Original article

Pleural effusion Still a Diagnostic Challenge

Alireza Emami Naeini, [1] Farzin Khorvash, [2*]Mohammad Emami, [3] Farzaneh Samiminia[4] , Hesam-al-din Khodadadi[4]

1-Associate Professor, Department of Infectious Diseases and Tropical Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.

2-Associate Professor, Department of Infectious Diseases and Tropical Medicine, Nosocomial Infection Research Center, Isfahan University of Medical Sciences, Isfahan, Iran.

3-Assistant Professor, Department of Pulmonary Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.

4-General Physician, Isfahan University of Medical Sciences, Isfahan, Iran.

Corresponding author; Farzin Khorvash. Email :Khorvash@med.mui.ac.ir

Abstract

Objective; Pleural effusion is the most common manifestation of pleural disease. Biochemical examination of this fluid is usually done to try to identify the cause of a pleural effusion. Distinguishing whether the effusion is an exudates or transudates is the first step and is based on Light's criteria. The aim of this study was comparing this pleural fluid categorization by using this criteria to the ultimate diagnosis of pleural disease.

Patients and Methods; In a cross – sectional survey, we selected all patients with pleural fluid analysis, admitted in Alzahra University hospital. Then by light's criteria we classified pleural fluid to Exudative and Transudate. The aim of this study was to review the help of this Scale and comparing to ultimate diagnosis.

Result; In this survey we found 71(74.7%) Exudative pleural effusion and 24(25.3%) transudate pleural effusion. Pleural fluid LDH and protein were the best parameter for this classification. Pleural fluid glucose was a significantly higher in transudate fluids. Cloudy appearance of pleural fluid is also a helpful criteria for differentiating exudates from transudates.

Conclusion; Light's Criteria is still the cornerstone to classify pleural fluid to exudates and Transudates and bounding the different etiologies producing fluid in the pleural space. Additional parameter like PCR, cytology and histology and other new tests are needed to add for pleural fluid analysis to reach the ultimate diagnosis.

Key words; *Pleural fluid, Light's Criteria, Pleural disease, pleural fluid analysis*

Introduction

Fluid collection in the pleural space always indicates a disease. Pleural fluid may be consequence of a variety of infectious, inflammatory, primary pleural or secondary pleural malignant conditions, and medical conditions like congestive heart failure (CHF), liver failure and etc.(1,2) The Pathophysiology of pleural effusion includes raising lung capillary pressure , decrease Oncotic pressure, increase pleural membrane permeability or lymphatic obstruction.(3) In addition to clinical symptoms and chest physical examination, Chest radiography is the first approach to show existence of fluid in this space.(4) Decubital chest radiography may also help to differentiate free or loculated pleural fluid. Other radiologic modalities, lung computerized tomography (CT) detects small pleural effusion.(5) Thickening of the visceral and parietal pleura as well as enhancement of the visceral and parietal pleura after injection of intravenous contrast medium

("the split pleural sign '') suggest the presence of inflammation and thus an exudate rather than a transudate effusion. Ultrasonography (US), (6) also can detect small pleural fluid. Pleural effusion can also be delineated by Magnetic Resonance Imaging (MRI). The main roles of MRI in the evaluation of a pleural effusion are to characterize a hemothorax and determine whether a pleural tumor extends into the surrounding soft tissues of chest wall.(7) Biochemical and microbiologic examination of pleural fluid is usually done to try to identify the cause of pleural effusion.(8) light's criteria was published in 1972 and since then additional parameters have been proposed to increase sensitivity and specificity of the primary criteria. Light's Criteria are widely used to categorize pleural fluids as either exudates or transudates. Light's criteria include fluid/ serum ratios and therefore require a blood sample.(9)

Methods

Patients and samples

In a cross – sectional survey, during the period of 2011- 2014, we reviewed all patients' hospital records with pleural effusion in departments of Infectious diseases, Pulmonary, and Internal medicine in Alzahra university hospital, Isfahan, Iran. The study was approved by the Ethics Committee of Isfahan University of Medical Sciences (research project number 393527). Including criteria was patients with pleural effusion who underwent pleural tap and pleural fluid analysis (Biochemical, cytological, Gram's stain, culture and pleural biopsy if needed). Then we classified the pleural fluid to exudate and transudate using Light's criteria (Table 1). After collecting the data, statistical analysis was done on a computer using SPSS version 22.Variables were expressed as mean± standard deviation (SD). Student t- test, Chi – square and ANOVA were used to compare.

Table 1. Light's criteria[9]

Exudative effusions will have at least one of the following:
- Pleural fluid protein / Serum protein > 0.5
- Pleural fluid LDH / Serum LDH >0.6
- Pleural fluid LDH > 2/3 Serum LDH Upper Limit of Normal

Results

In this survey we found 71(74.7%) exudative pleural effusion and 24(25.3%) transudate pleural effusion. Data analysis in exudative and transudate group was shown in Table.2. Overall mean age of patients was 59.6±19.3 with age extreme of 15-87 year. 54(56.8%) male and 41(43.2%). Mean age of patients with exudates and transudates was 59.6±18.7 and 59.9±21.4 respectively and there was no significant differences between two groups (p= 0.95). Also in exudates and transudates groups there was 42(59.2%) and 12(50%) male respectively, and by Chi- square test there was no significant differences between two groups (p= 0.43). By exact fisher test appearance of pleural fluid (clear or cloudy) had significant differences between transudate and exudative groups (p= 0.001). Fluid glucose was significantly higher in transudates than exudates (p= 0.001). Red blood cells (RBC) in exudates was significantly higher than transudates groups (p = 0.045). By ROC analysis, pleural fluid glucose level ROC/ AUC = 0.295(range 0.18-0.41), for pleural fluid PH ROC/AUC = 0.54 (range 0.35-0.73), pleural fluid Leukocyte count ROC/ AUC= 0.62 (range 0.49-0.76). So Pleural fluid glucose, PH, Leukocyte count were not good criteria for differentiating exudates from transudates. ROC analysis for pleural fluid protein / serum protein (AUC= 0.77, range0.64-0.89) which has a significant differences between two groups (Figure 1). According to this test the best cut off point for this scale was 0.5.By Chi – square test there was a significant differences between two groups (p<0.001). The specificity and sensitivity for this parameter was 66.7% and 83.1% respectively. The sensitivity, specificity, false positive, false negative, Positive predictive value (PPV), Negative predictive value(NPV) for pleural protein/serum protein AUC for pleural fluid LDH/Serum LDH was 0.81(range 0.7 – 0.93) (Figure 2), which has a significant differences between two groups(p < 0.001) (Table 3). According to this test the best cut off point for this scale was 0.6. According to this cut of point 62 (91.2%) in Exudative and 6(8.8%) in transudate had a >0.6. which was statistically significant (p<0.001). Definite diagnosis of patients with pleural effusion is shown in Table 4.

Table 2. Data analysis in exudate and transudate group.

	Exudates No. (%)	Transudates (No. %)	p- value
Appearance Clear	26 (36.6)	18 (75)	0.001
Turbid	45 (63.4)	6 (25)	
PH	6.7± 2.9	7.25±0.4	0.55
Pleural Protein	3.86±1.63	4.67±2.5	0.59
Pleural LDH	1607.8±437	272.5±52.2	0.08
Leukocyte	11209±5689.33	1316.8±696.5	0.32
Pleural Protein /serum protein	20.06±3.42	9.34±3.8	0.092
Pleural fluid Glucose	109.8±57.4	158±69.5	0.001
Red Blood Cell	3396.3±2655	5500±350	0.84
White Blood Cell	6.27±5.7	8.13±12.1	0.34
Polymorph nuclear	48/.6±27.5	49.8±27.6	0.86
Lymphocyte	51.4±27.7	49.8±27.3	0.79
Amylase	85.8±38.8	49.5±4.1	0.39
Pleural fluid LDH/Serum LDH	33.24±12.8	9.16±6.32	0.29

Table 3.Characteristics of pleural fluid protein and LDH to serum

Parameter	Sensitivity	Specificity	PPV	NPV	False positive	False negative	Accuracy
Pleural fluid Protein/Serum protein	83.1	66.4	88.1	57.1	12.7	25	79
Pleural fluid LDH/Serum LDH	87.3	75	91.2	66.7	16.9	57.1	84

Table 4. Definite diagnosis of patients with pleural effusion.

COPD: Chronic obstructive pulmonary disease ESRD: End stage renal disease

Transudates	No. Cases
- CHF	8
- COPD	4
- Liver cirrhosis	2
- Pulmonary hypertension	1
- Pulmonary edema	1
- Pulmonary thromboembolism (PTE)	5
- ESRD	3
Exudates	
- Para pneumonic effusion	13
- Primary lung cancer	14
- Metastasis	23
- Bronchogenic carcinoma	5
- Mesothelioma	4
- Thoracic rhabdomyosarcoma	1
- Empyema (pneumonia)	5
- Myocardial infarction	1
- Lymphoma	5
Total	**95**

CHF: Congestive heart failure

Figure 1. AUC/ROC Pleural fluid

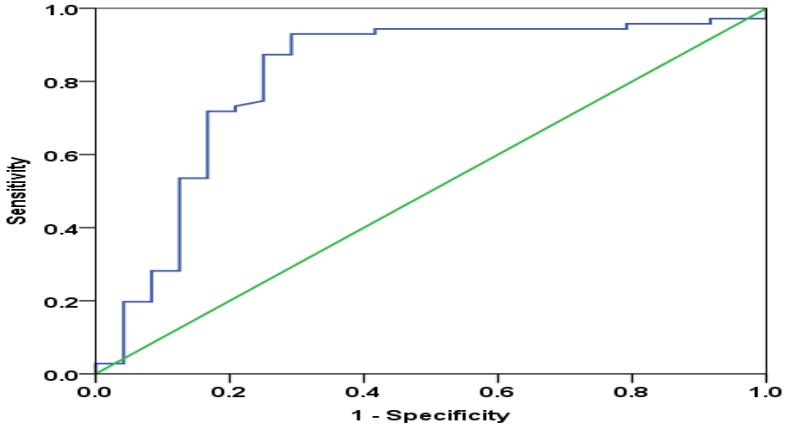
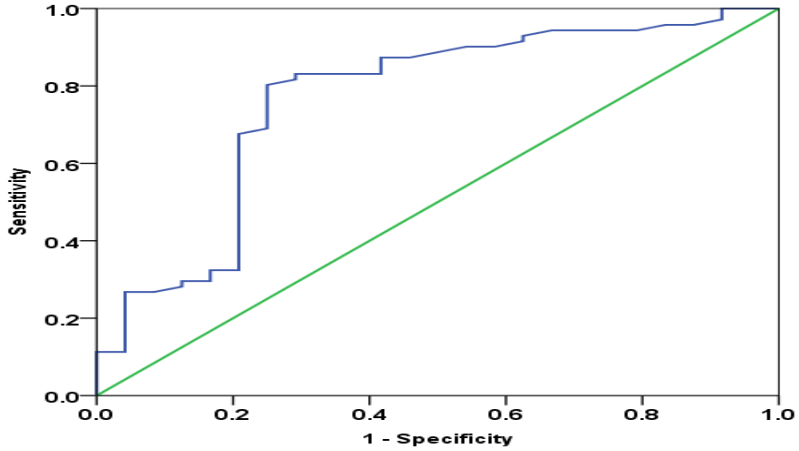


Figure 2. AUC/ROC Pleural fluid LDH/Serum protein/Serum



Discussion

In this study we reviewed the analysis of 95 pleural effusion samples. 71(74.7%) exudate pleural effusion and 24 (25.3%) transudate pleural effusion. There was no significant differences between age and gender of patients to kind of fluid. In our survey we show Cloudy appearance of fluid can help to differentiate Exudative from transudate. We found no references for a relationship of pleural fluid appearance and character of fluid. Fluid glucose was significantly higher in transudate group. Glucose may indicate an effusion associated with rheumatoid arthritis. Red blood cell count was significantly higher in exudative fluid than transudate. White blood cell count was not a good criteria for differentiating exudate from

transudate fluid. The most important marker was pleural fluid LDH / serum LDH level. Pleural fluid protein / serum protein was also another important criterion. In one study, LDH ratio had highest sensitivity (79.1%) and among combination of two parameters, Protein with LDH ratio had highest (87.5%) sensitivity, cell count with LDH ratio showed highest specificity (100%).(10) The most disease in transudate group was left ventricular heart failure, and in exudative group was metastatic malignancy to pleura by different origin including breast, Ovaries, and gastrointestinal as the most common. Primary lung cancer and parapneumonic effusion were other common etiology of exudative effusion. Serum and pleural NGAL levels can differentiate PPE from other diseases causing pleural fluid with high sensitivity and specificity.(11) In our survey although PH was not a proper parameter for differentiating exudates from transudates but pleural fluid PH may aid decisions over drainage of a para pneumonic effusion.(12) In Murphy's study it was included that in most cases, analysis of pleural fluid protein and lactate dehydrgenase

alone produces the same categorization as modified Light's criteria. Omission of a blood sample rarely affects the categorization of pleural fluids in routine clinical practice.(13) Although Light's Criteria is still the cornerstone to classify pleural fluid to exudate and transudate and bounding the different etiologies producing fluid in the pleural space. Other new tests are needed to complete the puzzle. At present Adenosine deaminase (ADA) is a useful biochemical marker to suggest exudate effusion.(14,15) Surviving X- linked inhibitor of apoptosis (XlAP) are inhibitors of apoptosis that are expressed highly in most malignancies and may be diagnostic markers of cancer. Jian Li et al showed that measuring these tumor markers in pleural effusion can discriminate malignant from benign pleural effusion.(16) in one study showed that the discriminative value of serum – effusion albumin gradient and pleural fluid to serum albumin ratio appears to be similar in the diagnostic separation of transudates from exudates.(17) Molecular tests such as nucleic acid amplification tests are used for detection of infective pleural effusion specially tuberculosis pleurisy.(18) Li Z *et al* Showed for the first time that M. tuberculosis-specific CD3(+)TCRvβ11(+) NKT cells participated in the local immune responses against M. tuberculosis through the production of IFN-γ and the secretion of cytolytic molecules.(19) Combination of cholesterol and LDH had the highest discriminatory potential and the added advantage that no patient plasma is needed for correct classification.(20) Cytology of pleural fluid and pleural biopsy (closed or open) to take a tissue sample are valuable to reach the diagnosis.(21,22) Pleural effusion due to pleural or nonpleural disease is still a diagnostic challenge and we should use many conventional and new tests on pleural effusion sample and taking pleural biopsy to reach a definite diagnosis.(23)

Conclusion

Chemical analysis of pleural fluid is now the most important and routine tests as the first approach to diagnose the character of fluid aspirated from pleural space. Although this exam is the mainstay for differentiating exudate from transudate fluid, many other tests including microbiological and molecular tests are needed for ultimate diagnosis of pleural disease and sometimes invasive procedures like closed pleural biopsy or open pleural biopsy may be needed.

Acknowledgments:

Conflicts of Interest: All authors report no conflicts of interest relevant to this article.

Financial Support: none reported.

References

1-Emmet E. McGrath, Paul B. Anderson. Diagnosis of pleural effusion: A systematic approach. AJCC.2011; 20 119-123.

2-Andrew R. Hass, Daniel H. Steman. Advances in pleural diseases management including updated procedural coding. Chest. 2014; 146(2)508-513.

3-Maskell NA, Butland RJ.British Thoracic Society (BTS) guidelines for the investigation of pleural effusion in adults.Thorax.2003; 58:8-17.

4-Edward J. Septimus. Pleural effusion and empyema. In: Mandell GL , Benntt JE, Dolin R. Principle and practice of Infection Diseases.7th ed. Philadelphia: Churchill Livingstone:2010.P.917-924.

5-Kraus GJ. The split pleural sign. Radiology 2007; 243-297.

6- Moore CL, Copel JA. Point- of – care ultrasonography. N Engl J Med 2011; 364-746-757.

7-Gamsu G, Sostman D. Magnetic resonance imaging of the thorax. Am Resv Respir Dis 1989; 139:254.

8-Tarn AC, Lapworth R. Biochemical analysis of pleural fluid: what should be measure? J Clin Pathol 2008; 61(5): 684-5.

9-Light RW, Clinical practice. Pleural effusion. N Eng J Med. 2002; 346(25); 1971- 7.

10Jadhav MV, Ketkar S, Patil T, Shingade MS. Pleural fluid analysis with traditional and additional parameters. Indian J Pathol Microbiol. 2007; 50(2):415-9.

11-Gümüs A, Ozkaya S, Ozyurt S, Cınarka H, Kirbas A, Sahin U, Ece F. A novel biomarker in the diagnosis of parapneumonic effusion: neutrophil gelatinase-associated lipocalin. Multidiscip Respir Med. 2014;15:9:49.

12-Saguil A, Wyrick K, Hallgren J. Diagnostic approach to pleural effusion. Am Fam Physician. 2014 15; 90 (2): 99-104.

13-Murphy MJ, Jenkinson F. Categorization of pleural fluids in routine clinical practice: analysis of pleural fluid protein and lactate dehydrogenase alone compared with modified light's criteria. Indian J Physiol Pharmacol. 2007; 51(2): 170-4

14-Jadhav AA. Bardapukar JS.Diagnostic value of adenosine deaminase to differential exudates and transudates. Clin Chem Lab Med. 2007; 45(10):1332-8.

15-Jian Li, Zhen – Nan Li, Qian – Lei Bao, Li – Ping De, Xiao – Quin Li, Ping Chen. Evaluation of pleural fluid surviving and XIAP for diagnosis of malignant pleural effusion. Tumor Biology. 2012; 33:1803- 1810.
16-Gui X, Xiao H. Diagnosis of tuberculosis pleurisy with adenosine deaminase (ADA): a systematic review and meta-analysis. Int J Clin Exp Med. 2014;15;7:3126-35.
17-Jose Joseph, Padmanabhan Badrinath, Gurnam S Basran, Steven A Sahn. Is albumin gradient or fluid to serum albumin ratio better than the pleural fluid lactate dehydroginase in the diagnostic of separation of pleural effusion? BMC Pulm Med. 2002; 2: 1-5.
18-Pai M, Flore LL, Hubbard A, Riely LW, Colford JM. Nucleic acid amplification tests in the diagnosis of tuberculous pleuritic: a systematic review and Meta – analysis. BMC Infectious Dis. 2004; 4: 6 – 12.
19-Leers MP, Kleinveld HA and Scharnhorst V. Differentiating Transudative from Exudative pleural effusion: should we measure effusion cholesterol dehydro0genase? Clin Chem Lab Med. 2007; 45(10): 1332-8
20-Sherwani R, Akhtar K, Naqvi AH, Akhtar S, Abrari A, Bhargava R. Diagnostic and prognostic significance of cytology in effusions . J Cytol 2005; 22: 73-77.
21-Li Z, Yang B, Zhang Y, Ma J, Chen X, Lao S, Li B, Wu C. Mycobacterium tuberculosis-specific memory NKT cells in patients with tuberculous pleurisy. J Clin Immunol. 2014;34:979-90.
22-Khan N, Sherwani RK, Afroz N,m Kapoor. Cytodiagnosis of malignant effusion and determination of primary site. J Cytol 2005; 22: 107 – 110.
23-Rolandas Zablockis, Remigijus Nargèla, Bronislavas Šatkauskas. Needle pleural biopsy. Acta medica Lituanica 2002; 9: 104- 7.