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ORIGINAL ARTICLE

To Study the Utility of Cancer Ratio (Serum LDH: Pleural Fluid ADA Ratio) in Identifying Malignant Pleural Effusion in Central Rural India

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ABSTRACT

In this study we tried to evaluate the diagnostic ability of Cancer ratio in patients of exudative pleural effusion. Malignant and Tubercular pleural effusion are the two most common exudative pleural effusion encountered. Both of them can present with similar clinical and radiological features. A diagnostic tool that can differentiate between them early is awaited since long time.

Methods: This is study of pleural effusion (exudative) in patients admitted in Department of Respiratory Medicine

Results: LDH levels in serum and ADA levels in pleural fluid, their ratio which will be known as "Cancer Ratio". Pleural fluid ADA is assumed to be negatively correlated with malignant effusion, on the other hand serum LDH with Serum LDH: pleural fluid ADA ratio to be positively linked with patients of malignant pleural effusion.

Conclusion: Serum LDH: pleural fluid ADA ratio will distinguish malignant from non-malignant effusion. This can be done very early after admission or on outpatient basis and can yield result as early as within one hour of admission. This is one of the pioneer study in India.

KEYWORDS:

• Pleural effusion (PE) • Lactate dehydrogenase (LDH) • Adenosine deaminase (ADA)

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INTRODUCTION

Pleural effusion is commonly encountered in the practice of Respiratory Medicine. Light's Criteria is used to differentiate between exudative and transudative pleural effusion.[1] Pleural involvement in tuberculosis has been reported in approximately 5% of all Tuberculosis (TB) patients.[2] Pleural effusion is the second most common form of extra pulmonary tuberculosis, first being Lymph node TB.[3] Frequency of Tubercular pleural effusion is variably reported from 4% in US to 23% in Spain.[4]

Malignant pleural effusions (MPE) constitute the second most common cause of exudative pleural effusions in the developing countries[5] and most common in developed countries, where the incidence of tuberculosis is low. About 50 to 65% of MPE are associated with lung and breast cancer, while 25% are associated with lymphoma, gastrointestinal and genitourinary cancers.[6]

Once a diagnosis of Pleural effusion is made radiologically, Thoracocentesis is performed and further biochemical workup to determine pleural fluid pH, ADA, LDH, protein, sugar, cytology and fluid culture is done to make a diagnosis. If the diagnosis is inconclusive then pleural biopsy is attempted. The yield of pleural fluid cytology is limited and biopsy is an invasive procedure with serious complications like pneumothorax and is also not available everywhere especially in rural setups.

Tubercular and Malignant pleural effusions have very similar clinical and radiological presentation. Both can present with cough, fever, loss of weight and appetite and hemoptysis. Malignancy is mostly seen in elderly patients but due to high prevalence of Tuberculosis it is also commonly seen in elderly age groups. Many times the biochemical tests are inadequate to differentiate between them. Tubercular effusion generally have a good prognosis and responds well to Anti Tubercular Treatment if diagnosed in time and prompt treatment is initiated. On the other hand Malignant pleural effusion carries a poor prognosis. Thus it is extremely important to discriminate Malignant effusion from others. Timely detection and early treatment can increase the 5 year survival in a cancer patient.

ADA is an enzyme in the purine catabolism by catalysing deamination of adenosine into inosine and deoxyadenosine into deoxy inosine. A raised ADA level is seen in Tubercular pleural effusion.[7] ADA levels of more than 40U/L is estimated to be for Tubercular effusion. However there is no authentic marker to aid the diagnosis of Malignant effusion. So many times the Malignant effusion remains undiagnosed or is diagnosed very late and prompt treatment is not started on time. A marker is needed that can detect malignant effusion early, which is time saving and cost effective.

Serum Lactate Dehydrogenase is an enzyme which is raised when there is tissue damage. It is raised in conditions like sepsis, cancer, hemolysis, HIV infection etc.[8] It is said to be raised in Malignancy as cancer cells uses glycolysis pathway instead of oxidative phosphorylation for energy production. LDH is an enzyme raised during anaerobic respiration.[9] As tumour cells are rapidly dividing they start undergoing anaerobic metabolism to meet their energy demands as aerobic pathways gets over engaged.

In his study we combined two markers with high sensitivity and specificity to derive a new indicator to differentiate between malignant and tubercular effusions. We analysed Serum LDH: pleural fluid ADA ratio as predictor of malignant pleural effusion and described it as a ''cancer ratio'' and will utilize it to discriminate between Tubercular and Malignant pleural effusion. It's utility is compared with the pre-existing ones.

MATERIAL AND METHODS

The cross-sectional study with 82 inpatients enrolled. The purpose of the study was to determine Cancer Ratio (Serum LDH: Pleural fluid ADA).

Patients were subjected to following within 24 hours of admission Serum LDH/protein/sugar Sputum AFB/CBNAAT/Cytology, Chest x-ray, Thoracocentesis / ICD tube, Pleural fluid cytology / ADA / Ph / protein / sugar / TLC / DLC, Pleural biopsy / CT or USG guided biopsy and Written informed consent.

SPSS, version 16; was used for statistical analyses. The results were compared using a Wilcoxon two-sample test or Fisher exact test. P values were two sided and considered indicative of a significant difference if <0.01.

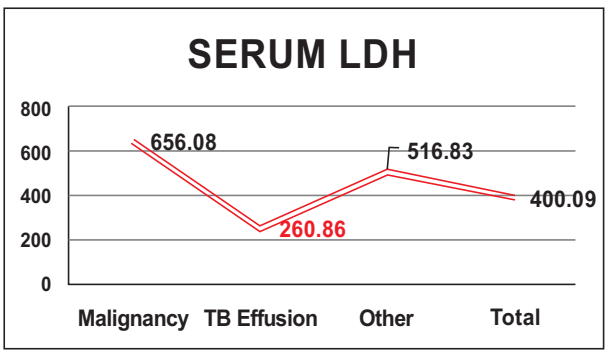
OBSERVATIONS AND RESULTS

82 patients participated out of which 51 had tubercular pleural effusion and 25 had malignant pleural effusion while 6 had exudative effusion due to other cause like pancreatic disease, parapneumonic effusion, connective tissue disease etc. Tuberculosis was found to be the leading cause giving rise to exudative pleural effusion followed by Lung cancer.

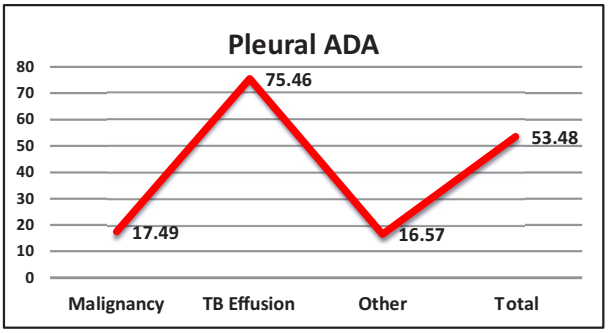
The mean age of the patients was 47.44 ± 14.67. In younger age group ie less than 50 years of age the predominant diagnosis is of tubercular effusion and in the age group of above 50 years both malignant and tubercular effusion is seen. Out of 25 malignant patients 11 were females and 14 were males and out of 51 tubercular patients 11 were females and 40 were males. Out of 25 Malignant Effusion patients 17 were of Adenocarcinoma (68%), 7 were of Squamous cell carcinoma (28%) while 1 was of Small cell carcinoma (4%).

Serum LDH was found to be elevated in patients of Malignant Effusion, Serum LDH was more than 280 in 20 out of 25 patients (80%). On the other hand Serum LDH was less than 280 in 38 out of 51 tubercular patients (74.5%). This was statistically significant with p value less than 0.001Average value in malignant effusion patients is 656 and in tubercular patients was 260.

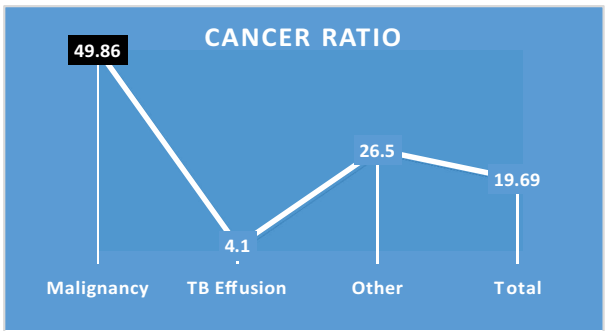
In patients of diagnosed malignant pleural effusion the value of pleural fluid ADA is found to be less than 40 in 21 (84%) out of 25 patients. In Tubercular Effusion 42 out of 51 (82.3%) patients showed value between 40 to 100. The average pleural fluid ADA in Malignant pleural effusion patients is 17.49 while that in tubercular effusion patient is found to be 75.46.



Graph 1: Average serum LDH



Graph 2: Average pleural fluid ADA

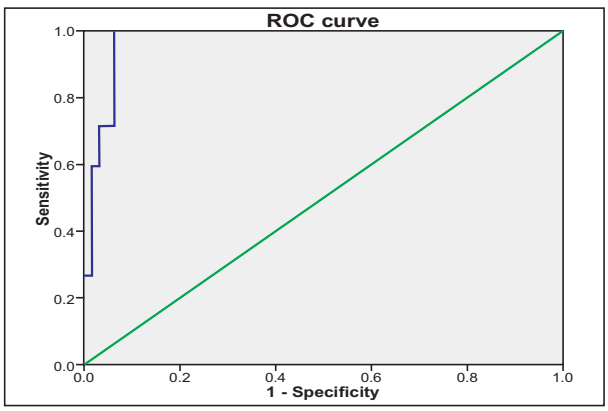


Graph 3: Shows average value of Cancer ratio

Out of 25 patients of malignant pleural effusion 10 patients had cancer ratio of more than 50 i.e. 40% while 13 (52%) had Cancer Ratio between 20 to 50. 2 out 25 patients i.e. 8% had Cancer Ratio between 11 to 20 while none of the patient diagnosed with Malignant Pleural effusion had Cancer Ratio of less than 10. 100% of Tubercular Effusion patients had Cancer Ratio below 10. In Malignant Pleural Effusion the mean value is 49.86 while mean value in Tubercular Effusion is 4.1.

Table 1: Sensitivity and Specificity of Cancer ratio as compared serum LDH and pleural fluid ADA compared to Cancer ratio

	Sensitivity	Specificity
Serum LDH	80%	68.42%
Pleural fluid ADA	84%	75%
Cancer Ratio	92%	96%



Graph 4: ROC curve

Table 2: Area under the curve

Area	Std. Errora	Asymptotic Sig.b	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.971	0.017	< 0.001	0.938	1.003

ROC (Receiver Operating Characteristic) curve for Cancer Ratio is calculated using SSPS 16 software and area under the curve is calculated using Trapezoid method.

Area under the ROC curve is calculated to be 0.971 with standard error of 0.017 at a confidence interval of 95%. The upper bound being 1.003. In his study AUC of ROC curve is 0.971, which shows that Cancer ratio has 97.1% chance to differentiate between malignant and non malignant pleural effusion.

Cancer ratio was found to be higher in Cytology positive cases of Malignant effusion. The average ratio in cytology positive cases was 54.8 while in cytology negative cases was 43.5 and average ratio in study being 49.8. Higher the cancer ratio better are the chances of pleural fluid cytology coming positive and better is the yield of cytology.

Cancer ratio was higher in Closed pleural biopsy positive cases of Malignant effusion. The average ratio in biopsy positive cases was 53.3 while in negative cases was 40.8 and average ratio in study being 49.8. Higher the cancer ratio better are the chances of closed pleural biopsy to yield a result.

Table 3: Mean values of various parameter diagnosis wise:

Factors	Malignancy	TB Effusion	Other	Total
Serum LDH	656.08 ± 504.38	260.86 ± 124.89	516.83± 431.41	400.09 ± 360.46
Serum Protein	6.46 ± 0.87	6.85 ± 0.95	6.52 ± 0.66	6.70 ± 0.92
Serum Glucose	109.60 ± 35.52	118.14 ± 58.08	101.17 ± 14.12	114.29 ± 49.97
Pleural LDH	1189.04 ± 1934.37	2330.08 ± 7007.55	852 ± 472.13	1874.05 ± 5638.06
Pleural Protein	4.06 ± 1.25	4.73 ± 1.42	3.80 ± 1.48	4.45 ± 1.4
Pleural Glucose	71 ± 43.44	72.94 ± 84.28	61 ± 57.84	71.48 ± 71.83
Pleural ADA	17.49 ± 13.58	75.46 ± 44.27	16.57 ± 8.66	53.48 ± 45.54
Cancer Ratio	49.86 ± 35.23	4.1 ± 1.87	26.5 ± 21.24	19.69 ± 28.9

Table 4: Logistic Regression Analysis for the prediction of malignancy:

Factors	Coeffcient	Odd ratio	p-value
Serum LDH	0.473	1.005 (1.002 ± 1.008)	<0.001 S
Serum Protein	- 0.18	0.642 (0.374 ± 1.101)	0.107 NS
Serum Glucose	- 0.063	0.997 (0.987 ± 1.008)	0.574 NS
Pleural LDH	- 0.081	1.00 (1.00 ± 1.00)	0.52 NS
Pleural Protein	- 0.19	0.744 (0.528 ± 1.048)	0.09 NS
Pleural Glucose	- 0.004	1.00 (0.993 ± 1.007)	0.968 NS
Pleural ADA	- 0.527	0.908 (0.868 ± 0.95)	<0.001 S
Cancer Ratio	0.696	1.148 (1.076 ± 1.225)	<0.001 S

The "p value" is calculated to be significant (i.e. less than 0.001) for serum LDH, pleural fluid ADA and cancer ratio.

DISCUSSION

Incidence of pleural effusion is approximately around 400 per 100,000 population.[10] Pleural effusion is diagnosed based on history, clinical presentation, radiological findings on X-ray chest, USG Thorax and HRCT (as indicated).

Malignancy was diagnosed by pleural fluid cytology or pleural biopsy or CT or USG guided biopsy or FNAC from the mass lesion. Diagnosis of tubercular pleural effusion was done by pleural fluid AFB or cytology or culture or CBNAAT or Pleural biopsy.

Out of 81 patients in this study Tubercular pleural effusion is diagnosed in 63% of subjects followed by malignant pleural effusion in 31%. High incidence of Tubercular pleural effusion is due high prevalence of Tuberculosis in India.[11]

The mean age of the study participants was 47.44 ± 14.67 years. The maximum incidence of patients of Malignant effusion were above 51 years of age (64%) and none of the patient was below 25 years of age. The results of this study is comparable with a study performed by Groot *et al.*[12] Lung cancer is mostly seen in elderly population above the age of 65 years.[13] On the other hand tuberculosis incidence was seen in all the age categories but majority of tubercular effusion were in the age group of 25-50 and 51-75. Similar result were obtained by Zhang *et al.*[14] Due to high prevalence of tuberculosis, it is observed in all the age groups but 25-65 years being the most common age group.[15]

Serum LDH (lactic dehydrogenase) is an enzyme that rises in malignancy and many other conditions like fracture, heart failure,

sepsis etc. Verma et al reported a higher serum LDH levels in Malignant pleural effusion than in Tubercular effusion.[16] Similar result is found in the present study. A high serum LDH is due to fast dividing cancer cells shift to glycolysis from oxidative phosphorylation for their ATP production, this is mediated by LDH. Purnamasidhi *et al* have in a study reported high levels of LDH associated to substandard chemotherapy respond and guarded prognosis in patients of cancer.[17] Serum LDH as a diagnostic and prognostic marker has also been reported by Forkasiewicz *et al*.[18] Present study revealed the sensitivity of serum LDH to diagnose malignant pleural effusion is 80% and specificity is 68.42%, with Positive Predictive Value (PPV) of 52.6% and Negative Predictive Value (NPV) of 88.64%. Cancer ratio on the other hand has a high sensitivity (92%) and specificity (96.4%) compared to serum LDH alone.

Enzyme ADA is involved in purine catabolism. It does deamination of adenosine to inosine and deoxyadenosine to deoxy-inosine. ADA2 is raised in TPE and ADA1 is raised in empyema. Though ADA2 is a better marker of tuberculosis, in practice, total ADA is used and not isoform ADA2. There is an advantage in calculation of total ADA because of low cost and fast turnover time.

ADA activity is raised in TPE.[19] Goto el al also in their study found a higher ADA levels in TPE and concluded that "the test performance of ADA in tuberculous pleural effusion is reasonably good".[20] Aggarwal *et al* in a meta analysis revealed that the cut off value of ADA is 40-45 U/L is indicative of Tubercular effusion.[21] In present study most of the patients of TPE had value of ADA above 40 U/L. The average value in our study for TPE is 75.46 U/L and that in MPE is 17.49 U/L.

Sensitivity & specificity in our study for ADA to diagnose tubercular pleural effusion is 82.3% and 83.9% respectively. High ADA i.e. value more than 40 is suggestive of Tubercular effusion.

Pleural fluid ADA has a negative correlation for diagnosing malignant effusion, that means lower the value of ADA higher the chances for malignant effusion. For ADA value of less than 40 U/L the sensitivity of ADA for diagnosing MPE is 84% and specificity 75%. In a study by Korczyński *et al*[22] determined sensitivity & specificity of 97.3% and 68% respectively for ADA to determine malignant effusion. Sensitivity and Specificity of Cancer ratio in this study in diagnosing malignant effusion is 92% and 96% respectively while pleural fluid ADA has 84% and 75%.

Cytology offers the advantage of being inexpensive with greater specificity, but the sensitivity remains approximately at 0.6. In a study by Sahn *et at* sensitivity of pleural fluid cytology was 66%.[25] In different studies by Grunze *et al*[26] and Bueno *et al*[27] the accuracy of cytological diagnosis of MPE is reported between 40% and 87%. In this study diagnostic accuracy of pleural fluid cytology to diagnose MPE is 56%.

In our study the average value of cancer ratio in pleural fluid cytology is 54.8 compared to the mean value of 49.86. Higher the cancer ratio, more are the chances for cytology report coming positive for malignant pleural effusion.

The next most widely employed diagnostic aid for MPE is Pleural biopsy, but is an invasive technique involving certain complications of pain, bleeding and subcutaneous emphysema. Also, the operator's and observer's experience significantly affects its accuracy[29] In a review, 2,893 biopsies, yield was 57% in MPE and 75% with TPE.[25] Factors like stage of Malignancy, site of biopsy, number of biopsies play an important role to determine the yield of closed lung biopsy.[30] complications, and patient experience with thoracocentesis. Pleural fluid analysis in conjunction with the clinical presentation placed 78 pleural fluids into diagnostic categories: definitive 14 (18 percent In the present study the diagnostic yield of pleural biopsy to detect MPE is 68%. Equivocal results found by Rajawat el al in their publication where yield of pleural biopsy was 64.40%.[31]

Higher value of CR was found in case in which closed pleural biopsy was positive. The average CR in patients of MPE was 49.8 and in biopsy positive cases was 53.3. More is the cancer ratio, it is more likely to be detected on cytology or biopsy.

In the study 100% patients of Tubercular effusion had Cancer Ratio of less than 10. In the patients of Malignant pleural effusion none of the patient's Cancer Ratio of less than 10, 8% patients had Cancer Ratio between 10 to 20 and 92% had values above 20. The average value of Cancer Ratio in patients of Malignant Pleural effusion in this study is 49.86 while

that of Tubercular effusion is 4.1. The study of Dalia E. ElSharawy[32] showed "cancer ratio validity (serum LDH/pleural ADA)" as a non invasive tool for differentiation of MPE. from lymphocytic types with their findings presented at cut off values >22, and 91.5% sensitivity, 87.5% specificity, 93.4% "Positive predictive value and 84% negative predictive value". The overall accuracy accounted to 90.1% with AUC of 0.947. Similar findings were found in the study of Verma *et al*[16] with ROC derived cut of values of > 20 for "cancer ratio" yielding sensitivity of 95%, specificity of 85%, P L R of 16 and N L R of 0.13.

In separate studies by Verma et al[16] in 2016 in Singapore showed Sensitivity of 0.98 and specificity of 0.94, a study by Zhang *et al*[33] in 2016 in China showed a sensitivity of 0.94 and specificity of 0.73, by Elmsahalawy et al[32] in Egypt in 2107 showed sensitivity and specificity of 1.0 and Korczyński *et al*[22] in 2108 in Poland demonstrated sensitivity of 0.95 and specificity of 0.68. Similar values were demonstrated in the present study. The sensitivity was found to be 0.92 and specificity of 0.96 at confidence interval of 95%.

CONCLUSION

Cancer ratio can help differentiate between malignant and tubercular effusion without need for any extra investigation or test. It is cost effective and the results can be obtained as within one hour of admission to hospital. This can guide the treating physician about further management of pleural effusion and give an idea about the origin of the effusion. Cancer ratio can also predict the outcome of histopathological investigation. In India this is the pioneer study.

Conflict of Interest: The authors declare no conflict of interest.

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