Value of Fluid C-Reactive Protein Level as added Marker to Light's Criteria in Etiological Diagnosis of Pleural Effusion

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ABSTRACT

Introduction: Pleural fluid analysis starts with the classification of pleural fluid into transudates and exudates. Light's criteria serves a good purpose in this differentiation. But it sometimes misclassifies transudates as exudates. Assessment of pleural fluid C- reactive protein (CRP) may be of some help in this regard. We undertook the present study to find out whether fluid CRP is an added marker to Light's criteria in etiological classification of pleural fluid, and to determine fluid CRP cut – off value for this.

Material and Methods: Analysis of pleural fluids of all the patients referred to the department of Pathology in College Of Medicine and JNM Hospital, Kalyani from March 2016 to August 2016 were done based on Light's criteria, fluid CRP value, other clinical, biochemical and radiological parameters. The cases were grouped according to etiology.

Results: Out of total 138 cases, 20.29% were transudates and 79.71% were exudates. CRP cut off value 20mg/L can distinguish exudates with 66.36% sensitivity and 100% specificity. The higher the fluid CRP value the lesser is the chance of tubercular effusion. Light's criteria misclassified 39.13% of transudates as exudates where fluid CRP value was of help.

Conclusions: Fluid CRP value should be considered as an additive marker to Light's criteria in analysis of pleural effusion cases.

Keywords: C-reactive protein, Light' criteria, Pleural effusion, transudate, exudate

INTRODUCTION

Accumulation of fluid in the pleural space is called pleural effusion. There are various etiologies of pleural effusion. These may be due to lung and pleural pathologies or diseases involving other systems, which may be inflammatory / non-inflammatory and malignant / non-malignant causes. To pinpoint the diagnosis, the first step is classification of pleural fluid into transudates and exudates. Transudative effusions are mainly due to hemodynamic disturbances, whereas infection (tubercular or non-tubercular) and malignancy are the cause of exudative effusions. Light's criteria is used to differentiate transudates and exudates.[1] The parameters included are pleural fluid / serum protein ratio >0.5, pleural fluid / serum LDH ratio >0.6, pleural fluid LDH >2/3rd of serum LDH. If at least one criteria is positive then the effusion is termed as exudative and transudative is when all are negative.

Several studies have pointed out that Light's criteria can misclassify transudates as exudates in 18% to 29% of cases.[2-4] C - reactive protein (CRP), an acute phase reactant, can have some role in etiological analysis of pleural fluid, more importantly in distinguishing tubercular and malignant effusion.[5-10] But definite cut off value of fluid CRP in this regard is not much available. So we undertook the present study to determine the cut off value of fluid CRP for etiological classification of pleural effusion. This study also aims to assess whether fluid CRP level should be considered as an additional marker along with Light's criteria for every case of pleural effusion.

MATERIAL AND METHODS

The study was conducted in the Department of Pathology, College of Medicine and JNM Hospital, Kalyani, Nadia, West Bengal, India for a period of six months from March 2016 to August 2016. Clearance from Institutional Ethical Committee was obtained. All the patients of pleural effusion referred to the department of Pathology from various departments of College of Medicine and JNM Hospital for pleural fluid analysis were assessed. Patients with bleeding diathesis, patients on anticoagulant treatment were excluded from the study. All other patients who gave informed written consent were included in the present study. Detailed clinical history, results of thorough clinical examination, reports of radiological and other relevant investigations were filled up in a predesigned case record proforma. Aspiration of pleural fluid was done in the department of Radio diagnosis of our institute and the samples were subjected to cytological (cell type, cell count and abnormal cell) and biochemical (protein, LDH, CRP) analysis. Cytosmears for cytological examinations were prepared from centrifuged deposits of the fluids and stained with Leishman's and Papanicolaou stain. Samples of serum were also obtained for biochemical (protein, LDH) analysis from each patient. Protein and LDH analysis of both serum and fluid were performed in the autoanalyzer by using biurate and enzymatic methods respectively. Protein value is given in gm/dl and LDH value is given in U/L. The CRP level of the fluid was measured in an autoanalyzer by using immunoturbidimetric method. CRP values are expressed in mg/L.

All the results were analysed. Based on Light's criteria the fluids were classified into transudates / exudates. Exudates were further sub-classified into tubercular, non-tubercular, malignant and other groups based on clinical, biochemical, radiological and pathological investigations. Diagnosis of tubercular pleural effusion was based on high tuberculin positivity, lymphocytic pleural fluid, AFB positive sputum smear or sputum culture for Mycobacterium tuberculosis, pleural fluid positive for

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How to cite this article: Anindita Sinha Babu, Dipanwita Das, Manisha Sarkar. Value of fluid c-reactive protein level as added marker to light's criteria in etiological diagnosis of pleural effusion. International Journal of Contemporary Medical Research 2016;3(11):3357-3360.

AFB, ADA level in pleural fluid >40 IU/L or pleural biopsy showing caseating granuloma.[11-13] If fluid cytosmears / pleural biopsy showed malignant cells then the effusion were termed malignant effusion. Parapneumonic effusion was diagnosed when clinical, biochemical and radiological signs suspected acute inflammation and pleural fluid showed predominance of neutrophils / gram reactive organism / culture positive for bacteria other than mycobacteria. When all these were non-contributory then they were included in the 'other' category.

STATISTICAL ANALYSIS

At the end of the study, all the data was compiled and analysed using descriptive statistics. Microsoft office 2007 was used for making tables.

RESULTS

In our study a total of 138 cases of pleural effusion were assessed. Table 1 showed that 110 cases (79.71%) were of exudative type and 28 cases (20.29%) were of transudative type. Among the exudative effusions 54.55% were tubercular, 10.91% were non-tubercular and 18.18% were malignant effusions. About 16% of the exudative effusions were 'others'.

Table 2 showed that fluid CRP value > 20 mg/L included no transudates, <20 mg/L included 100% of transudates and 33.64% of exudates. These 33.64% of exudates comprised of no infective effusion, but 95% of malignant effusions and 100% of 'other' effusions. Later on these 'other' cases came out to be transudative type considering their clinical, radiological and other biochemical parameters. Out of a total 60 cases of tubercular effusions, 59 had fluid CRP value <60 mg/L and the lone case had value 61.9 mg/L. All the cases having higher range of fluid CRP value (>70 mg/L) were of non-tubercular etiology. Table 3 revealed that the fluid CRP cut off value 10 mg/L can differentiate transudates and exudates with a sensitivity of 72.73% and specificity of 92.85%. When the cut off value is 20 mg/L, then they are 66.36% and 100% respectively.

Table 4 - Fluid CRP cut off value 10 mg/L and 20 mg/L can distinguish between transudative and malignant effusion with sensitivity of 92.86% and 100% respectively but with specificity of 40% and 5% respectively.

Table 5 - Fluid CRP cut off value 40 mg/L can differentiate non-tubercular and tubercular effusion with sensitivity of 100% but specificity of 60%. When the cut off value is 50 mg/L then the sensitivity and specificity are 58.33% and 93.33% respectively. If the cut off value is 60 mg/L then they are 50% and 98.33% respectively. So the higher the value of fluid CRP the lower is the chance of tuberculosis.

DISCUSSION

The present study was conducted in the Department of Pathology, College of Medicine and JNM Hospital, Kalyani, Nadia, West Bengal, India for a period of six months from March 2016 to August 2016. A total of 138 cases of pleural effusions were included in the present study. They were classified into transudates and exudates according to the Light's criteria.[1,2] Though the Light's criteria has been highlighted for

CRP cut off value	CRP value (mg/L)	Exudative	Transudative	Total	Sensitivity	Specificity	Positive predictive value
10 mg/L	≥ 10	80 (TP)	2(FP)	82	72.73%	92.85%	97.56%
	< 10	30 (FN)	26 (TN)	56			
	Total	110	28	138			
20 mg/L	≥ 20	73 (TP)	0 (FP)	73	66.36%	100%	100%
	< 20	37 (FN)	28 (TN)	65			
	Total	110	28	138			

Table-3: Differentiation of Exudative and Transudative based on fluid CRP cut off value (mg/L)

CRP cut off value	CRP (mg/L)	Transudative	Malignant	Total	Sensitivity	Specificity	Positive predictive value
10 mg/L	< 10	26(TP)	12(FP)	38	92.86%	40%	68.42%
	≥ 10	2(FN)	8(TN)	10			
	Total	28	20	48			
20mg/L	< 20	28(TP)	19(FP)	47	100%	5%	59.57%
	≥ 20	0(FN)	1(TN)	1			
	Total	28	20	48			

Table-4: Differentiation of transudative and malignancy based on fluid CRP cut off value (mg/L)

CRP cut off value	CRP (mg/L)	Non-tuberculosis	Tuberculosis	Total	Sensitivity	Specificity	Positive predictive value
40 mg/L	≥ 40	12(TP)	24(FP)	36	100%	60%	33.33%
	< 40	0 (FN)	36 (TN)	36			
	Total	12	60	72			
50 mg/L	≥ 50	7(TP)	4(FP)	11	58.33%	93.33%	63.64%
	< 50	5(FN)	56(TN)	61			
	Total	12	60	72			
60 mg/L	≥ 60	6(TP)	1(FP)	7	50%	98.33%	85.71%
	< 60	6(FN)	59(TN)	65			
	Total	12	60	72			

Table-5: Differentiation of Non-tuberculosis and Tuberculosis based on fluid CRP cut off value (mg/L)

differentiation of transudates and exudates since 1972[1], several studies have pointed out its fallacies. It had been described by Light himself in 2013 that about 25% of transudates might be falsely classified as exudates.[2] Romero-Candeira et al in their study had shown that Light's criteria correctly identifies only 75% of transudates.[3] In another study, 29% of transudates due to heart failure and 18% of transudates due to hepatic hydrothorax were misclassified as exudates by Light's criteria.[4] The difficulty arises in case of lymphocytic exudative pleural effusion that can be either tubercular effusion or malignant effusion. Hence several other parameters were tried (like cholesterol, albumin, BNP etc.) but none were sufficient enough to supplement Light's criteria. Some studies have shown that CRP, an acute phase reactant protein, can have some role in pleural fluid analysis particularly in these cases.[5-8] Several studies have shown that pleural fluid CRP value can distinguish between tubercular and malignant effusion.[9,10] We undertook the present study to find out whether fluid CRP can be used as an added marker to Light's criteria in differentiating transudates and exudates, particularly in identifying those misclassified transudates and to find out the cut off value of fluid CRP in etiological classification of transudates / exudates.

In our study we found that fluid CRP value > 20 mg/L includes no transudates, whereas <20 mg/L includes all of the transudates and 33.64% of exudates. These exudates included non-infective effusions, which are 95% of the malignant effusions and the exudates mentioned as 'others'. The fluid CRP value in these 'others' group ranged from 1.1 mg/L to 3.9 mg/L. These were actually transudates, as based on radiological and clinical findings, hence misclassified as exudates by Light's criteria. The sensitivity of detecting exudates is 66.36% and specificity 100% using CRP cut off value 20 mg/L. The fluid CRP value in malignant effusions ranged from 7.2 mg/L to 20.6 mg/L. The sensitivity and specificity in detecting exudates is 72.73% and 92.85% respectively, when the fluid CRP cut off value is changed to 10 mg/L. Present study highlighted that Light's criteria designated exudative effusions having fluid CRP value <20 mg/L is either malignant effusion or a false positive one. Hence exudative effusions determined by Light's criteria having fluid CRP value <20 mg/L and showing no malignant cell, need to be analysed with caution. Before initiating any definitive therapy, transudative effusion should be excluded in these situations. This study also showed that whatever be the CRP cut off value (10 or 20), it differentiates transudates and malignant effusion with high sensitivity but low specificity. Therefore it is difficult to differentiate transudates and malignant effusion. In our study Light's criteria falsely classified 39.13% of transudates as exudates. Though Light's criteria is very much reliable in distinguishing transudates vs exudates, several studies pointed out its fallacies. Richard Light himself in 2013 had shown that about 25% of transudates are misclassified as exudates.[2] In the study by Kummerfeldt et al, Light's criteria misclassified 81 of 290 transudates (28%).[14] Dantu et al in their study found that the sensitivity of Light's criteria in identifying exudates was 100% but for transudates it was 90%.[15] In the review article in 2013, Porcel also mentioned that about 25% of transudates are misclassified as exudates.[16] Most of these cases were congestive heart failure (CHF) on diuretic therapy or cirrhotic patient. Roth et al (1990) also commented that Light's criteria misclassified transudates as exudates in CHF patients especially on diuretic therapy.[17] In the present study fluid CRP value varied from 20 – 70 mg/L for tubercular effusions and 40 – 100 mg/L for non-tubercular effusions. The highest fluid CRP value in tubercular effusion was 61.9 mg/L. Fluid CRP cut off value 60 mg/L identified non-tubercular effusions with 50% sensitivity and 98.33% specificity. Porcel et al[7] in their study had shown that the sensitivity and specificity of fluid CRP value in identifying tubercular effusion is 49% and 93% respectively considering fluid CRP cut off value 80 mg/L. But in the present study no tubercular effusion was identified if the cut off value of fluid CRP was taken as 70 IU/L. Thus the more the fluid CRP value the less is the chance of being tuberculosis and value >70 IU/L is most likely to be non-tubercular origin. The reason behind this is CRP, being an acute phase reactant protein, more likely to

Type of effusion		No of cases (N=138)	Total
Exudative	Tubercular	60 (43.48%)	110(79.71%)
	Non-tubercular	12(8.70%)	
	Malignant	20(14.49%)	
	Others	18(13.04%)	
Transudative		28(20.29%)	28(20.29%)
Total		138(100%)	138(100%)

Table-1: Types of effusion

Fluid CRP value (mg/L)	Exudative				Transudative	Total
	Tubercular	Non tubercular	Malignant	Others		
<10	0 (0%)	0 (0%)	12 (21.43%)	18(32.14%)	26 (46.43%)	56 (100%)
10-19.999	0 (0%)	0 (0%)	7 (77.78%)	0 (0%)	2 (22.22%)	9 (100%)
20-29.999	2 (66.67%)	0 (0%)	1 (33.33%)	0 (0%)	0 (0%)	3 (100%)
30-39.999	34 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	34 (100%)
40-49.999	20 (80%)	5 (20%)	0 (0%)	0 (0%)	0 (0%)	25 (100%)
50-59.999	3 (75%)	1 (25%)	0 (0%)	0 (0%)	0 (0%)	4 (100%)
60-69.999	1 (50%)	1 (50%)	0 (0%)	0 (0%)	0 (0%)	2 (100%)
70-79.999	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
80-89.999	0 (0%)	2 (100%)	0 (0%)	0 (0%)	0 (0%)	2 (100%)
90-99.999	0 (0%)	2 (100%)	0 (0%)	0 (0%)	0 (0%)	2 (100%)
>100	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)
Total	60 (43.48%)	12(8.70%)	20 (14.49%)	18(13.04%)	28 (20.29%)	138 (100%)
	110 (79.71%)					

Table-2: Differentiation of Exudative and Transudative based on absolute fluid CRP value (mg/L)

rise to a higher level in non-tubercular bacterial effusions (acute inflammatory condition) than chronic tubercular effusions.

The main strength of present study was the tertiary care hospital set up that enabled all the necessary investigations to be done in the same hospital premise. We were able to have large number of cases in this short period of time. But our study result did not reflect the situation of general population in the community. Being a tertiary care centre, only specialised cases were found in the study population. This study needs to be extrapolated to a large cohort to get the exact situation in the community.

CONCLUSIONS

Therefore we conclude that fluid CRP value can point out those transudates that were falsely classified as exudates by Light's criteria. Exudative effusions having fluid CRP value <20 mg/L showing no malignant cell needs to be analysed according to clinico-radiological features. It also helps to differentiate tubercular and non-tubercular effusions. Hence fluid CRP value should be considered as an additive marker to Light's criteria in analysis of pleural effusion cases.

REFERENCE

1. Light RW, MacGregor MI, Lichsinger PC et al. Pleural effusions: the diagnostic separation of transudates and exudates. Ann Intern Med. 1972;77:504-14.
2. Light RW. The Light criteria- the beginning and why they are useful 40 years later. Clin Chest Med. 2013;34:21-26.
3. Romero-Candeira S, Hernandez L, Romero-Brufao S et al. Is it meaningful to use biochemical parameters to discriminate between transudative and exudative pleural effusions/ Chest. 2002;122:1524-9.
4. Bielsa S, Porcel JM, Castellote J et al. Solving the Light's criteris misclassification rate of cardiac and hepatic transudates. Respirology. 2012;17:721-6.
5. Abu-Youssef H, Amin S, Amin H, Osman E. Value of C-reactive protein in etiological diagnosis of pleural effusion. Egyptial Journal of Bronchology. 2010;4:124-130.
6. Petkovic TR, Pezcic T, Savic V, Vlahovic P, Borovac DN, Radojkovic D. ActaFac Med Naiss. 2007;24:89-93.
7. 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;34:1383-1389.
8. Turay UY, Yildirim Z, Turkoz Y, Biber C, Erdogan Y, Keye AI et al. Use of pleural fluid C-reactive protein in diagnosis of pleural effusion. Respiratory Medicine. 2000;94:432-435.
9. Gracia E, Pachon E, Soler MJ, Padilla-Navas, Romero V, Shum C. C- reactive protein in lymphocytic pleural effusions: a diagnostic aid in tuberculous pleuritic. Respiration. 2005;2:1392–3.
10. Nitipatana Chierakul, Apichart Kanitsap, Angkana Chaiprasert, Ronnachai Viriyataveekul. A simple C-reactive protein measurement for the differentiation between tuberculous and malignant pleural effusion. Respirology (Carlton, Vie) (Respirology). 2004;9:66-9.
11. Mathur PC, Tiwari KK, Trikha S, Tiwari D. Diagnostic value of Adenosine Deaminase (ADA) activity in Tubercular serositis. Indian J Tuberc. 2006;53:92-95.
12. Maldhure BR, Bedarkar SP, Kulkarni HR, Paplnwar SP. Pleural Biopsy and Adenosine Deaminase in Pleural Fluid for the diagnosis of Tubercular pleural effusion. Ind J Tub. 1994;41:161-165.
13. Valdes L, Alvarez D, Jose ES, Juanatey JRG, Pose A, Valle JM et al. Value of adenosine deaminase in the diagnosis of tuberculous pleural effusions in young patients in a region of high prevalence of tuberculosis. Thorax. 1995;50:600-603.
14. Kummerfeldt CE, Chiuzan CC, Huggins JT, DiVietro ML, Nestor JE, Sahn SA et al. Improving the Predictive Accuracy of Identifying Exudative Effusions. CHEST. 2014;145:586-592.
15. Dantu P, Pusuluri S. Diagnostic value of serum-Effusion Albumin Gradient in the Differential Diagnosis of Pleural Effusion. International Journal of Health Sciences and Research. 2012;1:5-10.
16. Review article: Porcel JM. Identifying transudates misclassified by Light's criteria. Curr Opin Pulm Med. 2013;19:362-7.
17. Roth BJ, O'Meara TF, Cragun WH. The serum-effusion albumin gradient in the evaluation of pleural effusions. Chest. 1990;98:546-9.

Source of Support: Nil; **Conflict of Interest:** None

Submitted: 24-10-2016; **Published online**: 07-12-2016