and sometimes they even need to do biopsies.[4] With new technology it is still hard to find the exact cause of the exudative pleural effusion especially in places that do not have a lot of resources.[4] In Pakistan and lots of developing countries exudative pleural effusion is a big problem for healthcare systems. A study from a hospital in Peshawar, Pakistan found that about 9 percent of patients each year had exudative pleural effusion. This shows how important it is to create affordable diagnostic methods, for regular use so doctors can diagnose exudative pleural effusion easily.[5]

Tuberculosis and cancer are the reasons people get fluid in the lungs in Pakistan just like in other parts of the world. Tuberculosis is the cause of this problem in countries where it is common. This shows that Tuberculosis is an issue for public health. When parts of the bacteria that cause Tuberculosis get into the space around the lungs it causes a reaction that leads to building up. This reaction is slow to happen. On the hand cancer is often the cause of fluid in the lungs when it is related to cancer. This type of buildup can come from cancer that started in the lungs or from cancer that spread to the lungs from other parts of the body. It can also come from types of cancer like lymphomas. Now even though Tuberculosis is the common cause of fluid in the lungs overall in places where Tuberculosis is not common and in people who are over sixty years old cancer is more likely to be the cause. Tuberculosis is still a problem but cancer is a bigger issue, in these cases.[6]

It is really important to tell the difference between malignant pleural effusions because the way we treat them and the results are very different. If we can find out someone has tuberculosis on we can start treating them right away which helps to stop the disease from spreading. When we find out someone has pleural effusion doctors can take a close look at the cancer and come up with a plan to treat it.[7] To figure out if someone has tuberculosis we usually look for Mycobacterium tuberculosis in the fluid or tissue around the lungs. However this can be very hard to do in a doctors office. The problem is that pleural tuberculosis does not have a lot of bacteria in the fluid so we call it paucibacillary. This makes it tough for tests to find the bacteria. They often do not work well. In fact these tests only work 30% of the time when we look at the fluid and about 50% of the time when we use tissue samples. This is a problem because the old way of testing, which is called a culture can take up to 60 days to get the results. This means that people have to wait a time to find out what is wrong, with them before they can start treatment.[7,8]

Over the years several tests for diagnosing pleural effusion have become really important. These include ADA, interferon-ã assays, lysozyme measurements, PCR-based methods and antibody tests.[9] Also tuberculous pleural effusions usually show several lymphocytes which is also helpful. Although these tests have made diagnoses more accurate many low-resource areas cannot access them. The problem is these tests need special lab equipment, expert technicians and financial constraints. Closed pleural biopsy to diagnose tuberculous pleural effusion and lung cancer is efficient. However biopsies are a very invasive in nature, they might not work for everyone, leading the doctors to start with tests for tuberculous pleural effusion.[10] Usually tests for protein and LDH levels are checked in the fluid. This helps to see wether fluid buildup is transudative or exudative which can indicate problems like tuberculosis or lung cancer.[11,12] In areas where doctors do not have access to tests, it is really important to find chemical markers. These markers help doctors make diagnoses while they wait for the final test results. For example one common test is to check the protein levels in the fluid. This study is about how useful those protein levelsre at telling the difference, between tuberculous and malignant pleural effusions in a large hospital. The goal of the research is to support decisions in places where advanced tools are not available.

METHODOLOGY

This cross-sectional analytical study was conducted in the Department of Pulmonology, Ayub Teaching Hospital, Abbottabad, which is acknowledged as a tertiary teaching institution. The time span covered in the given data is from October 2020 to March 2021. Patients who presented to the Pulmonology unit with pleural effusions and were sourced from the outpatient or emergency department. The departments and private practice clinics. A detailed historical and clinical examination was done. Patients with exudative pleural effusion underwent an Abrams needle biopsy, after obtaining written, informed consent. The biopsy material obtained was submitted for histopathological examination. The result of the biopsy was recorded and put on the structural proforma developed for the study. To ensure that there were

no confounding factors, the following steps were done: (a) There was one standardized laboratory used for the pleural fluid analyses, and the pleural tissue analyses were done by one histopathologist. (b) The pleural biopsy procedure in the patients was done by the researcher, using one standardized Abrams needle. Common tubes and bottles, with commonly used lab chemicals, were used. Patients who fit the inclusion criteria were recruited for this trial after they had given their consent. Baseline clinical details such as age, gender, and pleural fluid protein concentration were collected and documented with the help of a proforma. In an attempt to determine the significant difference in pleural fluid concentrations between cases of tuberculous and malignant pleural effusion, three groups were developed: Category 'A' with pleural fluid protein concentrations measuring from 3-4g/dl, Category 'B' with concentrations measuring from 4-5g/dl, and Category 'C' with concentrations above 5g/dl. A total of 109 patients with eligible characteristics were obtained through sequential non-probability sampling. The study was approved by the Institutional Ethics Committee of Ayub Teaching Hospital, Abbottabad, Pakistan (Approval No. 17-19 Dated 11-08-2020).

After approval from Institutional Ethics Committee the study was done in accordance with Declaration of Helsinki. We informed each participant about the study, benefits, and risks. After getting written consent, people could join the study. It was made sure that participants' information would remain confidential and they could drop out anytime without impacting their medical care. Demographics like age, gender, were collected. The lead researcher recorded everyone's history when they became ill, their current issues, and their exam results. Plus, we screened the participants for signs of tuberculosis or malignant pleural effusion and took note of any additional health complications they faced.

Thoracentesis, which is the process of removing fluid from the chest, was carried out carefully by the medical team in a sterile environment and stored. In the lab, they observed the fluid's appearance, color, and clarity. Next up, they performed tests to count the various types of white blood cells and ran some biochemistry and protein tests with standard procedures. Tissue samples were stored in a preserving solution called 10% buffered formalin and then sent off to the lab. There, expert pathologists checked the tissue for signs of tuberculosis, cancer, or other diseases. Using their expertise, the pathologists figured out the diagnosis and sorted the patients into the tuberculous pleural effusion group or the malignant pleural effusion group. The software used for the analysis of the results was SPSS version 24. The continuous variables such as age were presented using mean and standard deviation, while the categorical variables such as gender, the levels of proteins in the pleural fluid, and the histological diagnosis were presented using frequency and percentage. A 2x2 contingency table was formed in order to calculate the value of the sensitivity and specificity of the levels of proteins in the pleural fluid for the histological outcomes. The results will be analyzed in the context of the clinical utility of the measurement of proteins in the pleural fluid as a supplementary diagnostic method for the differentiation of tuberculous and malignant effusions.

RESULTS

In all, 109 subjects were involved. Table 1 shows the demographic information of interest. The mean age was 45.65 years, with a standard deviation of 15.34 years. There was thus a good representation across virtually all age spectrums. There was also near parity in the gender distribution, with 54 males constituting 49.5% and 55 females making up 50.5%. This indicates that pleural effusion occurred with relatively equal frequency in both sexes. Histopathological diagnosis revealed that 61 patients (56%) had TBPE and 48 patients (44%) had MPE, which are summarized in Table 2. The protein level in the pleural fluid was varied among the subjects. 57.8% of the patients had less than 5 g/dL, while 42.2% had 5 g/dL or higher. Table 2 illustrates the variations in protein concentration that coincide with the individual's aging. The highest levels of protein, =5 g/dL, were more incident in individuals between 20 to 40 years of age at 21 cases, while older age brackets were inclined towards a low protein level. The trend exhibited here shows that the pleural protein concentration also oscillates with age; however this variation itself is incapable of being an independent predictor sans histological correlation.

Table 3 presents a higher incidence of TBPE in young patients, ie, between ages 20 and 40 years, with a total of 30 cases recorded. Patients above 60 years showed a higher tendency to develop MPE. Table 3 shows a marginal rise in the incidence of malignant effusions in men, with a total of 28 cases, whereas a higher incidence of tuberculous effusions was observed in women with a total of 35 cases. Table 4 illustrates the diagnostic validity criteria for protein concentration in pleural fluid, taken above 5 g/dL. The trial showed a sensitivity of 81.97%, which indicates its effectiveness in diagnosing TBPE, and specificity of 72.92%, which indicates its ability to exclude malignancy. The positive predictive value was fixed at 79.37%, while the negative predictive value was determined to be 76.09%. The overall value for diagnosis was found to be 77.98%. The following Table 5 shows the association between the protein levels and histological indexes. Of the 63 patients having protein levels of 5g/dL and above, 50 were found to be suffering from tuberculous pleural effusion and 13 from malignant pleural effusion. In contrast, 35 out of 46 patients with protein levels below 5g/dL were found suffering from malignant pleural effusion, thereby revealing a stronger link between reduced levels of proteins and malignancy.

Table 1. Baseline Characteristics of the Study Population

Variable	Mean ± SD
Age (years)	45.65 ± 15.34
Gender	**n (%)**
Male	54 (49.5%)
Female	55 (50.5%)

Summary of demographic characteristics including age and gender distribution among patients with pleural effusion

Table 2. Histopathological Diagnosis and Distribution of Pleural Fluid Protein Levels

Diagnosis	Frequency (n)	Percentage (%)
Tuberculous Pleural Effusion	61	56
Malignant Pleural Effusion	48	44
Protein Level (g/dL)		
< 5 g/dL	63	57.8
= 5 g/dL	46	42.2
Age Group (years)	**<5 g/dL (n)**	**=5 g/dL (n)**
20–40	23	21
41–60	24	16
>60	16	9

Frequency and percentage of biopsy-confirmed tuberculous and malignant pleural effusions, and distribution of pleural fluid protein levels across age groups

Table 3. Age and Gender Distribution According to Histopathological Diagnosis

Age Group (years)	TBPE (n)	MPE (n)
20–40	30	14
41–60	21	19
>60	10	15
Gender		
Male	26	28
Female	35	20

Distribution of TBPE and MPE across age groups and gender

Table 4. Diagnostic Validity of Pleural Fluid Protein Level (Cutoff =5 g/dL)

Parameter	Value (%)
Sensitivity	81.97
Specificity	72.92
Positive Predictive Value (PPV)	79.37
Negative Predictive Value (NPV)	76.09
Overall Accuracy	77.98

Sensitivity, specificity, predictive values, and overall accuracy of pleural fluid protein for distinguishing TBPE from MPE

Table 5. Cross-Tabulation of Pleural Fluid Protein Level vs. Histopathology

Protein Level	TBPE (n)	MPE (n)	Total
=5 g/dL	50	13	63
<5 g/dL	11	35	46
Total	61	48	109

Distribution of TBPE and MPE across protein level categories

DISCUSSION

Pleural effusion is affecting people globally. Knowing whether it's caused by tuberculosis or cancer is crucial, especially in regions where both are major concerns. Quick diagnosis is essential since each illness needs a specific treatment. Our study found that 56% of patients had pleural effusion from tuberculosis, while 44% had the cancerous kind. This is what other studies have shown in developing countries, where TB remains a top cause of pleural effusion due to the widespread Mycobacterium tuberculosis infection. The high rate of TBPE in this study shows how much tuberculosis still affects low- and middle-income countries. This really makes you think about how important it's to have easy and cheap ways to diagnose tuberculosis early on so people can start treatment right away. The study found that patients with pleural effusion have a lot more protein in their pleural fluid compared to those with malignant pleural effusion.[13] For example the study says that a pleural fluid protein level of least 5 g/dL is a good way to diagnose TBPE. It correctly identifies about 81.97 percent of cases and rules out malignant causes around 72.92 percent of the time.[14] This means that measuring the protein in the fluid could be very helpful for telling TBPE apart from malignant pleural effusion especially in places that do not have access to advanced lab tests. The test is also good at finding TBPE in patients with tuberculous pleural effusion and it is fairly reliable, at ruling out malignant pleural effusion. The results are very similar to what we have seen before in studies. These studies have shown that people with pleural effusion have more protein in the fluid around their lungs than people with malignant effusion. This is what we would expect because tuberculosis causes a lot of inflammation. When someone gets tuberculosis their body reacts strongly to the infection.

The bodys reaction happens mostly in the area around the lungs. This reaction makes the tiny blood vessels in that area more permeable. As a result a lot of fluid that is rich in protein gets into the space around the lungs. Tuberculous pleural effusion also leads to a buildup of cells that are very active and other substances that cause inflammation. This buildup increases the amount of protein in the fluid more. The protein levels in the fluid of patients, with tuberculous pleural effusion are higher because of all these things.[15] On the hand malignant pleural effusions happen when tumors block lymphatic drainage. These effusions are also exudates.. Research shows they do not always have very high protein levels like tuberculous effusions do. Because of these biological processes checking protein levels in pleural fluid can help figure out what kind of infection someone has. Malignant pleural effusions and tuberculous effusions have protein levels, in pleural fluid. This difference can help doctors diagnose the infection.[16,17] The study also shows how age is important when it comes to the type of effusion people get. Younger people are more likely to get pleural

effusion while older people are more likely to get the malignant type. This is what other studies from around the world have found too. Tuberculosis tends to affect people when they're young and working and it spreads through the community. On the hand cancer-related pleural effusions usually affect older people because they have been around harmful things for a long time.[19]

Past studies have shown that people with pleural effusion are usually younger than those with the malignant type. Knowing these patterns is very helpful when doctors first see patients with effusion. The current study found that there were equal numbers of men and women. This means that pleural effusion affects both men and women equally. However there might be some differences because of things like job hazards, smoking, money and access to doctors. These things might cause some differences, between men and women sometimes.. Since the numbers are almost equal it is probably not a good idea to use gender to figure out if someone has tuberculous or malignant pleural effusion. The diagnosis of effusion is still a problem in many healthcare systems especially where they do not have a lot of resources. Doctors can use tests like adenosine deaminase and interferon-ã to diagnose tuberculosis with accuracy.. These tests are not used all the time because they are expensive and need special equipment and laboratory support. The same thing happens with tests to detect cancer in the fluid these tests are not always available in smaller hospitals. So doctors usually rely on fluid tests to make a diagnosis.[20] In these cases simple biochemical tests of the fluid are very helpful for a quick and affordable diagnosis. Things like protein, lactate dehydrogenase, glucose and cell makeup give doctors clues, about what is causing the problem. Protein tests are especially useful because they are cheap and easy to do. Our study shows that using protein levels is a way to tell if the fluid problem is caused by tuberculosis or cancer before getting the final diagnosis. If doctors can diagnose tuberculosis early they can start treatment faster which can prevent the disease from spreading. If cancer is suspected this allows doctors to take the steps to deal with the pleural effusion and the cancer.[21,22] This study could have impacts on health policy and how doctors work in developing countries. Using biochemical tests in regular fluid checks from the lungs can help doctors diagnose patients faster and start treatment sooner. While checking protein levels in the fluid is not enough on its own to make a diagnosis using it along with signs, X-rays and test results can make the diagnosis more accurate. This supports doctors in making decisions based on evidence. Even though the findings are promising we need to consider some limitations. The protein levels in the fluid can be affected by things like what a person eats other infections, overall inflammation and how bad the disease is. Because of this relying on one test might not always give us complete certainty. Future research could look at groups of people and more hospitals. Adding tests like checking for certain proteins and inflammation markers could also help. All of this could lead to ways to diagnose and tell apart different types of fluid buildup in the lungs. This study shows how checking the fluid in the lungs can really help diagnose buildup especially in places where tuberculosis is common and resources are limited. The results show that measuring protein in the fluid is a easy and affordable way to tell if the fluid buildup is due to TB or something else like cancer. Adding these tests to procedures could lead to earlier detection, better patient care and more efficient use of health resources in areas, without advanced diagnostic tools.

CONCLUSION

Pleural fluid protein estimation is not a standalone diagnostic test but serves as a practical and accessible adjunct in differentiating tuberculous from malignant pleural effusions. With a cutoff level of =5 g/dL, reasonable sensitivity and specificity were observed, supporting its use in early clinical assessment, particularly in resource-constrained settings. In spite of the availability of advanced diagnostic tools in developed countries, the diagnosis of tuberculous or malignant pleural effusion is a challenge. The data obtained from this study revealed that the level of protein in the pleural fluid is an adjunct useful criterion. The values were considerably higher in tuberculous and lower in malignant effusions. With the cutoff level of = 5 g/dL, considerable sensitivity, specificity, and performance of this method were observed in diagnosing TPE. The two causes prevail as the major unrecognised causes of lymphocytic exudative pleural effusion till date. Being one of our developing countries, the major diagnostic procedure utilised is closed pleural biopsy, as no modern and costly investigations have been included, though its sensitivity is suboptimal. With the above limitations in mind, the level of total protein in the pleural fluid, in association with clinical correlation, might help in distinguishing whether it is tuberculous or malignant.

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Authors Contribution:
Bushra Arif: Study conception, data collection, interpretation of results, and manuscript drafting.
Sada Saeed: Study supervision, methodology design, statistical oversight, critical revision of the manuscript, and correspondence with the journal.
Hamid Nisar Khan: Data acquisition, clinical evaluation, and assistance in manuscript preparation.
Sabeen Sajjad: Clinical assessment, literature review, and data interpretation.
Muhammad Mamoon: Data collection, validation of results, and manuscript editing support.
Fazal Mustan: Patient recruitment, procedural assistance, and data documentation.

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