Accurate and Rapid Diagnosis of Exudative Pleural Effusion

Therese Sobhy Ghatas[1],* MD; **Moheb Wadea Elfaizy** [1] MD

chest diseases

*Corresponding Author:

Therese Sobhy Ghatas

healthychest@yahoo.com

[1]*chest diseases Department, Al Sahel Teaching Hospital, Cairo , Egypt.*

ABSTRACT

Background: Accurate diagnosis of exudate pleural effusion is definitely important. Few studies have been published on this topic. The current work present evidence for the importance of the pleural fluid markers like high sensitivity-C reactive protein[hsCRP]; tumor necrosis factor alpha[TNFα]; and cholesterol levels measurement in differentiating types of exudative from transudative pleural effusion.

Aim of The Work: to determine and evaluate the diagnostic importance of measured levels of pleural fluid cholesterol, high sensitivity-CRP and tumor necrosis factor α in diagnosing and differentiating transudate from exudate pleural effusion.

Patient and Methods: This study was carried out on 100 patients suffering from pleural effusion who subjected to diagnostic evaluation at Al Sahel Teaching Hospital. The full biochemical analysis of the pleural fluid,pleural fluid culture, and cytology examination were also performed. TN Fα ,hsCRP, and cholesterol level were assessed in the samples of pleural fluid.

Results: One hundred patients were initially evaluated, in accordance to Light's criteria, of 100 patients suffering from pleural effusion, 67 had exudative effusions while 33 patients had transudative pleural effusion. The concentrations of pleural fluid hsCRP and TNF α, found to be significantly elevated in the exudative nature group of pleural fluid than the transudative pleural effusion group ($p < 0.05$). Also, pleural fluid cholesterol level was elevated in the exudative pleural effusion than transudative pleural effusion($P<0.001$).

Conclusion: Patients presented with pleural effusion, simple markers of elevated pleural fluid hsCRP, TNFα, and cholesterol levels may be helpful in discrimination between exudates and transudates effusion.

Keywords: *Exudative; Pleural Effusion; Transudative.*

INTRODUCTION

Pleural effusion incidence is about one million person every year. To diagnose and decide treatment plan for pleural effusions the fluid must be classified and differentiate into transudate or exudate effusion. If there are misdiagnosis severe complications may occur. The established criteria to differentiate exudates from transudates is only(Light's criteria). But results may be false positive may occur in patients with transudative effusions when (Light's criteria) were applied.[1]

The cholesterol level of pleural fluid can be used as a variable in diagnosing effusion of exudative natur eand even can replace (Light's criteria). Approaches to diagnos epleural effusion patients must be precise as multiple procedures depend on nature and analysis of the effusion fluid. Until present, no specific biochemical test is perfect alternative to (Light's criteria).[2]

The combinations of inflammatory markers of pleural fluid may be more clinically and diagnostically useful than the use of these markers separetely.[3]

Pleural (CRP) has recently been considered, as a valuable biological marker for the differentiation between exudate and transudate type pleural

effusions and show higher specificity and sensitivity than serum level of CRP.[4](C reactive protein)is considered an appropriate marker due to its (1000) fold elevation in response to any infection and the presence of positive association between the pleural and serum level of CRP. However, there are few studies that were published on this topic.[5]

High levels of (CRP) and tumor necrosis factor-alpha are seen in many inflammatory conditions such as infectious diseases, tissue injury and malignancy. Inflammatory responses result in pleural effusion of exudative nature.[6]

This current study is aiming to evaluate the diagnostic importance of measured levels of cholesterol, high sensitivity-CRP and tumor necrosis factor- alpha present in pleural fluid in differentiating exudate pleural effusion from transudate pleural effusion

PATIENTS AND METHODS

This study was conducted between January 2019 and March 2020, on 100 patients attending to Al Sahel Teaching Hospital during the time of the study. The study included patients with pleural effusion diagnosed clinically and radiographically. The study was approved by the local ethics committee of

general organization of Teaching Hospital and Institutes (GOTHI). Written informed consent was obtained from each participant.

Inclusion criteria

Exudative pleural effusion diagnosed first by using Light's criteria, suggesting that pleural effusion is an exudate if effusion protein/serum protein ratio greater than 0.5 and, effusion lactate dehydrogenase (LDH)/serum LDH ratio greater than 0.6, or pleural fluid LDH concentration is less than 2/3 of the upper reference limit.[1]

Exclusion criteria

All patients with the following criteria were excluded: patients without pleural effusion, more than one possible etiology based on their effusion, and those with a hemothorax, or chylothorax were excluded, also HIV positive patients were excluded.

All patients subjected to the following: thorough medical history and physical examination, routine laboratory investigations: CBC, ESR, CRP, coagulation profile, lipid profile, fasting, and two hours post-prandial blood glucose, also liver and kidney functions tests were done ,serum total proteins and LDH. Also, radiological examination with Plain chest X-ray (PA and lateral views), CT scans of the chest, abdominal U/S, and echocardiography whenever needed. Tuberculin skin test in T.B suspected cases: Using the Mantoux method, Sputum examination for acid-fast alcohol fast bacilli (AFB) by ziehl –neelsen stain in T.B suspected cases.

Diagnostic thoracocentesis was performed under local anesthesia. About 200 mL of pleural fluid was collected, the pleural fluid samples were centrifuged at 2000 g for 10 minutes. During the next step, the cell-free supernatants were aliquoted and stored at - 70°C until final assessment. protein levels, LDH and glucose were measured in both pleural fluid and the serum. Gram staining and aerobic and anaerobic culture were performed on the pleural fluid samples. Ziehl-Neelsen staining was performed after homogenization and samples were cultured in Lowenstein-Jensen media in order to diagnose mycobacterium tuberculosis. Cholesterol levels were measured by photometry. HsCRP analysis was performed by an autoanalyzer using an immunoturbidimetric method. TNFα levels were measured with a commercially available enzyme immunosorbent assay (ELISA) kit (Novex KHC3011). The patients were divided into two groups of transudative and exudative pleural effusion according to Light's criteria (on the basis of LDH and protein levels in the pleural fluid and serum). The pleural effusion was classified as exudative with at least one criterion present; otherwise, it was considered as transudative. The diagnosis of tuberculous pleurisy was justified by closed pleural biopsy or through thoracoscopy. Diagnostic criteria for parapneumonic effusions were positive Gram stain, positive culture, a purulent effusion or empyema, and a white blood cell count of 5000-25000 accompanied with neutrophil predominance.

Malignancy was confirmed by positive cytology or pleural biopsy.

Statistical analysis

Values were expressed as mean ± SD. Statistical comparison of

the mean values of different groups were performed using the

nonparametric Mann-Whitney. P value < 0.05 was considered

statistically significant. Statistical analyses were conducted by SPSS (version 11.5).

RESULTS

One hundred patients were initially evaluated, according to Light's criteria. There were 67 subjects had exudative effusions while 33 subjects had transudative effusion. The mean age of patients with transudative pleural effusion group was 68.3 ± 9.1and the mean age of exudative pleural effusion group was 51.2 ± 12.3, p value < 0.05. (Table 1).

Patients included with transudative effusion were 18 (54.5%) women and 15 (45.5%) men while the patients with exudative effusion were 35 (52.3%) and 32 (47.7%) women and men, respectively. (Table 1).

	Transudative Pleural Effusion Group	Exudative Pleural Effusion Group
Number of patients	33	67
Age	68.3 ± 9.1	51.2 ± 12.3
Gender F/M	18/15	35/32

Table 1: Patient Characteristics

hsCRP mean levels were 3.2 ± 1.1mg/l in the transudative effusion patients and 14.3 ± 6.2 mg/l in exudative effusion patients. There was a statistically significant difference in the mean hsCRP levels between the two groups (p < 0.05). (Table 2). To determine the efficacy of pleural fluid hsCRP measurement in distinguishing between exudative and transudative effusions a cutoff value of > 5 mg/l was determined by standard ROC analysis. The sensitivity of hsCRP in differentiation between exudative and transudative pleural effusions based on this optimal cut off level was 95%. The specificity of exudative pleural effusion was 97%. The mean total TNFα level of exudative samples was 17.2 ± 8.7 ng/dl, which is significantly higher in comparison with the transudative group (p < 0.05) (Table 2).

The sensitivity and specificity of TNF α level in differentiating between exudates and transudates at a cut-off point of 12.9 ng/dl were 96% and 92%, respectively.

The mean level of cholesterol was 29 ± 11.55 mg/dl in transudative pleural effusion versus 69.67 ± 23.1 mg/dl in exudative pleural effusion. The cut-off value for pleural fluid CHOL level of ≥39 mg/dL had a sensitivity of 84% and specificity of 82%.

	Transudative Pleural Effusion Group	Exudative Pleural Effusion Group	P Value
Protein	1.5 ± 0.657mg/dL	5.3 ± 2.2 mg/dL	P < 0.05
LDH	179 ± 18.4 u/l	488 ± 19.5 u/l	P < 0.05
hsCRP	3.2 ± 1.1 mg/l	14.3 ± 6.2 mg/l	P < 0.05
TNFα	4.92 ± 2.1ng/dl	17.2 ± 8.7 ng/dl	P < 0.05
cholesterol	29 ± 11.55 mg/dl	69.67 ± 23.1 mg/dl	P < 0.001

Table 2: Pleural Fluid Characteristics of The Study Population

DISCUSSION

Several parameters like cholesterol level of pleural fluid and the ratio of pleural fluid to serum cholesterol level, value of the alkaline phosphatase, ratio of pleural fluid in relation to serum cholinesterase, and the ratio of pleural fluid in relation to bilirubin concentration of the serum have been proposed in differentiating the exudates from transudates fluid are more efficient than those of (Light's criteria).[7 &8]

In the current study, the diagnostic importance of cholesterol,[hsCRP]&[TNFα] level in the pleural fluid to discriminate exudate pleural effusion from transudate pleural effusion were evaluated. in exudate pleural effusion, these cholesterols and two acute phase response markers were significantly raised.

Is it valuable to depend on biochemical criteria for discrimination between exudative pleural effusions and transudative pleural effusions? The perfect answer to this important question has been successfully considered to be affirmative. But(Light's criteria) did not supply appropriate discrimination between these diagnostic entities despite its high differentiating power. By application of(Light's - criteria), about 15-30% of transudate pleural effusion are misclassified as exudate pleural effusion. Despite of the presence of unsuspected exudative pleural effusion, in cases receiving diuretic therapy, most patients show false exudative nature pleural effusion by (Light's criteria) occur.[9]

The role of action of (CRP) is to bind phospho-choline and to detect foreign pathogens. Also, it can activate and stimulate the complement system by binding to its ligands and also can combine to phagocytic cells. Also, other pro-inflammatory effects are the activation of monocyte tissue factor and inflammatory cytokines. The changes in (CRP) levels reflect occurrence of inflammation and its extent andintensity and have been defined as a marker for the diagnosis and further management of different diseases. Although many previous studies have searched and investigated the levels of C

reactive protein in various diseases, few studies have focused on its role and action in patients presented by pleural effusion.[10]

While pleural effusion levels of (C reactive protein) (not hsCRP) were estimated in other studies,[11&12] in our study the evaluation was performed for the levels of high sensitivity (C reactive protein) [hsCRP] and gave outstanding results. Porcel in 2010and Porcel and his associates in 2009[11&13] evaluated CRP levels in pleural effusion and other several markers such as, interleukin-8, myeloperoxidase atrixmetalloproteinase-2, but not (hsCRP). They concentrated on parapneumonic effusion and tried to differentiate between both complicated and non-complicated parapneumonia.

Botana and his associates 2011[14]compared CRP pleural fluid levels in benign diseases such as infectious diseases and in malignant exudative pleural effusion. They also, compared with another previously related studies,[10&15]they achieved different specificity and sensitivity which may be due to the assessment of high sensitivity-C reactive protein [hsCRP] instead of (C reactive protein) and they determining a different results and cutoff point.

In the current study results for measurement of pleural effusion levels of TNFα were in agreement with other previous studies,[16-19]despite several discrepancies.[20,21] However, these previous studies assessed pleural fluid levels of (TNF-α) just for only pleural effusions with underlying infectious disease.

According to the current study, the pleural fluid levels ofhsCRP >5 mg/l and (TNFα) levels >12.9 ng/dl are valuable in discriminating transudative from exudative pleural effusion.

(TNF-α), is an important mediator and regulator of the immune system response, showed high levels in both inflammatory and malignant exudate pleural effusion, compared to transudates.[22]

In the current study pleural fluid cut off point ≥39 mg/dL had a sensitivity of 84% and 82% specificity. This is in accordance with Hamal and his associates in 2013 who found that determination of pleural fluid cholesterol level is of great value in distinguishing between transudate and exudative pleural effusion.[23]

Yongchun and his associates in 2014 suggested that raised cholesterol level in pleural fluid associated with the presence of exudate pleural effusion, they stated that cholesterol contributes to the pathogenesis of exudate pleural effusion. It is not explained how this mechanism happens, so further research should investigate this question and provide a biological basis and explanation for this observation of association. They emphasized on the need to investigate the effect of cutoff value on the accuracy of diagnosis of the levels of pleural cholesterol. The values from 38 - 65 mg/dl. This variation in cutoff value reflects many differences in clinical context. A lower cutoff result is used for patients with cardiac problem presented with pleural effusion rather than for patients suffering from cancer. Further researches should direct to determine the cutoff value with optimal diagnostic accuracy.[24]

CONCLUSION

Pleural fluid level of HsCRP, TNFα, and cholesterol introduces beneficial diagnostic factors for differentiating exudates from transudates pleural effusion.

REFERENCES

1. Sandeesha V, Ravi Kiran CV, Ushakiran P, Sulemani MD, Lakshmanakumar NJ.A comparative study of serum effusion albumin gradient and Light's criteria to differentiate exudative and transudative pleural effusion.*Family Med Prim Care*. 2020 Sep 30;9(9):4847-52.

2. Shkolnik B, Judson MA, Austin A, Hu K, D'Souza M, et al.Diagnostic Accuracy of Thoracic Ultrasonography to Differentiate Transudative From Exudative Pleural Effusion.*Chest*. 2020 Aug;158(2):692-7.

3. Naoki Watanabe, Tomoya Ishii, Nobuyuki Kita, Nobuhiro Kanaji, Hiroyuki Nakamura, Nobuki Nanki, Yutaka Ueda, et al.The usefulness of pleural fluid presepsin, C-reactive protein, and procalcitonin in distinguishing different causes of pleural effusions.*BMC Pulm Med*. 2018; 18: 176.

4. Kapisyzi, D. Argjiri, A. Mirte et al., "The use of pleural fluid C-reactive protein level as a diagnostic marker for pleural effusions," *International Journal of Scientific Research*, 2015; vol. 4, no. 3, pp. 206-13.

5. Gabhale, P. Taparia, D. Yadav et al., "Usefulness of pleural fluid CRP level in differential diagnosis of exudative pleural effusion—a pilot study," *International Journal of Clinical Biochemistry and Research*, 2015; vol. 2, no. 2, pp. 97–109.

6. Botana-Rial M, Casado-Rey P, Leiro-Fernandez V, Andrade-Olivie M, Represas-Represas C, Fernandez-Villar A. Validity of procalcitonin and C-reactive protein measurement when differentiating between benign and malignant pleural effusion. *Clin Lab*. 2011;57(5-6):373–8.

7. V. Sandeesha, Ch.V. Ravi Kiran, P. Ushakiran, Md. D. Sulemani, N. Lakshmanakumar A comparative study of serum effusion albumin gradient and Light's criteria to differentiate exudative and transudative pleural effusion. *J Family Med Prim Care*. 2020 Sep; 9(9): 4847–52.

8. Light RW, Mac Gregor I, Luelisinger PC, Ball WC. Pleural effusions: The diagnostic separations of transudates and exudates. *Ann InternMed*. 1972; 77:507–73.

9. Candeira, SR.; Herna´ndez, L.; Brufao, S R.; Orts, D; et al., Is It Meaningful to Use Biochemical Parameters to Discriminate Between Transudative and Exudative Pleural Effusions? *CHEST* .2002; 122:1524–9.

10. Yilmaz Turay U, Yildirim Z, Turkoz Y et al. Use of pleural fluid C-reactive protein in diagnosis of pleural effusions.Respir. Med.2000;94: 432–5.

11. Porcel JM. Pleural fluid tests to identify complicated parapneumonic effusions. *Curr Opin Pulm Med*.2010;16(4):357–61.

12. Botana-Rial M, Casado-Rey P, Leiro-Fernandez V, Andrade-Olivie M, Represas-Represas C, Fernandez-Villar A.Validity of procalcitonin and C-reactive protein measurement when differentiating between benign and malignant pleural effusion. *Clin Lab*. 2011;57(5-6):373–8.

13. Porcel JM, Vives M, Cao G, Bielsa S, Ruiz-Gonzalez A, Martinez-Iribarren A, et al. Biomarkers of infection for the differential diagnosis of pleural effusions. *Eur Respir J*. 2009;34(6):1383–9.

14. Botana M, Casado P, Leiro V, AndradeM, Represas C, Fernandez A.Validity of procalcitonin and C-reactive protein measurement when differentiating between benign and malignant pleural effusion. *Clin Lab*. 2011;57(5-6):373–8.

15. Kiropoulos TS, Kostikas K, Oikonomidi S, Tsilioni I, Nikoulis D, Germenis A, et al. Acute phase markers for the differentiation of infectious and malignant pleural effusions. *Respir Med*.2007;101(5):910–8.

16. Smith S, Liggitt D, Jeromsky E, Tan X, Skerrett SJ, Wilson CB. Local role for tumor necrosis factor alpha in the pulmonary inflammatory response to Mycobacterium tuberculosis infection. *Infect Immun*. 2002;70(4):2082–9.

17. Wong CF, Yew WW, Leung SK, Chan CY, Hui M, Au-Yeang C, et al. assay of pleural fluid interleukin6, interferon-gamma and tumor necrosis factoralpha and in the diagnosis and outcome correlation of tuberculous effusion. *Respir Med*.2003;97(12):1289–95.

18. Porcel JM, Vives M, Esquerda A.Tumor necrosis factor-alpha in pleural fluid: a marker of complicated parapneumonic effusions. *Chest*. 2004;125(1):160–4.

19. Stathopoulos GT, Kollintza A, Moschos C, Psallidas I, Sherrill TP, Pitsinos EN, et al. Tumor necrosis factor-alpha promotes malignant pleural effusion. *Cancer Res*. 2007;67(20):9825–34.

20. Yamada Y, Nakamura A, Hosoda M, Kato T, Asano T, Tonegawa K, et al. Cytokines in pleural liquid for diagnosis of tuberculous pleurisy. *Respir Med*. 2001;95(7):577–81.

21. Yang CS, Lee JS, Lee HM, Shim TS, Son JW, Jung SS, et al. Differential cytokine levels and immunoreactivities against Mycobacterium tuberculosis antigens between tuberculous and malignant effusions. *Respir Med*. 2008;102(2):280-6.

22. Xirouchaki, N; Tzanakis, N; Bouros, D; Kyriakou, D; Karkavitsas, N; Alexandrakis, M; Siafakas, N M. Diagnostic Value of Interleukin-1α, Interleukin-6, and Tumor Necrosis Factor in Pleural Effusions. *CHEST* . 2002; 121:815–20

23. Hamal, K. N. Yogi, N. Bam, S. K. Das, R. Xirouchaki, N; Tzanakis, N; Bouros, D; et al., Diagnostic Value of Interleukin-1α, Interleukin-6, and Tumor Necrosis Factor in Pleural Effusions. *Pulm Med*. 2013; 2013: 135036.

24. Yongchun, Hong, Chun, Lei Chen, Tao Wang, Ting Yang, et al., Can cholesterol be used to distinguish pleural exudates from transudates? evidence from a bivariate meta-analysis. *BMC Pulm Med*. 2014; 14: 61.