International Journal of Research in Medical Sciences
Paul SK et al. Int J Res Med Sci. 2023 Sep;11(9):3195-3200
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20232767

Original Research Article

Usefulness of pleural fluid cholesterol in the diagnosis of tuberculous pleural effusion

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Received: 17 July 2023
Accepted: 09 August 2023

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ABSTRACT

Background: Tuberculous pleural effusion (TPE) is the most common etiology of exudative pleural effusion in high tuberculosis burden countries like Bangladesh. The usefulness of pleural fluid cholesterol for the diagnosis of TPE is not evaluated yet. This study aimed to assess the usefulness of pleural fluid cholesterol for the diagnosis of TPE.
Methods: This cross-sectional study was conducted at the department of respiratory medicine at Bangabandhu Sheikh Mujib medical university. A total of thirty-five TPE was included in this study. Pleural fluid aspiration followed by cytological (total count, differential count), and biochemical (protein, glucose, lactate dehydrogenase, adenosine deaminase, and cholesterol) investigations were done. At the same time, blood was sent for biochemical (protein, glucose, and lactate dehydrogenase) investigation. Pleural biopsy followed by a histopathological examination was done to confirm TPE. Ethical clearance was obtained from the institutional review board (IRB) prior to starting this study.
Results: In our study, the mean age of the participants was 35.54±14.13 years, and male predominant (74.3%). The mean pleural fluid cholesterol was 99.87±23.82 mg/dl. With a cut of value 69.85, the sensitivity, specificity, and accuracy were 97.14%, 57.14%, and 77.14% respectively.
Conclusions: Pleural fluid cholesterol has significant diagnostic usefulness for the diagnosis of tuberculous pleural effusion.

Keywords: Diagnosis, Pleural fluid cholesterol, Tuberculous pleural effusion

INTRODUCTION

According to Light's criteria, 99% of pleural effusion could be categorized into exudative and transudative effusion.[1] In contrast with transudative effusion, the cause, and management of exudative effusion are difficult. Tuberculous pleural effusion (TPE) is the most common etiology of exudative effusion in most of the studies conducted and is often diagnosed and treated empirically due a to lack of sensitive markers and facilities. The confirmation of diagnosis can be made through the identification of tuberculous basil in sputum, pleural fluid, pleural tissue sample, or the histopathological demonstration of caseating granuloma in a pleural tissue specimen.[2] In TPE, microscopic examination and mycobacterial culture of pleural fluid is virtually negative due to very low acid-fast bacilli (AFB) load. Culture positivity is present in only 15% to 20% of pleural fluid and around 60% to 80% of pleural biopsy specimens.[3] Pleural biopsy is an invasive technique and is not available in most centers. On the other side, culture requires time and is not accessible ubiquitously. Therefore, TPE is diagnosed with pleural biopsy for histopathological examination (HPE) but may be falsely negative in 15-20% of the cases. After the advent of adenosine deaminase (ADA), the diagnosis of TPE has

become simple and the necessity for pleural biopsy is greatly reduced. ADA not only increases in TPE but also in other infections, lymphoma, empyema, malignancy, and collagen vascular disease.[4] Interferon-Gamma (IFN-ɤ) and lysozyme for the diagnosis of TPE are currently used for research in several centers but direct measurements of PE INF-ɤ are technically complex, expensive, and not available everywhere.[5] Tubercular antigens and antibodies are suggestive for easier diagnosis but need further validation. Pleural fluid cholesterol has been used to categorize exudative and transudative pleural effusion as it misclassifies fewer cases than any other Light parameters. Different studies showed that pleural fluid cholesterol was significantly associated with TPE.[6-9] However, in our country, there is no available study to assess the usefulness of pleural fluid cholesterol in the diagnosis of TPE. This study was undertaken to evaluate the usefulness of pleural fluid cholesterol in the diagnosis of TPE.

METHODS

This cross-sectional study was conducted at the department of respiratory medicine, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, from 01 February 2022 to 31 January 2023. A total of 35 biopsy-proven tuberculous pleural effusion was taken as a study sample. Pleural fluid was sent for the cytological, microbiological, and biochemical study, which includes total protein, glucose, lactate dehydrogenase (LDH), ADA, and cholesterol. At the same time 5 ml of blood was collected from the antecubital vein and sent for complete blood count, ESR at the first hour, serum protein, glucose, and LDH. Data was compiled and analyzed by using the SPSS-23 version. The categorical variables were described as frequency and percentages and continuous variables as mean±SD or median. Student's t-test or Mann-Whitney U test was used to compare the mean differences of continuous variables and the chi-square test or Fisher's exact test for categorical variables. The receiver operator characteristic (ROC) curve was used to evaluate the threshold value of pleural fluid cholesterol to diagnose TPE. For each ROC, a cut-off point was determined as the value of pleural fluid cholesterol that maximized the sum of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy. A value of $p<0.05$ was considered statistically significant. Written informed consent was obtained from each subject voluntarily to participate in the study. Before starting the study, ethical clearance was obtained from the Institutional Review Committee (IRB) of BSMMU, Dhaka.

Inclusion criteria

Patients with a diagnosis of biopsy-proven tuberculous pleural effusion. Age above 18 years of both sexes. Patients who were willing to give informed written consent to participate

Exclusion criteria

Malnourished patients, patients with nephrotic syndrome, chylothorax, lymphoma, blood diathesis, and patients who were on lipid lowering agents.

RESULTS

This cross-sectional comparative study was conducted in the Department of Respiratory Medicine of BSMMU, from February 2022 to January 2023. A total of 35 biopsy-proven TPE patients were included in this study The main objective of this study was to find out the usefulness of pleural fluid cholesterol in the diagnosis of TPE.

Table 1: Distribution of the participants in study groups.

Baseline characteristics	TPE (n=35)	P value
Age (years)		
18-30	16 (45.7)	<0.001
31-50	14 (40.0)	
51-70	5 (14.3)	
>70	0 (0.0)	
Mean±SD	35.54±14.13	
Gender		
Male	26 (74.3)	0.597
Female	9 (25.7)	
Co-morbidity		
Hypertension	3 (8.6)	0.101
Diabetes mellitus	6 (17.1)	0.255
Hypothyroidism	1 (2.9)	>0.99
Smoking	5 (14.3)	>0.99

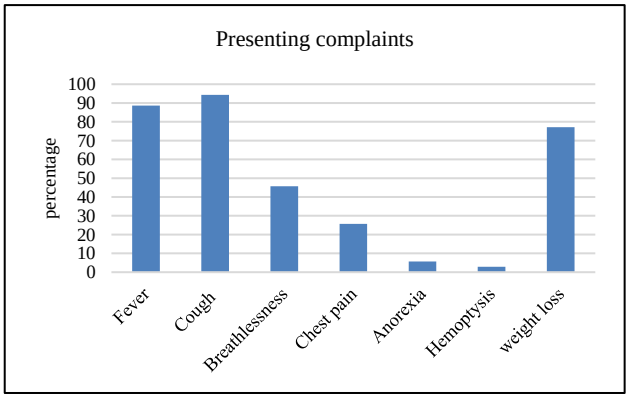

Figure 1: Presenting complaints of the participants

Table 1 is showing the baseline characteristics of the participants. The mean age of the participants suffering from a TPE was 35.54±14.13 years. The majority of the participants suffering from TPE were in the 18-30 (45.7%) and 31-50 (40%) years age groups. Our study was male predominant 26 out of 35 participants (74.3%). Among the participants, the most common comorbidity

was diabetes mellitus 17.1% followed by smoking behavior 14.3%, and hypertension 8.6%.

Figure 1 is demonstrating the presenting complaints of the participants. The most predominant presenting complaints of the study participants were cough (94.3%), followed by fever (88.6%), weight loss (77.1%), shortness of breath (45.7%), and chest pain (25.7%) (Figure 1).

Table 2: General and systemic examination findings of the study participants.

General and systemic examination		TPE (n=35)	P value
Anemia		6 (17.1)	0.01
Cervical lymphadenopathy		2 (5.7)	0.493
Side of the lung	Right	15 (42.9)	0.144
	Left	19 (54.3)	
	Bilateral	1 (2.9)	
Pulse	Mean±SD	87.17±10.43	0.766
Systolic blood pressure	Mean±SD	118.71±11.90	0.316
Diastolic blood pressure	Mean±SD	69.71±10.07	0.882
Respiratory rate	Mean±SD	21.40±2.95	0.268

Table 2 is representing the general and systemic examination findings of the participants. Anemia was present in about 17.1% of patients followed by cervical lymphadenopathy in 5.7%. Left-sided pleural effusion was 54.3%, and right-sided effusion was 42.9%.

Table 3 is showing the laboratory findings of the study subjects. The mean white blood cell count ($\times 10^9$ mm^3) was 8.01±3.06 (p value 0.027). The mean serum protein and creatinine were 6.94±0.62, and 0.84±0.21 respectively. Table 4 is displaying the cytological and biochemical characteristics of the pleural fluids. The percentage of lymphocytes was 84.45±23.26%. Protein concentrations were 44.66±23.57 gm/dl. The mean ADA and cholesterol levels were 55.72±26.49 U/l, and 99.87±23.82 mg/dl.

Table 3: Laboratory investigations of the study participants.

Laboratory investigation (Mean±SD)	TPE (n=35)	P value
Hemoglobin (Hb)	11.81±1.54	0.917
ESR	55.19±37.68	0.655
White blood cell ($\times 10^9$ mm^3)	8.01±3.06	0.027
Neutrophil	69.62±8.41	0.127
Lymphocyte	22.67±6.67	0.148
Serum LDH	318.19±133.95	0.155
RBS	6.81±2.09	0.991
Serum creatinine	0.84±0.21	0.015
Serum protein	6.94±0.62	0.006

Table 5 is demonstrating the cut-off value with the Youden index of pleural fluid cholesterol in TPE. A cut-off value of ≥69.85 showed the highest Youden index (0.54) with 97.1% sensitivity and 57.1% specificity. In addition, the accuracy was 77.1%. Moreover, the cut-off value of ≥69.85 showed, PPV and NPV of 69.3% and 95.2% respectively.

Table 4: Pleural fluid parameters of the study participants.

Pleural fluid parameters (Mean±SD)	TPE (n=35)	P value
Cell count	1331.42±1970.13	0.407
Neutrophil	15.54±23.27	<0.001
Lymphocyte	84.45±23.26	<0.001
Protein	44.66±23.57	0.006
Glucose	4.72±2.52	0.036
LDH	524.05±423.84	0.029
ADA	55.72±26.49	0.001
Cholesterol	99.87±23.82	<0.001

Table 5: Determination of cut-off value with Youden index.

Cutoff value	Sensitivity	Specificity	PPV	NPV	Accuracy	Youden index (j=sen+spe-1)
≥61.40	0.971	0.514	0.666	0.947	0.742	0.49
≥67.50	0.971	0.542	0.680	0.950	0.757	0.51
≥69.85	0.971	0.571	0.693	0.952	0.771	0.54
≥73.35	0.942	0.571	0.687	0.909	0.757	0.51
≥76.41	0.914	0.571	0.680	0.869	0.742	0.49

Table 6 is showing the sensitivity, specificity, PPV, NPV, and accuracy of pleural fluid cholesterol in TPE. ROC analysis of pleural fluid cholesterol to predict TPE found an area under the curve (AUC) value of 0.721 (95% CI 0.598-0.844) which was statistically significant (p value 0.001) sensitivity [97.14% (95% CI: 85.08% to 99.93%)] and specificity [57.14% (95% CI: 39.35% to 73.68%)] found from the derived cutoff was supporting that the derived cutoff of pleural fluid cholesterol can predict tubercular pleural effusion with about 77.14% accuracy.

Table 6: Sensitivity, specificity, PPV, NPV, and accuracy of pleural fluid cholesterol for predicting TPE.

Statistic	Value	95% confidence interval
AUC	0.721	0.598-0.844
Sensitivity	97.14%	85.08% to 99.93%
Specificity	57.14%	39.35% to 73.68%
PPV	69.39%	60.62% to 76.94%
NPV	95.24%	73.94% to 99.30%
Accuracy	77.14%	65.55% to 86.33%

DISCUSSION

Exudative pleural effusion is most often observed in clinical practice and frequently causes challenging diagnostic issues. Tuberculous and malignant pleural effusion are the two most common causes of exudative pleural effusion. For TPE, there are limitations of diagnostic tools including few positive staining and time-consuming culture from the pleural fluid for identification. The present study was conducted in the department of respiratory medicine of BSMMU to determine the usefulness of pleural fluid cholesterol in the diagnosis of TPE.

In the present study mean age of the TPE participants was 35.54±14.13 years, and ranged from 18-70 years. A similar age group is observed by Dave et al and Ungerer et al.[10,11] The mean age of TPE is rising and both middle-aged and old people are typically affected by this infectious disease. In this present study, male to female ratio was 2.8:1. Different factors are responsible to explain this gender difference including biological differences, disease presentation, and healthcare access. Additionally, men have more chance of TB exposure than female. This was in concordance with the previous study.[12-14] However, contrary to the other studies.[10,15,16]

According to the statistics men are more likely to develop lung cancer and tuberculosis than women. Though the last few decades the prevalence of lung cancer has increased in females.[17] Smoking is the most important risk factor for lung cancer and is also associated with tuberculosis. Generally, men smoke more than female. Consequently, smoking is a larger contributor to the TB disease burden for men. Left-sided TPE was 1.3 times more commonly affected than right and right-sided non-tuberculous pleural effusion was 2 times more common than the left. These findings were similar to this study. However, various studies showed that the right side was more commonly involved than the left for TPE.[18-21]

In this present study hemoglobin (%), total WBC count, serum creatinine, and protein were normal. In tuberculous pleural effusion hemoglobin and peripheral WBC counts are usually near normal on the other side parapneumonic and empyema are associated with high WBC count. Our finding is comparable to the findings of Dave et al.[10]

In the present study, the mean pleural fluid protein levels were higher for the TPE group which is correlating with the other study.[10,17,22-24] Pleural fluid LDH is a commonly used biomarker to differentiate empyema from parapneumonic effusion, and a very high and isolated pleural fluid LDH level might be of specific diagnostic significance, especially for empyema.[25] We found that the pleural fluid LDH level was significantly lower in patients with TPE.

Pleural fluid cholesterol is now an established marker to differentiate exudative and transudative pleural effusion. Pleural fluid cholesterol is derived mainly from damaged cells and vascular leakage due to increased permeability. Though inflammation might be the main reason for vascular permeability in tuberculosis, however, decrease serum albumin with raised levels of gamma globulin is also responsible. The exact reason for increasing cholesterol in pleural exudates is unknown. Two possible explanations have been put forward. Firstly, pleural cells synthesize cholesterol for their own metabolic needs, and secondly the concentration of cholesterol in the pleural cavity increases due to the degeneration of leucocytes and macrophages, which contain a large amount of cholesterol.[8,26]

In our study, the mean pleural fluid cholesterol in TPE was 99.87±23.82. This finding is similar to the previous study.[7,9] With a cut-off value of 69.85 mg/dl, the sensitivity, specificity, PPV, NPV, and accuracy of pleural fluid cholesterol to diagnose TPE was 97.14%, 58.14%, 69.39%, 95.24%, and 77.14% respectively. This study reveals that the estimation of fluid cholesterol is really useful in the diagnosis of TPE. The best cut-off of fluid cholesterol that should be used in the diagnosis of TPE is 69.85 mg/dl. This sensitivity is comparable to the study by Goyal et al.[27] However, the specificity was higher in the previous study. The previous study used the cut-off value of 50 mg/dl for the diagnosis of TPE which was lower than our study.

The limitations of our study were a single-center study with a small sample size. In our study, we considered pleural biopsy as a gold standard. However, it would be better if we performed a culture or polymerase chain reaction (PCR) of pleural tissue for confirmation of tuberculosis. In our study, we didn't compare TPE with non-tuberculous pleural effusion.

CONCLUSION

Our study concludes that it is possible to diagnose TPE with 77.14% accuracy using 69.85 mg/dl as the cut-off value of pleural fluid cholesterol. Therefore, pleural fluid cholesterol might be useful as a single non-invasive test for the diagnosis of TPE.

ACKNOWLEDGEMENTS

We would like to thank all the participants in this study and the staff of the respiratory medicine department of BSMMU for their continuous support.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Paul SK, Ahmed S, Chakrabortty R, Majumder S, Sarker DJ, Paul SK, et al. Usefulness of pleural fluid cholesterol in the diagnosis of tuberculous pleural effusion. Int J Res Med Sci 2023;11:3195-200.