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Cross-sectional Study

# Diagnostic value of pleural cholesterol in differentiating exudative and transudative pleural effusion

Santosh Gautam [a], Shiva Raj K.C. [b,g], Binita Bhattarai [c], Geetika K.C. [b], Gauri Adhikari [d,*], Purnima Gyawali [e], Keshab Rijal [f], Milesh Jung Sijapati [a]

[a] Department of Internal Medicine, KIST Medical College and Teaching Hospital, Imadol, Lalitpur, Nepal
[b] Department of Pathology, KIST Medical College and Teaching Hospital, Imadol, Lalitpur, Nepal
[c] Department of Biochemistry, KIST Medical College and Teaching Hospital, Imadol, Lalitpur, Nepal
[d] Nepalese Army Institute of Health Sciences-College of Medicine, Kathmandu, Nepal
[e] KIST Medical College and Teaching Hospital, Imadol, Lalitpur, Nepal
[f] Department of Radiology, KIST Medical College and Teaching Hospital, Imadol, Lalitpur, Nepal
[g] Department of Pathology, Patan Academy of Health Sciences, Lagankhel, Lalitpur, Nepal

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ABSTRACT

*Background:* Pleural effusions are most commonly classified as transudative or exudative based on Light's criteria which has shown misclassification in 10%–20% of cases. Studies have demonstrated lesser misclassification with pleural fluid cholesterol criteria. Thus, this study aimed to find the diagnostic properties of pleural fluid cholesterol in differentiating the type of effusion.

*Materials and methods:* This cross-sectional study involving 72 patients was undertaken in a tertiary center in Nepal for a duration of 2 years. On the basis of Light's, Heffner's, etiological, and pleural fluid cholesterol criteria, pleural effusion was classified as exudative or transudative. The findings were then evaluated to determine the diagnostic value of each approach in identifying the effusion type and comparing them on the basis of sensitivity, specificity, positive predictive value and negative predictive value.

*Result:* Pleural fluid cholesterol detected effusion as exudative with sensitivity of 91.94% and specificity of 80.00% against Light's criteria; with a sensitivity of 98.28% and specificity of 85.71% against the etiological diagnosis. Additionally, against the etiological diagnosis, sensitivity of both Light's and Heffner's criteria was 100%; however, specificity was 71.43% and 64.29% respectively, which is far less than that of pleural fluid cholesterol (85.71%). Furthermore, pleural fluid cholesterol was also found to have better results than protein ratio, LDH ratio and pleural fluid protein ratio in determining the type of effusion.

*Conclusion:* When considering the avoidance of confusing outcomes in equivocal instances and cost effectiveness in developing nations, pleural fluid cholesterol can be one of the most useful alternative diagnostic methods for differentiating between exudative or transudative effusions.

## 1. Introduction

A pleural effusion is an abnormal collection of fluid in the pleural space resulting from excess production or decreased resorption [1]. It is one of the most common clinical manifestations of pleural diseases, including cardiopulmonary failure, systemic inflammatory response, or malignancies Since the underlying mechanism and subsequent management changes depend on whether the effusion is exudative or transudative, it is important to make this distinction. The mechanism for transudative pleural effusion is either an increase in hydrostatic pressure or a reduction in plasma colloid-osmotic pressure. However, the mechanism of exudative effusion is altered pleural surface permeability brought on by inflammation or poor lymphatic drainage [2]. Typically a diagnosis is made without much difficulty. However, in 10%–20% of cases, the cause of effusion remains inconclusive despite the employment of extensive diagnostic tools [3–5].

Most frequently, the Lights criteria have been used to differentiate effusions as transudative or exudatives [6]. Despite its high sensitivity and specificity, it has shown limitations in identifying the type of pleural effusion in certain circumstances, most notably heart failure on diuretic

* Corresponding author.
*E-mail address:* gaury.research@gmail.com (G. Adhikari).

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therapy [7,8]. Due to this, many diagnostic tools have been proposed to address these shortcomings. For instance, a diagnostic tool that comprised pleural fluid cholesterol (pf-cholesterol) along with pleural fluid protein (pf-protein) and pleural fluid lactate dehydrogenase (LDH) was proposed in 2002 [9]. Similarly, pleural fluid cholesterol alone has also been proposed to classify the types of effusion with fewer misclassifications [10].

In relation to pleural fluid cholesterol, it has not been clear as to why cholesterol levels rise in pleural fluid exudates. However, two possible explanations have been put forward. The first one explains that after leukocytes and erythrocytes degenerate, pleural cells synthesize cholesterol for their own requirements, and its level rises in the pleural cavity [11]. The second one states that because pleural cholesterol is derived from plasma, and pleural capillaries are more permeable in pleural exudate, plasma cholesterol could enter the pleural cavity [12].

This study aimed to analyze the possible use of pleural fluid cholesterol as a way to differentiate the types of effusion, which can be of great benefit in terms of reduced misclassification as well as cost-effectiveness in developing countries.

## 2. Material and methods

This study is a cross-sectional study conducted in the department of medicine of KIST Medical College and Teaching Hospital from February 2018 to February 2020. Ethical approval was obtained from the Institutional Review Committee of the hospital with an ethical approval number of 2074/2075/11. Patients with pleural effusion meeting the inclusion criteria were enrolled in the study.

Inclusion criteria:

- Age≥14 years
- Patients giving informed consent
- Patients with definite clinical and radiological evidence of pleural effusion

Exclusion criteria:

- Patients not giving consent
- Age <14 years
- Patients with bleeding disorders

A detailed clinical history, physical examination, and investigations including hematological, biochemical, radiological, and microbiological parameters were done on all the patients. Once pleural effusion was confirmed, an ultrasonogram guided diagnostic thoracocentesis was performed. Collected pleural fluid samples were tested for cell count, protein, glucose, LDH, pleural cholesterol, gram stain, bacterial culture, Ziehl Neelsen stain, and cytology. Blood samples were concomitantly obtained to test for counts and biochemical parameters, including protein and LDH. Serum and pleural LDH were estimated using the UV kinetic method via Siemens Dimension XLR, with a typical reference range of serum taken as 240–480 IU/L. Serum and pleural protein were estimated using the biuret method. The enzymatic colorimetric technique was used to estimate the amount of pleural cholesterol.

Then pleural effusion was classified as exudative or transudative based on modified Lights criteria, Heffner's criteria, pleural cholesterol and etiology.

Firstly, based on Light's criteria, effusion was classified as exudative if one or more of the following was present [6].

a. Pleural protein to serum protein ratio (protein ratio) ≥ 0.5
b. Pleural LDH to serum LDH (LDH ratio) ≥ 0.6
c. Pleural LDH >2/3 of the upper limit of the serum LDH

Secondly, based on Heffner's criteria, effusion was classified as exudative when it fulfills at least one of the following three criteria [9].

a. Pleural fluid protein >2.9 g/dl
b. Pleural fluid cholesterol >45 mg/dl
c. Pleural LDH> 2/3 of the upper limit of the serum LDH

Thirdly, based on pleural fluid cholesterol level, effusion with a cholesterol level of >45 mg/dl was classified as exudative.

A cholesterol cutoff value of 45 mg/dl has been employed in this study since it has been found to improve the accuracy of separating the effusions and eliminate the risk of being ambiguous between transudate and exudate [13].

Lastly, effusion was classified on the basis of etiology established with the help of clinical evaluation aided with investigations such as bronchoscopy, computed tomography, sputum microbiology, pleural adenosine deaminase, fine needle aspiration cytology, echocardiography, and Monteux test when needed.

### 2.1. Statistical evaluation

Microsoft Excel was used to compile all the data, and SPSS version 17 and Excel were used for analysis. Data was represented in the form of mean, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Following the calculations of the total number of patients with exudative or transudative effusion on the basis of different criteria as mentioned above, first a comparison was made between the findings of Heffner's and pleural fluid cholesterol against Light's criteria, and then a comparison was made among the findings of Light's criteria, Heffner's criteria, and pleural cholesterol against the etiological diagnosis.

The work has been reported in line with the STROCSS criteria [14].

## 3. Results

During the study period, a total of 72 patients were found who met the inclusion criteria and were included. The mean age of the participants was 48.92 years, with 38 males and 34 females for a male to female ratio of 1.12:1. The age group distribution of the study subjects is depicted in Fig. 1.

Among 72 patients, 37 of them were smokers, and 25 of them consumed alcohol.

About 15 (20.83%) patients out of 72 had bilateral effusion, 29 (40.28%) had it on the left side, and the remaining 28 (38.88%) had it on the right.

Cough was the most frequent presenting complaint, affecting 65 patients. Out of 72 patients, 25 had non-productive cough, 31 had mucoid sputum, 12 had purulent sputum, and 4 had the production of blood mixed sputum. With 45 of them experiencing it, breathlessness was the second most frequent symptom, followed by fever in 44 cases, chest pain in 43 cases, significant weight loss in 16 cases, and hemoptysis in 9 cases.

According to etiology, in the majority of the 72 patients, 38 (52.78%) were found to have tuberculous effusion, followed by pneumonia with parapneumonic effusion in 16 (22.22%) and heart failure in 13 (18.06%). Other less frequent causes of effusion were malignancy in four of them (5.56%) and renal disease in one of them (1.39%) (Fig. 2).

Patients were classified as having an exudative or transudative pleural effusion based on the aforementioned criteria. It was clear that, depending on the sort of criteria used, the number of people classified changed markedly, as shown in Fig. 3.

Comparing pleural fluid parameters and Heffner's criteria with Light's criteria, the results demonstrated that LDH ratio has the highest sensitivity (100%) and pf-protein has the highest specificity (100%) for differentiating the type of effusion. Comparing Heffner's criteria (which comprises two more criteria in addition to pf-cholesterol) with pf-cholesterol, both of them showed the same specificity (80%), almost similar PPV. However, pf-cholesterol showed sensitivity of 91.94% and NPV of just 61.54%, while Heffner's showed sensitivity of 98.39% and

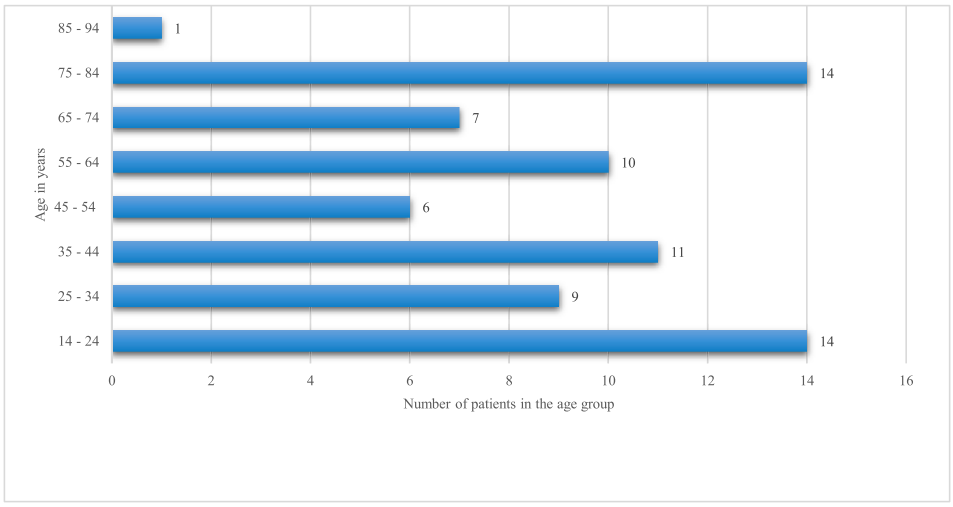


**Fig. 1.** Graph representing the age group of the patients.

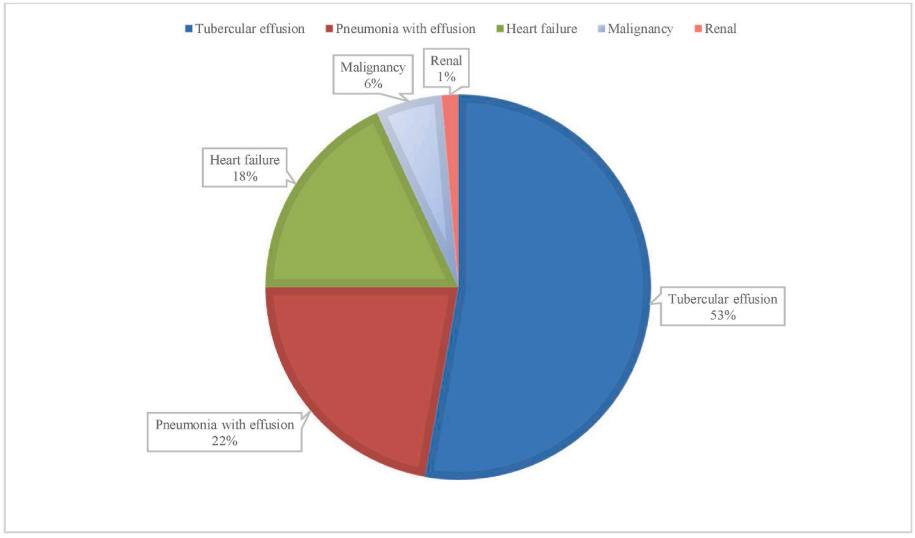


**Fig. 2.** Distribution of causes of pleural effusion among total patients.

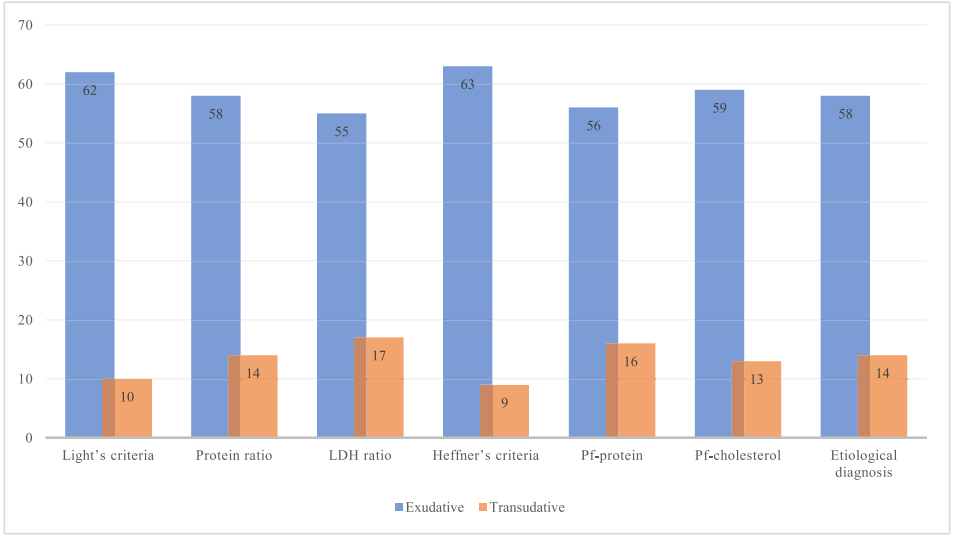


**Fig. 3.** Total number of patients classified as exudative or transudative on the basis of various criteria.

NPV of 88.89%. All the parameters were found to have a significant probability value (p-value) of less than 0.0001 (Table 1).

Comparing pleural fluid parameters along with pleural fluid cholesterol, Heffner's criteria and Light's criteria with etiological diagnosis, the sensitivity of Light's and Heffner's criteria was 100% and that of pf-cholesterol was 98.28%, which was comparable with the above two. Specificity in differentiating types of effusion was highest with pf-cholesterol, LDH ratio and pf-protein (85.71%), while it was least with Heffner's (64.29%). PPV was found to be the highest in protein ratio among all and lowest in Heffner's. In Light's and Heffner's criteria, NPV was found to be the highest (100%) and lowest in LDH ratio. The NPV of pf-cholesterol was 92.31% in differentiating effusion as exudative or transudative. All the parameters had a significant p-value of less than 0.0001 (Table 2).

## 4. Discussion

This study demonstrated the presence of a greater number of patients with exudative effusion than transudative; 62 exudative and 10 transudative according to Light's criteria. This finding was similar to other studies. The most frequent cause of exudative effusion in this study was tuberculosis, followed by pneumonia with parapneumonic effusion. Similarly, TB was found to be the most common cause in the study done by Muaz et al. A B Hamal et al. and C K Liam et al. [15–17] Subsequent analysis in this study revealed that effusion was more prevalent in males (38) than females (34), which matched the findings reported in the study done by Muaz O. Fagere [15]. The most common symptoms encountered by patients with effusion in the study were cough (90.28%), breathlessness (64.28%), fever (61.11%), chest pain (59.72%) and hemoptysis (12.5%). These findings were consistent with the findings of the study done by Moudgil et al. [18].

The sensitivity and specificity of protein ratio in determining the type of effusion were 81.4% and 82.6% in one of the studies done in Nepal. The study also showed an LDH ratio with sensitivity and specificity of 86.0% and 94.7%, respectively; pleural cholesterol criteria with a cutoff of 45 mg/dl had sensitivity, specificity, PPV, and NPV of 97.7%, 100%, 100%, and 95%, respectively [16]. The previously stated study used comparable study conditions and the same pleural cholesterol cutoff as this study did. However, not all the findings corresponded with our study. Nonetheless, both the studies can be compared as both of them were done in similar settings in Nepal.

In their study done by Shen et al. they found pleural cholesterol was associated with high sensitivity (88%) and specificity (96%) [19]. Mathie P.G et al. identified exudates with sensitivity, specificity, PPV, and NPV of 75.7%, 98%, 99.1%, and 59.2%, respectively, using pleural cholesterol criteria [20]. These studies were also comparable with the findings in our study.

Guleria et al. kept a cutoff of pleural cholesterol of 60 mg/dl and detected the exudates with a sensitivity and specificity of 88.2% and 100%, respectively. Lights criteria in their study detected exudates with a sensitivity of 98.0% and a specificity of 80.0% [21]. The study was similar to ours in terms of methodology except for the cutoff value of pleural fluid cholesterol, with a high sensitivity of 100% and a low specificity of 71.43% in our study.

As discussed above, there were different data and findings seen with different methods used to detect the type of effusion. Nevertheless, pleural fluid cholesterol detected exudates with high sensitivity, specificity, PPV, and NPV in comparison to other pleural fluid parameters, Light's criteria, and Heffner's criteria in this study.

**Table 1**
Comparison of pleural fluid parameters and Heffner's criteria with Lights criteria.

| Parameters | Sensitivity | Specificity | PPV | NPV | p-value |
|---|---|---|---|---|---|
| pf-protein | 90.32% | 100.00% | 100.00% | 62.50% | <0.0001 |
| LDH ratio | 100.00% | 71.43% | 93.55% | 100.00% | <0.0001 |
| pf-cholesterol | 91.94% | 80.00% | 96.61% | 61.54% | <0.0001 |
| Heffner's criteria | 98.39% | 80.00% | 96.83% | 88.89% | <0.0001 |

**Table 2**
Comparison of pleural fluid parameters, Lights criteria and Heffner's criteria with etiological diagnosis.

| Parameters | Sensitivity | Specificity | PPV | NPV | *P* value |
|---|---|---|---|---|---|
| Protein ratio | 94.83% | 78.57% | 94.83% | 78.57% | <0.0001 |
| LDH ratio | 91.38% | 85.71% | 96.36% | 70.59% | <0.0001 |
| pf-protein | 93.10% | 85.71% | 96.43% | 75.00% | <0.0001 |
| pf-cholesterol | 98.28% | 85.71% | 96.61% | 92.31% | <0.0001 |
| Light's criteria | 100.00% | 71.43% | 93.55% | 100.00% | <0.0001 |
| Heffner's criteria | 100.00% | 64.29% | 92.06% | 100.00% | <0.0001 |

## 5. Conclusions

Based on the results of this study and a review of research done by other authors, it can be concluded that:

- Tuberculosis is one of the most commonly observed cause of exudative pleural effusion.
- Analysis of the pleural cholesterol can be used as one of the best diagnostic tools to differentiate the type of effusion.
- Pleural cholesterol has a better sensitivity, specificity, PPV and NPV in differentiating effusion into exudative and transudative than other criteria of pleural fluid.

## 6. Limitation

The study does have certain restrictions. The study was conducted at a single center with a sample size of only 72 people, thus the result may not be generalizable to the entire nation. To accurately verify the conclusion, a multicenter investigation with a high sample size will be needed. The authors would agree that a change in diagnostic workup is unlikely to take immediate effect based on the results from 72 patients.

## Ethical approval

The study was conducted after approval from the Review Committee.

## Sources of funding

The study has no financial assistance of any kind.

## Consent

Only patients providing consent were included in the study. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

## Provenance and peer review

Not commissioned, externally peer-reviewed.

## Author contribution

Authors with their contribution is as mentioned below.

Dr. Santosh Gautam: Study concept, designing, literature review and interpretation of the data.

Dr. Shiva Raj K.C.: Study designing, data analysis and interpretation.

Dr. Binita Bhattarai: Data collection, literature review and writing the paper.

Dr. Geetika K.C.: Data collection and writing the paper.

Dr. Gauri Adhikari: Data analysis and interpretation, literature review and writing the paper.

Dr. Purnima Gyawali: Data collection, literature review and writing the paper.

Dr. Keshab Rijal: Literature review and writing the paper.

Dr. Milesh Jung Sijapati: Study concept, designing, literature review and writing the paper.

## Declaration of competing interest

The authors report no conflicts of interest.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2022.104479.

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