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A Cross Sectional Study to Determine The Efficacy of Serum LDH: Pleural Fluid Ada Ratio As A Biomarker of Malignant Pleural Effusion in IRD, SMS Medical College, Jaipur

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Abstract

Introduction: The malignant pleural effusion is one of the most common causes of exudative pleural effusion. There is no accurate and commonly accepted biochemical marker of MPE, hence using common parameters two ratio serum LDH: pleural fluid ADA (cancer ratio) and cancer ratio: pleural fluid lymphocyte count (cancer ratio plus) derived and their efficacy in identification of MPE is studied.

Methods: 60 undiagnosed pleural effusion patients were studied in a hospital based cross sectional observational analytical study. The values of cancer ratio and cancer ratio plus which were calculated on the first day of admission were correlated to the final diagnosis of the patients.

Results: Out of 60 patients, 35% (n = 21) were diagnosed with malignancy and 65% (n = 39) with tuberculosis. The Mean (SD) value for serum LDH: pleural fluid ADA ratio (Cancer ratio) for MPE was 35.83 (11.81) and for TPE it was 7.92 (4.38). The p value is <0.0001. At ROC derived cut-off level >20 the sensitivity, specificity, PPV, NPV, PLR, and NLR for cancer ratio in the identification of MPE was 95.24%,94.87%, 90.91%, 97.37%, 18.37, and 0.05, while The Mean (SD) value for cancer ratio: pleural fluid lymphocyte count (Cancer ratio plus) for MPE is 45.79 (14.10) and for TPE it is 9.27 (5.87). The p-value is <0.0001. At ROC derived cut off level >30the sensitivity, specificity, PPV, NPV, PLR, and NLR for cancer ratio plus in the identification of MPE was 95.24%, 97.44%, 95.24%, 97.44%, 37.14, and 0.05. AUC was found to be 0.984 (95% CI 0.954-1.000) for cancer ratio and 0.982 (95% CI0.951-1.000) for cancer ratio plus.

Conclusion: The serum LDH: pleural fluid ADA ratio (Cancer ratio) and cancer ratio: pleural fluid lymphocyte count ratio (cancer ratio plus) are biomarkers with high sensitivity and specificity for identification of MPE. They are simple, cost-effective, reliable, and easily available biomarkers that may help in the early identification of MPE in people with exudative lymphocytic pleural effusions and can be used in routine clinical practice.

Keywords: Malignant pleural effusion, Serum LDH: Pleural fluid ADA, Cancer ratio, Cancer ratio: pleural fluid lymphocyte count, Cancer ratio plus

Introduction

Both the lungs and the chest wall are lined with thin membranes called 'pleura'. As such, the normal 'pleural space' (the area in between the lung and the chest wall) only contains a small amount of fluid .[1] When the rate of formation (around 0.01ml/kg/hour) exceeds the rate of absorption by lymphatics (capacity of 0.20ml/kg/hour) leads to the accumulation of pleural fluid in pleural space called pleural effusion.[2]

The foremost step in the evaluation of a pleural effusion is to determine whether it is atransudative or an exudative effusion.[3] Light's criteria is the principal method to make this differentiation, satisfying any one criterium means it is exudative[2]

- Pleural fluid protein/serum protein greater than 0.5
- Pleural fluid LDH/serum LDH greater than 0.6
- Pleural fluid LDH greater than two third of the upper limit of normal serum LDH

Among the exudative pleural effusions common etiologies found in clinical practice are tuberculous pleural effusion (TPE), malignant pleural effusion (MPE), and para pneumonic pleural effusion.[4,5] In contrast to tuberculous pleural effusion, where pleural fluid ADA serves as a reliable biomarker, no accurate and commonly accepted biochemical marker of malignant pleural effusion has been established.[6,7,8] Although low level of ADA and many tumor markers such as carcinoembryonic antigen, cytokeratin-19 fragments, and cancer antigen 125 were extensively studied, none of them were found sensitive and specific to be implemented in routine clinical practice.[8] Diagnosis of malignant pleural effusion is usually made with pleural fluid cytology or pleural biopsy. Cytology is however inexpensive and has high specificity but its sensitivity is only around 0.6. Pleural biopsy is an invasive tool associated with some complications such as pain, subcutaneous emphysema, and bleeding. Also its accuracy is affected by the experience of the operator and observer.[9]

Recently Verma et al[4,5] used serum LDH, pleural fluid ADA and pleural fluid lymphocyte count and proposed two new biomarkers, Serum LDH: Pleural fluid ADA as Cancer ratio and Cancer ratio: pleural fluid lymphocyte count as Cancer ratio plus. Their studies have shown that cancer ratio and cancer ratio plus at a cut-off level >20and >30 respectively have high sensitivity and specificity for the identification of malignant pleural effusion.

Objective

To determine the efficacy of serum LDH: pleural fluid ADA ratio (cancer ratio) as a biomarker of malignant pleural effusion.

Materials and Methods

This was a hospital based cross sectional study carried out at Department of Respiratory Medicine, Institute of Respiratory Diseases, SMS Medical College, Jaipur, over a period of one year (2020-2021) after seeking permission from the Research Review Board. This study enrolled 60 patients aged >18 years with exudative and

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lymphocyte predominant pleural effusion (as per Light's criteria) after obtaining written informed consent.

Detailed history was elicited from the patients, general physical examination and systemic examination was carried out and routine blood investigations like CBC, blood sugar, renal function test, liver function test, serum LDH, serum total protein, and albumin were done. After chest radiography diagnostic thoracentesis was done and pleural fluid was sent for biochemical analysis (protein, sugar, albumin, LDH, ADA), cytology, cell count and differential lymphocyte count, CBNAAT (when tuberculosis is suspected), microbiology (gram stain, pyogenic culture, AFB smear).

The values of cancer ratio and cancer ratio plus were calculated following initial investigations and correlated to the final diagnosis of the patients.

Data was entered in a Microsoft Excel. Statistical analysis was performed using SPSS (version 18.0). Categorical variables were summarized as frequencies and percentages. Continuous variables were presented as mean and standard deviation or median and interquartile range based on the normality of data. Normality was assessed using the Kolmogorov-Smirnov test. Pleural fluid and serum parameters between the malignancy and tuberculosis groups were compared using the independent t-test or Mann Whitney test after assessing the symmetry of data distribution. ROC curves were constructed to calculate the area under the curve(AUC) and 95% confidence intervals for AUC were calculated. Sensitivity, specificity, and predictive values were calculated based on the cut-offs derived from ROC. A p-value less than 0.05 was considered for statistical significance during hypothesis testing.

Results

Out of the total 60 patients, 55% (n = 33) were male and 45% (n = 27) were female. and 35% (n = 21) were diagnosed with malignancy and 65% (n = 39) with tuberculosis. Among the malignant group (n = 21), 57.14% (n = 12) had Adenocarcinoma, 28.57% (n = 6) had Squamous cell carcinoma, 9.52% (n = 2) had Small cell carcinoma and 4.76% (n = 1) had Malignant round cell tumor. The mean (SD) Age (in years) in this study was 52.9 (17.15) years, ranging from 19 years to 88years. The mean (SD) Age (in years) for the malignant group was 58.76 (13.09) years and 49.82 (18.02) for the tuberculosis group.

Univariate analysis showed that variables such as pleural fluid LDH, pleural fluid protein and serum LDH were significantly higher in malignant pleural effusion while pleural fluid ADA and pleural fluid lymphocyte count were significantly higher in tuberculous pleural effusion. Both serum LDH: pleural fluid ADA ratio (cancer ratio) and cancer ratio: pleural fluid lymphocyte count ratio (cancer ratio plus) were significantly higher in MPE as shown in Table-1

Table 1: Univariate analysis

Variable	Statistics	Malignancy	Tuberculosis	p-value
Pleural fluid ADA	Mean (SD)	18.14 (10.32)	55.20 (18.84)	<0.0001
Pleural fluid LDH	Mean (SD)	492.95 (304.06)	352.66 (89.16)	0.0093
Serum LDH	Mean (SD)	566.42 (222.70)	377.17 (111.03)	<0.0001
Pleural fluid lymphocyte	Mean (SD)	78.52 (8.77)	87.71 (6.77)	<0.0001
Pleural fluid protein	Mean (SD)	4.76 (0.55)	4.24 (0.48)	0.0003
Cancer ratio	Mean (SD)	35.83 (11.81)	7.92 (4.38)	<0.0001
Cancer ratio plus	Mean (SD)	45.79 (14.10)	9.27 (5.87)	<0.0001

P-value <0.05 is considered statistically significant

ROC analysis was done to derive cut off levels providing best trade-off between sensitivity and specificity for each of the ratios.

Serum LDH: pleural fluid ADA ratio (Cancer ratio): At a cut-off level of >20 the sensitivity and specificity of the cancer ratio were 95.24% and 94.87 respectively. The

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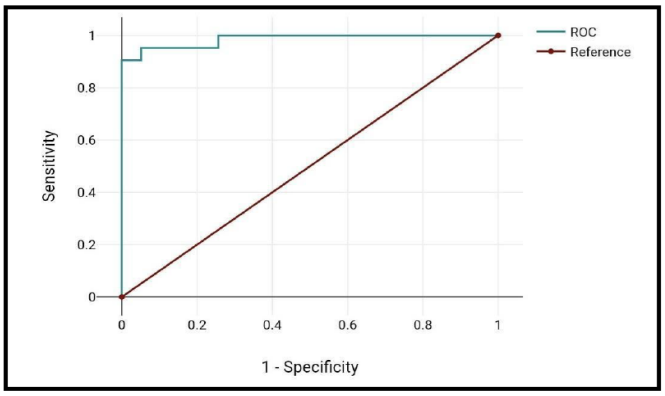
PPV, NPV, PLR, and NLR at this cut-off was 90.91%, 97.37%, 18.37, and 0.05, Table-2. The area under the ROC curve (AUC) was found to be 0.984 (95% CI 0.954-1.000). Figure- 1

Table 2: Statistical analysis for cancer ratio at different cut-off levels

Cut off	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	PLR (95% CI)	NLR (95% CI)
>10	95.24 (76.18-99.88)	79.49 (63.54-90.70)	71.43 (57.23-82.37)	96.87 (81.97-99.53)	4.64 (2.48-8.68)	0.06 (0.01-0.41)
>20	95.24 (76.18-99.88)	94.87 (82.68-99.37)	90.91 (72.10-97.48)	97.37 (84.51-99.60)	18.57 (4.80-71.88)	0.05 (0.01-0.34)
>30	71.43 (47.82-88.72)	100 (90.97-100)	100	86.67 (76.77-92.74)		0.29 (0.15-0.56)
>40	33.33 (14.59-56.97)	100 (90.97-100)	100	73.58 (67.31-79.03)		0.67 (0.49-0.90)
>50	14.29 (3.05-36.34)	100 (90.97-100)	100	68.42 (64.53-72.07)		0.86 (0.72-1.02)
>60	4.76 (0.12-23.82)	100 (90.97-100)	100	66.10 (63.93-68.21)		0.95 (0.87-1.05)

Figure 1: ROC curve for serum LDH: pleural fluid ADA ratio (Cancer ratio)

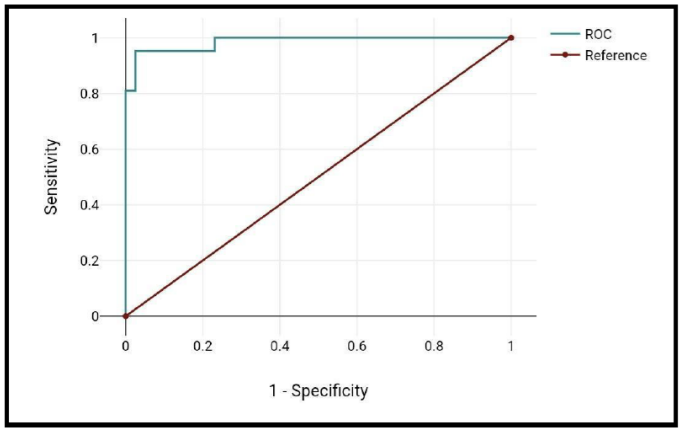


Cancer ratio: pleural fluid lymphocyte count (Cancer ratio plus): At a cut-off level of >30 the sensitivity and specificity of cancer ratio plus were 95.24% and 97.44 respectively. The PPV, NPV, PLR, and NLR at this cut-off was 95.24%, 97.44%, 37.14, and 0.05, Table- 3. The area under the ROC curve (AUC) is 0.982 (95%CI 0.951-1.000). Figure- 2

Table 3: Statistical analysis for cancer ratio plus at different cut-off levels

Cut off	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	PLR (95% CI)	NLR (95% CI)
>20	95.24 (76.18-99.88)	94.87 (82.68-99.37)	90.91 (72.10-97.48)	90.37 (84.51-99.60)	18.57 (4.80-71.88)	0.05 (0.01-0.34)
>30	95.24 (76.18-99.88)	97.44 (86.52-99.94)	95.24 (74.24-99.28)	97.44 (84.87-99.61)	37.14 (5.35-257.71)	0.05 (0.01-0.34)
>40	61.90 (38.44-81.89)	100 (90.97-100)	100	82.98 (73.86-89.37)		0.38 (0.22-0.66)
>50	42.86 (21.82-65.98)	100 (90.97-100)	100	76.47 (69.17-82.48)		0.57 (0.39-0.83)
>60	14.29 (3.05-36.34)	100 (90.97-100)	100	68.42 (64.53-72.07)		0.86 (0.72-1.02)

Figure 2: ROC curve for Cancer ratio plus



Discussion

Diagnosis of MPE usually relies on pleural fluid cytology or pleural biopsy. Cytology is however inexpensive and has high specificity but its sensitivity is only around 0.6. Pleural biopsy is an invasive tool associated with some complications such as pain, subcutaneous emphysema, and bleeding and its accuracy is affected by the experience of the operator and observer.[9] The diagnosis of MPE takes a considerable amount of time and it reduces the quality of lifespan of the people. There is no reliable biomarker to identify malignant effusion. Hence the new biomarkers serum LDH: pleural fluid ADA (Cancer Ratio) and cancer ratio: pleural fluid lymphocyte percentage (Cancer Ratio Plus) were evaluated for identification of MPE.

Age distribution: The mean age at presentation is 52.9 years (range 19-88 years). Though malignancy is more common in the elderly, the possibility of malignancies like leukemia, lymphoma, PNET, etc. in younger age

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groups should be carefully ruled out. The Mean (SD) for the malignant group was 58.76 (13.09) and for the tuberculosis group, it was 49.82 (18.02). This is in accordance with the study done by Asmita A. Mehta et al[6], in which they had studied the exudative effusions, and in contrast to the study by Akash Verma et al[5] in which the mean age for TPE was 69 and for MPE was 56.

Gender: The male participants were 55% (n=33) and the female participants were 45% (n=27). This correlates with the study done by Piotr Korczynski et al [8] where the male and female patients were 54.3% and 45.7% respectively. Initially, lung cancer and associated malignant effusions were more common in men, owing to smoking habits and industrialization. Recently there is a change in the trend where men and women are affected equally, possibly because of the change in lifestyle, habits, and indoor air pollution.

Diagnosis: Out of 60 patients, 39 (65%) had tuberculous pleural effusion while 21 (35%) had malignant pleural effusion. This is in contrast to the study done by Akash Verma et al[5] in which 71.18% were MPE and 28.8% were TPE. In our study out of these 21 MPE, 12 were Adenocarcinoma, 6 were Squamous cell carcinoma, 2 were Small cell carcinoma and 1 was malignant round cell tumor.

Pleural fluid protein: The Mean (SD) pleural fluid protein (g/dl) in MPE is 4.76 (0.55) and in TPE it is 4.24 (0.48). The p-value is 0.0003 and it is statistically significant. This result is in contrast with the pleural fluid protein levels in the study done by Piotr Korczynski et al[8] and Mine Gayaf et al[10] where TPE has higher pleural fluid protein levels than MPE.

Pleural fluid LDH: The mean pleural fluid LDH levels in MPE is 492.95 IU/L with SD of 304.06 and for TPE it is 352.66 IU/L with SD of 89.16. The p-value is 0.0093and it is statistically significant. This is in contrast to the study done by Akash Verma et al[4], Piotr Korczynski et al[8], and Mine Gayaf et al[10] where the pleural fluid LDH levels in TPE were higher than MPE.

Pleural fluid ADA: The mean pleural ADA is 18.14 U/L in MPE with a SD of 10.32 and in TPE it is 55.20 U/L with SD of 18.84. This is statistically significant with ap-value of <0.0001. This result correlates with the ADA levels in many other studies such as Akash Verma et al [4,5], Asmita A. Mehta et al[6], Piotr Korczynski et al[8], D.Jiménez Castro et al[11], Bojan Zarić et al[12] and Nariman A. Helmy et al[13] where the MPE has significantly lower pleural fluid ADA levels compared to TPE. These results re-establish the fact that estimation of ADA level in pleural fluid is extremely helpful in establishing the etiology of tubercular pleural effusion and ruling out other conditions, especially malignancy.

Serum LDH: The mean serum LDH in MPE is 566.42 IU/L with SD 222.70 and in TPE it is 377.17 IU/L with SD 111.03. The p-value is <0.0001 and it is statistically significant. This result correlates with the values in the study done by Akash Verma et al[4] and Piotr Korczynski et al[8], where the serum LDH levels were comparatively higher in malignancy than in tuberculosis. Also in the study done by Dong Soo Lee et al[14], they observed that most of the malignancy falls under the group with LDH >450U/L. The proposed explanation for the rise in serum LDH in malignancy because the cancer cells use LDH to increase their anaerobic metabolism (glycolysis and ATP production, and lactate production) even in the presence of oxygen. This process is known as the Warburg effect. The abnormal cancer cells benefit from switching to anaerobic metabolic phenotype by avoiding the generation of oxidative stress by the ETC. Additionally; the cancer cells also gain access to the metabolic intermediates of the tricarboxylic acid cycle, generated

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through glucose and pyruvate, to synthesize lipids and nucleic acid for rapid cell proliferation[15].

Pleural fluid lymphocyte counts: The mean pleural fluid lymphocyte count is 78.52 %for MPE and 87.71 % for TPE. The p-value is <0.0001 and it is statistically significant. These levels correlate well with the results of the study done by Lung T.Yam et al[16] and Akash Verma et al[5]. With these results, it is observed that, though both MPE and TPE are exudative lymphocytic effusions, the lymphocyte percentage varies. In TPE most of the samples were above 75%, whereas in MPE it is between 50 to 80 %. The proposed mechanism for higher lymphocyte count in TPE is the interaction between Mycobacterium tuberculosis and the human immune system, causing hypersensitivity reaction to mycobacterial proteins in the pleura[5]. This finding formed the basis of the formulation of cancer ratio and cancer ratio plus owing to the reciprocal change seen between pleural fluid lymphocyte count and serum LDH and pleural ADA in malignant pleural effusion.

Serum LDH: pleural fluid ADA (Cancer Ratio): The Mean (SD) for cancer ratio is 35.83 (11.81) for MPE and 7.92 (4.38) for TPE with a p-value of <0.0001 which is statistically significant. ROC derived cut-off value >20 has a sensitivity of 95.24%, specificity of 94.87%, PPV of 90.91%, NPV of 97.37%, PLR of 18.57, and NLR of 0.05 for identification of malignant pleural effusion. Our results are in accordance with the study done by Akash Verma et al[5] in which at cut-off level >20, the sensitivity, specificity, PPV, NPV, PLR, and NLR were 95%, 85%, 94%, 87%, 16 and 0.13 respectively. Our results differ from this study in having higher specificity and NPV. Similar observations were seen in the study by Piotr Korczynski et al[8], in which at a cut-off level >16.4, the sensitivity was 94.6% while specificity was only 68.2% Our results were in contrast to the study done by Mine Gayaf et al[10] where at cut-off value >12.13 cancer ratio had a sensitivity of 89.1% and much lower specificity of 82.2% in the differentiation of MPE from TPE. Also, PPV and NPV were 91.8% and 77.1%, lower than the results of our study.

Cancer ratio: pleural fluid lymphocyte count (Cancer Ratio Plus): The Mean (SD) for cancer ratio plus is 45.79 (14.10) for MPE and 9.27 (5.87) for TPE with a p-value of<0.0001 which is statistically significant. ROC derived cut off value >30 has as ensitivity of 95.24%, specificity of 97.44%, PPV of 95.24%, NPV of 97.44%, PLR37.14, and NLR 0.05 for identification of malignant pleural effusion. Our results are in accordance with the study done by Akash Verma et al[5] in which at cut-off level>30, the sensitivity, specificity, PPV, NPV, PLR, and NLR were 97.6%, 94.1%, 97%,84%, 41 and 0.06 respectively. Our results were in contrast to the study done by Mine Gayaf et al[10] where at cut-off value >36.88 cancer ratio plus had much sensitivity of74.3% and specificity of 88.9% in the differentiation of MPE from TPE. Also, PPV and NPV were 93.7% and 60.6%, lower than the results of our study.

We observed that serum LDH is raised in malignancy while there are low levels of pleural fluid ADA in MPE which is in accordance with several earlier studies. Hence combined use of serum LDH and pleural fluid ADA and formulation of Cancer Ratio as a biomarker remain a useful test for early identification of malignant pleural effusion with good sensitivity and specificity compared to other available biomarkers such as CEA, CA15-3, CA125, and cyfra 21-1 which are having sensitivity and specificity of 65% and 97%, 57% and 90%, 68% and 83%, 53%, and 79%respectively.[5]

From the above discussion, we can state that serum LDH: pleural fluid ADA (Cancer Ratio) and cancer ratio: pleural fluid lymphocyte percentage (Cancer Ratio Plus)

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are biomarkers with high sensitivity and specificity for identification of MPE.

Limitations

This is a single-center observational study with a limited sample size which includes lymphocytic exudative pleural effusions. Neutrophil predominance was seen in around 8% MPE, which should be further evaluated. Lymphoma-related MPE has high levels of ADA and can mimic TPE and alter the results, hence further studies with higher sample sizes and inclusion of lymphoma and other extra pulmonary malignancies are needed to validate our results. In this study, the diagnosis is either malignancy or tuberculosis, but there are many other differentials of lymphocytic exudative pleural effusion such as connective tissue diseases, empyema, chylothorax, pulmonary embolism, etc. A larger study with the inclusion of various differential scan give better results.

Conclusion

Early and precise diagnosis of malignant pleural effusion is important as the pleural effusions associated with malignant conditions have a poor prognosis. Results of our study suggested that serum LDH: pleural fluid ADA ratio (Cancer ratio) and cancer ratio: pleural fluid lymphocyte count ratio (cancer ratio plus) are biomarkers with high sensitivity and specificity for the identification of MPE and they are simple, cost-effective, reliable, and easily available biomarkers that may help in the early identification of MPE in people with exudative lymphocytic pleural effusions and can be used in routine clinical practice.

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