ISSN Print: 2394-7500
ISSN Online: 2394-5869
Impact Factor: 5.2
IJAR 2019; 5(4): 04-07
www.allresearchjournal.com
Received: 02-02-2019
Accepted: 05-03-2019

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Correlation of pleural fluid and serum C-reactive protein and lactate dehydrogenase level in relation to infection and malignant pleural effusion

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Abstract
Pleural effusion is a usually experienced clinical substance in medication. A few components are associated with pathology of pleural emanation like expanded porousness of pleural vessels, expanded pneumonic fine weight, negative intrapleural pressure, diminished oncotic pressure gradient, and lymphatic deterrent. In this study the estimation of the values of pleural fluid CRP and LDH and serum CRP and LDH and its ratio and its authenticity in differentiating infectious vs malignant effusions was analysed. The detailed clinical examination was done along with chest x ray. Based on chest x ray pleural effusion was classified as mild, moderate and massive. The results showed that Majority of patients were in the age group 40-60 years and ≤40 years. Male to female ratio was 1.8:1. The mean age among male was 52.41±14.61 years and in female was 49.42±15.85 years. In tuberculous effusions 35.4% were massive effusion, 33.3% were moderate effusions and 31.3% were mild effusions. this data is correlating between pleural to serum LDH ratio and pleural to serum CRP ratio in malignant effusions and infectious effusions, which found a significant correlation between them with p value 0.0065 and 0.0048 respectively.

Keywords: Pleural, malignant, CRP

Introduction
Pleural effusion is a commonly encountered clinical entity in medicine. Several mechanisms are involved in pathology of pleural effusion like increased permeability of pleural capillaries, increased pulmonary capillary pressure, negative intrapleural pressure, decreased oncotic pressure gradient, and lymphatic obstruction [1]. Establishing whether pleural fluid is transudate or exudate using Light's criteria is a very important step in determining it's etiology [2, 3]. Exudative pleural effusions can have numerous etiologies and very frequently cause diagnostic dilemma [4]. A thorough history, clinical examination and an accurate pleural fluid analysis can lead us to etiology quite often. The difficulty in determining the cause of pleural effusion is shown by the fact that in many series "unknown etiology" constitutes nearly 15% [5]. Exudative effusions can of infectious, non-infectious and malignant etiologies.

In the west the most common cause of pleural effusion is parapneumonic effusion followed by malignancy, while in India it is tubercular pleural effusion followed by malignant effusion [6]. Both tubercular and malignant pleural effusion have similarities in clinicoradiological profile as well as in pleural fluid studies both being exudates and predominantly lymphocytic effusions which can cause difficulty in diagnosis. In exudative pleural effusions Lactate dehydrogenase (LDH), adenosine deaminase (ADA), and C-reactive protein (CRP) levels are elevated as compared to transudative pleural effusions. ADA levels are raised in tuberculous pleurisy, an empyema, rheumatoid arthritis, lymphoma, and malignancy. LDH isoenzymes are elevated in malignancies like mesothelioma, lymphoma and small cell lung cancer. There are several reports in literature citing that malignant pleural effusions have low CRP levels as compared to infectious pleural effusions [7]. The current study is undertaken to estimate pleural fluid and serum values of CRP and LDH, and pleural fluid to serum ratios of LDH and CRP and to ascertain sensitivity, specificity, positive and negative predictive value of the

tests undertaken to differentiate benign and malignant pleural effusions basing on these parameters. Estimation of the values of pleural fluid CRP and LDH and serum CRP and LDH and its ratio and its authenticity in differentiating infectious vs malignant effusions.

Materials and Methods

Patients who were visiting to the Department of pulmonary medicine at IMS & SUM Hospital and diagnosed as pleural effusion. This study were carried out during Dec-2016 to Aug-2018. Its an observational case study. For this study the inclusion criteria was taken as Patients (18-85 years) with pleural effusion who didn't have previous H/O diagnostic and therapeutic Aspiration during this episode of illness. And the exclusive criteria was Hemodynamically unstable patient (above 85), Bleeding Diathesis, Pleural effusion associated with chest trauma.

In all patients initially, detailed clinical examination was done along with chest x ray. Based on chest x ray pleural effusion was classified as mild, moderate and massive. Patients with pleural fluid level up to 5th rib anteriorly were classified as mild, up to 2nd rib anteriorly as moderate and above the 2nd rib as massive pleural effusion. For this study Statistical analysis were done using SPSS for windows v17.0 & data presented as mean ± SD. For the tests used in this study, the differences are considered significant for p value < 0.05.

Results

Demographic data

Table 1: Age and sex distribution

Age In Year	Male		Female	
	No. of Cases	%	No. of Cases	%
≤40	15	23.4	10	27.8
40-60	31	48.4	17	47.2
60-80	16	25.0	9	25.0
>80	2	3.1	0	0.0
Total	64	100.0	36	100.0
Mean ± Sd	52.41 ± 14.61		49.42 ± 15.85	

100 consecutive patients with pleural effusion were studied from 2016 to 2018. There were 64 males and 36 females. The mean age was 51.33±15.06 years. The mean age among male was 52.41±14.61 years and in female was 49.42±15.85 years.

Age and etiology

Table 2: Age and etiology

Age In Yr	Malignant effusion		PPE		TB Plef	
	No. of Cases	%	No. of Cases	%	No. of Cases	%
≤40	5	17.2	2	8.7	18	37.5
40-60	14	48.3	19	82.6	15	31.3
60-80	10	34.5	2	8.7	13	27.1
>80	0	0.0	0	0.0	2	4.2
Total	29	100	23	100	48	100

Patients with age group ≤ 40years we have seen 5 malignant effusion cases, 2 Parapneumonic effusion cases and 18 Tuberculous effusion cases. 14 malignant cases, 19 parapneumonic effusion cases and 15 tuberculous effusion cases were seen in the age group between 40-60 yrs. In 60-80 years age group we have seen more cases of tubercular effusion followed by malignant effusion. All cases were tuberculous effusions in age group > 80 years.

Symptoms in different etiologies

Table 3: Symptoms in different etiologies

	Malignant effusion		PPE		TB Plef	
	No. of Cases	%	No. of Cases	%	No. of Cases	%
Fever	5	17.2	22	95.7	29	60.4
Cough	22	75.9	13	56.5	23	47.9
Sob	25	86.2	20	87.0	41	85.4
Chest Pain	23	79.3	18	78.3	26	54.2
Hemoptysis	3	10.3	0	0.0	4	8.3

Patients with tuberculous effusion presented with breathlessness as the predominant symptom (85.4%) followed by fever (60.4%), chest pain (54.2%), cough (47.9%) and hemoptysis 8.3%. In those with malignant effusion it was breathlessness (86.2%) and chest pain (79.3%) followed by cough (75.09%), fever (17.2%) and hemoptysis (10.3%). In parapneumonic effusion fever (95.7%) and shortness of breath (87%) were major symptoms followed by chest pain (78.3%) and cough (56.5%).

Size of effusion in relation to different etiology

Table 4: Size of effusion and etiology

	Massive		Mod		Mild	
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage
Malignant effusion	13	44.8	16	55.2	0	0.0
PPE	0	0.0	9	39.1	14	60.9
TB Plef	17	35.4	16	33.3	15	31.3

In malignant pleural effusion 44.8% were massive effusion and 55.2% were moderate effusion. In parapneumonic effusions 39.1% were moderate effusion and 60.9% were mild effusion. In tuberculous effusions 35.4% were massive effusion, 33.3% were moderate effusions and 31.3% were mild effusions.

Discussion

In our study tuberculosis was the predominant etiological factor for pleural effusion accounting for 48% cases followed by malignancy (29%) and parapneumonic effusion (23%). This is similar to the observation in another study from India by maldhure *et al*. [8] where they showed that the tuberculous effusions constitute 66% of the effusions, malignancy 15% and parapneumonic effusion 4.8%. This data differs from that of the West *et al*. where the incidence of parapneumonic effusion and malignant effusion are much higher as compared to that of tuberculous effusion. Most tuberculous effusions were seen in the age group of ≤ 40 years (mean age was 48.18±17.49 years). Malignant effusions were most commonly seen in the age group 40-60 years. (Mean age was 55.31±13.22 years) and parapneumonic effusions were seen in the age group of 40-60 years (mean age was 50.43±14.82 years). Earlier studies by S.K Sharma *et al* revealed mean age for tuberculous effusion was 33±14.4 years and for nontuberculous e effusion mean age was 47.3±16.5 years respectively. Patients with tuberculous effusion presented with breathlessness as the predominant symptom (85.4%) followed by fever (60.4%), chest pain (54.2%), cough (47.9%) and hemoptysis (8.3%). Studies done by Moudgil *et al*. [9] and Berger HW *et al*. [10] showed that patients with tubercular effusion had fever as the predominant symptom followed by cough and chest pain. Patients with malignant effusion had breathlessness as predominant symptom (86.2%) similar to a study by Chernov B *et al*. In this study, 44.8% of malignant pleural effusions were massive where as 55.2% were moderate effusion. On the other hand 35.4% of tuberculous pleural effusions were massive effusion, 33.3% were moderate and 31.3% were mild effusions. In parapneumonic effusions mild degree of pleural effusions predominated being 60.9% followed by moderate effusion (39.10%). Study done by Maher *et al*. [12] revealed out of 46 massive pleural effusions, 31 (67%) were due to malignancy and 15 (33%) were secondary to non-malignant conditions. Earlier study done by Turay *et al*. [14] showed that the pleural fluid to serum CRP ratio was significantly lower in neoplastic effusion than in the parapneumonic effusion. Mean of ratio in malignant effusion was 1±0.2, paraneumonic effusion was 6.6±2.7 and in tuberculous effusion 2.9±1.1 respectively. Vidriales *et al*. [14] reported that the pleural to serum CRP ratio was significantly elevated in the exudative effusions and this ratio was significantly lower in malignant effusions then in parapneumonic and tuberculous effusions. We are obtained similar results in our study. In our study, the ratio of pleural fluid to serum LDH value was higher in Parapneumonic effusion followed by malignant pleural effusion. Mean of pleural to serum LDH ratio in malignant effusion and infectious effusions were 3.94±2.91 and 2.34±1.9 respectively. As per study done by Kadri Cirak *et al*. [15] no significant difference was observed in terms of pleural to serum LDH ratio in the differentiation of malignant from nonmalignant pleurisy. In this *et al*. mean pleural fluid/serum LDH in malignant effusions and benign effusions were 2.59±4.37 and 3.77±9.29 respectively. In our study while correlating between Pleural fluid CRP to serum CRP ratio and pleural fluid LDH to serum LDH ratio in malignant effusions, we didn't get any statistically significant difference between these two groups p value being 0.1635 (p value <0.05 is significant) and correlation coefficient r=0.256. Similarly, in infectious effusions, the correlation of these two groups was also not significant with a p value of 0.237 and correlation coefficient -0.142. Correlating pleural fluid LDH to serum LDH ratio and pleural fluid CRP to serum CRP ratio in malignant effusions and infectious effusions, found a significant correlation between them with p value 0.0065 and 0.0048 respectively. Earlier study done by Kadri Cirak *et al*. [15] revealed that no significant correlation or difference was observed in terms of Pleural fluid to serum CRP, LDH and ADA levels, in differentiating malignant from benign pleurisy (p>0.05). Another study done by Turay *et al*. [15] suggested that the ratio of pleural fluid to serum CRP was significantly higher in exudative effusions and the ratio was significantly lower in malignant effusions than in the parapneumonic effusions (p<0.0002). In this study, cut off value of Pleural fluid to serum LDH ratio was 4.0 and sensitivity = 56% and specificity = 80% while comparing malignant effusion with infectious effusion. Similarly cut off value of Pleural fluid to serum CRP ratio was 1.0 and sensitivity = 33% and specificity = 89% while comparing malignant effusion with infectious effusion. Turay *et al*. [15] found that pleural fluid CRP levels >30mg/L had sensitivity of 93.7% and specificity for 76.5% for inflammatory pleural effusions.

Conclusion

After diagnosing exudative effusion by using Light's criteria, the biomarkers like CRP, LDH, ADA, Interlukin-6, Interferon-gamma and TNF-α can be used for their significance for differential diagnosis of exudative effusions (Tuberculosis, parapneumonic and malignant effusions). Higher pleural fluid CRP level indicate infective origin of pleural effusion i.e parapneumonic effusion. Increased level of LDH is a marker of inflammation found in malignant effusions and also in parapneumonic effusions. In this prospective study with a total sample size of 100 (29 cases of malignant effusions, 23 cases of parapneumonic effusions and 48 cases of tuberculous effusions) presented to department of pulmonary medicine, IMS & SUM Hospital from 2016 to 2018 were included. In our study, Pleural fluid to serum ratio of CRP value is almost same in both malignant and parapneumonic effusions. CRP ratio is increased in parapneumonic effusions when taking the value > 0.5. When combining tuberculous effusion and parapneumonic effusion together as infectious etiology of effusion, the pleural to serum CRP ratio was more than malignant effusion. No significant difference was observed between the pleural fluid/serum LDH ratios of malignant and parapneumonic effusions. When we correlating between pleural to serum LDH ratio and pleural to serum CRP ratio in malignant effusions and infectious effusions, found a significant correlation between them with p value 0.0065 and 0.0048 respectively.

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