Journal of
Cardio - Thoracic Medicine

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Utility of Cancer ratio (serum LDH: pleural fluid ADA) for predicting malignancy in patients with exudative pleural effusion

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ARTICLEINFO

Article type:
Original Article

Article history:
Received: 10 April 2021
Revised: 20 May 2021
Accepted: 05 June 2021

Keywords:
Cancer Ratio
Pleural Effusion
Malignancy
Exudates

ABSTRACT

Introduction: Pleural effusion is an accumulation of fluid in the pleural space. It can be transudative or exudative. Mechanisms like alteration in Starling's forces lead to transudative effusions while inflammation and infiltration by infections, malignancy, connective tissue diseases, etc lead to exudative effusions. Tuberculosis, viral, bacterial infections, and malignancy are common causes of exudative effusions whereas congestive heart failure, renal failure, and liver failure, etc are common causes of transudative effusions. Nearly 40% of patients with malignancy have pleural effusion at the time of presentation. Bronchogenic carcinoma, carcinoma of the breast, lymphoma are the leading causes of malignant pleural effusion (MPE) followed by gastrointestinal, genitourinary, and gynecological causes. Pleural fluid Adenosine DeAminase (ADA) has good diagnostic sensitivity and specificity for tuberculosis whereas pleural fluid cytology /biopsy are the main diagnostic modalities for MPE. However pleural fluid cytology is positive in only 48.5% of cases in the first sample but the yield increases with repeated analysis or other more invasive investigations like blind pleural biopsy/thoracoscopy. In cases with negative pleural fluid cytology, a biochemical marker known as Cancer ratio i.e serum LDH and pleural fluid ADA can be useful in predicting malignant causes. A cancer ratio cutoff of more than 20 helps in guiding the physician for further workups like FDG PET or tumor markers in evaluating malignancies. With this background our study aimed at the usefulness of cancer ratio in patients with exudative pleural effusion.

Materials and Methods: It's a cross sectional observational study done for a period of 18months.100 adult patients with exudative pleural effusions were recruited into the study. Those who didn't give consent, hemodynamically unstable, whose diagnosis is known were excluded. Serum LDH, pleural fluid ADA were done in all cases and the cancer ratio is validated for diagnosis of malignant effusions.

Results: The mean age of patients was 55.48±9.32 years. There were 57 malignant and 43 nonmalignant cases. Bronchogenic carcinoma was the leading cause of MPE and tuberculosis was the commonest cause of non-malignant pleural effusions. Mean serum LDH, Pleural fluid ADA, and cancer ratio in malignant cases and nonmalignant cases was 434.54 and 350.04IU/ml,19.05 and 32.97IU/ml and 25.13, 20.45 respectively. The sensitivity of cancer ratio was 70.17%, specificity was 76.74%, Positive predictive value was 80% and Negative predictive value was 66.6%.

Conclusion: Cancer ratio is an easy and valid diagnostic tool in suspecting malignant pleural effusions with good sensitivity and specificity.

►*kakarla, B., K, V., Deme, S., B, S., N, N., GK, P. Utility of Cancer ratio (serum LDH: pleural fluid ADA) for predicting malignancy in patients with exudative pleural effusion . J Cardiothorac Med. 2021; 9(2):* 817-823

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Introduction

Pleural effusion is a common medical condition with many possible underlying aetiologies. In countries like India with a high incidence of tuberculosis(TB), pleural effusion is the most common cause of lymphocytic pleural effusion followed by malignancy, lymphoma, connective tissue diseases, and chylothorax (1,2,3).

Neutrophilic predominant exudative effusions are due to acute processes like pneumonia or acute pulmonary embolism (4).

Approximately 20% of all pleural effusions are caused by neoplastic processes. Pleural metastases, which can occur during the evolution of all neoplasm types, are frequent in lung and breast cancers and are generally associated with diminished survival expectancy. In about 7%–15% of cases, the primary site of the metastatic tumor might not be identified even after extensive diagnostic investigation (5, 6).

The presence of tumor cells in pleural fluid or tissue defines the effusion as malignant. Although pleural fluid cytology is more sensitive than closed pleural biopsy, its sensitivity of 50%–60% is still insufficient for making clinical decisions and usually, the diagnosis is made in the remaining cases with the use of more invasive techniques such as thoracoscopy or thoracotomy. Other mechanisms of pleural effusion like nonspecific inflammatory effusion secondary to subpleural intraparenchymal lung tumor, lymphatic vessel obstruction, or immune-mediated inflammation can explain the failure of a cytology examination to provide a diagnosis (7).

In the latter scenario, the availability of rapid and reliable proof of malignancy by less-invasive procedures is a constant goal, especially in the case of patients who have a prior history of cancer and who develop pleural effusion during follow-up. Biomarkers like Adenosine deaminase(ADA), Lactate dehydrogenase(LDH), glucose, amylase, cholesterol, C- reactive protein (CRP), procalcitonin, interferon-gamma, polymerase chain reaction (PCR), etc. have been evaluated for their role in the etiological evaluation of exudative effusions along with several tumor markers like carcinoembryonic antigen (CEA), cancer antigen (CA)- 125, CA 15-3, CYFRA 21-1 which have low sensitivity (<30%) at their cutoff values of 100% specificity. All tumor markers mentioned above, even if combined, have the same sensitivity of pleural fluid cytology (approximately 50%) (8).To study these tumor markers in all cases of exudative pleural effusions would be expensive and may or may not help in diagnosis. So there is a need to find newer methods for diagnosing malignant pleural effusions.

Adenosine deaminase (also known as adenosine aminohydrolase, or ADA) is an enzyme involved in purine metabolism. It plays an important role in lymphoid cell differentiation. A pleural fluid ADA level greater than 40 U per L has a sensitivity of 90 to 100 percent and a specificity of 85 to 95 percent for the diagnosis of tuberculous pleurisy. (9, 10-13). Often low levels of ADA are used as a surrogate indicator of malignant effusion while waiting for cytology results. This is compounded by the low yield of cytology which is 50 % for malignant effusion (14-16). Lactate dehydrogenase (LDH) is a ubiquitous enzyme that catalyzes the conversion of lactate to pyruvate. Generally, the upper limit of normal for adults is in the range of 280 units/liter. Serum LDH can be elevated in numerous clinical conditions, such as hemolysis, cancer, sepsis, human immunodeficiency virus infection, and many others in a nonspecific manner (17). Its diagnostic and prognostic role has previously been reported mainly as a marker of poor outcomes in sepsis and cancer patients (18-26). The proposed explanation for its rise in cancer is the preferential use of glycolysis for energy, (instead of oxidative phosphorylation) by tumor cells, which is mediated by LDH (27, 28). However, the diagnostic potential of this simple clinical biomarker for malignant pleural effusion has not been reported. Since it is routinely done as part of the well-established initial workup of pleural effusion in all patients hospitalized for it, we did the current study to evaluate if its level on admission can also be utilized to discriminate between malignant and nonmalignant effusions in the form of cancer

ratio i.e Serum LDH:Pleural fluid ADA. AkashVarma et al retrospectively studied the role of serum LDH and pleural fluid ADA ratio in exudative effusions and found it to be a good distinguishing marker between malignant and nonmalignant pleural effusions. A cut-off ratio of above 20 had good sensitivity and specificity in diagnosing malignant pleural effusions (29).Our study aimed at further validating the ratio in exudative pleural effusions. To study the role of cancer ratio (Serum LDH / Pleural fluid ADA) in predicting malignancy in patients with exudative pleural effusion.

Materials and Methods

This study was conducted in the Department of Pulmonary Medicine, Nizams Institute of Medical Sciences, a tertiary care center, Hyderabad. This is a cross-sectional observational study conducted for a duration of one and half years from March 2016 to September 2017.250 patients were screened and 100 patients who fulfilled the inclusion criteria were included in the study after taking informed consent. Patients with transudative pleural effusion, patients who are on treatment with documented cause for pleural effusion, hemodynamically unstable patients, and those with coagulopathies were excluded. All the cases were routinely investigated with chest x-ray, computerized tomographic scan (CT) and were further investigated by needle thoracocentesis for pleural fluid ADA and venous blood to determine the serum LDH levels. The ratio of serum LDH to pleural fluid ADA was calculated and suspected cases with a value of more than twenty were further screened with relevant investigations, which are more likely to establish the diagnosis or to rule out malignancy. In cases, those who have pleural deposits on imaging, with negative results in cytology were subjected to pleural biopsy by using Abram's needle under CT, ultrasound guidance, or medical thoracoscopy to determine the usefulness of cancer ratio(serum LDH to pleural fluid ADA levels) in the prediction of malignancies.

Statistical Analysis

Sample size was calculated based on

$$k = \frac{(\alpha+ß)^2*(sd1^2+sd2^2)}{(\mu1-\mu2)^2}$$

Where alpha= 1.9608, where (1-a) (ß) =0.8416, SD1=std.dev of group1, SD2=std.dev of group2, μ1=mean of group1, μ2=mean of group2.

Data has been collected and stored in excel sheets with password protection. Thus collected data has been analyzed at the end of the study for descriptive statistics. Continuous variables are expressed as means and categorical variables are expressed as percentages. Validation has been done with sensitivity, specificity, positive predictive value, negative predictive values, and positive and negative likelihood ratios.SPSS® software was used for statistical analysis.

Results

In our study age of patients ranged from 18-90 years and most of them were in the age group of 51-70 years. Among the total number of patients, 53 were males and 47 were females. There were 57(57%) malignant and 43 (43%) nonmalignant effusions. Among malignant cytology positive patients, 27 were males, (47.30%) and 30 were females (52.70%).89% of patients with malignant pleural effusion, 86% of patients with nonmalignant pleural effusion presented with cough. No difference was observed in the cough as a presenting symptom between the two groups. Shortness of breath was the presenting feature in 94.70% of patients with malignant pleural effusion and 81.40% of patients with nonmalignant pleural effusion. Fever was the presenting symptom in 58% of patients with malignant pleural effusion while 72% of patients with nonmalignant pleural effusions had fever indicating that it's more common in nonmalignant effusion. Among nonmalignant pleural effusions, tuberculous effusions were the most common variant in 19/43 (44.2%) followed by synpneumonic effusions in 13 (30%) and undiagnosed in 7 (16%) patients. Among various types of malignant and para malignant pleural effusions, adenocarcinoma of the lung was the most common cause in 23/57 cases (40%), followed by unknown primary in 9(15%) and squamous cell carcinoma in 8

cases (14%).In patients with malignant pleural effusion 15.70% & 10.50% had hypertension and diabetes mellitus respectively. In the nonmalignant pleural effusion group, 11.62% were hypertensives, and 16.20% were diabetics. There was no statistically significant difference (p-value 0.80) in comorbid status between these two groups. only 17.6% of MPE patients were smokers whereas 34.80% non-MPE were smokers, an interesting and paradoxical finding related to smoking prevalence. This can be explained by the significant number of female patients in MPE. Mean protein value in MPE and was 4.17± 0.92 gm/dl& 3.78± 0.48 gm/dl respectively.

In comparison mean pleural fluid protein value was higher and statistically significant in malignant pleural effusions than nonmalignant pleural effusions. (p=0.015). Mean pleural fluid glucose value in MPE and non MPE was 76.54 ±23.30 mg/dl & 85.02 ± 25.80 mg/dl and the difference was statistically significant (p=0.08).The mean value of serum LDH levels in patients with malignant pleural effusion and nonmalignant pleural effusion was 434.54±135.59IU/L & 350.04±80 IU/L respectively. The mean value of serum LDH levels was significantly higher in patients with malignant pleural effusion (p=0.0004). The mean value of pleural fluid ADA levels in patients with malignant pleural effusion and nonmalignant pleural effusion was 19.056± 6.39IU/L &32.9±21.29IU/L respectively. The mean value of pleural fluid ADA level was significantly higher in patients with malignant pleural effusion (P=0.00001). Cancer ratio of more than 20 was seen in 50 patients (Malignant 40,nonmalignant 10) and less than 20 was in 50 patients (Nonmalignant 33 and malignant 17 patients)(Table 1).The mean value of cancer ratio (Serum LDH/Pleural fluid ADA) in patients with malignant pleural effusion was 25.134 and in patients with nonmalignant pleural effusion is 20.451. The cancer ratio was significantly higher in patients with malignant pleural effusions (Figure 1)(Table 2) with a sensitivity of 70.17%, specificity of 76.74%, a positive predictive value of 80%, and a negative predictive value of 66.6%, positive likelihood ratio of 0.46 and negative likelihood ratio was 0.38(p value <0.0000).

Table 1: Cancer ratio validation among malignant and non-malignant pleural effusions

	Malignant	Non malignant
Cancer ratio>20	40	10
Cancer ratio<20	17	33

Discussion

Cancer ratio is the ratio of serum LDH and pleural fluid ADA. ADA level is known to be low in malignant effusion. However, it is not appropriate to use these low levels to diagnose malignant effusion due to a lack of linear biochemical relationship between them. Serum LDH, however, is high in malignancies and is a well-known finding. Thus theoretically, the serum LDH: Pleural fluid ADA ratio should be significantly higher in patients presenting with malignant pleural effusion and hence help to discriminate between malignant and non-malignant effusion (29).

In our study dominant etiology of exudative pleural effusion was malignant which is in discordance with few studies from India where tuberculosis was the commonest (30). This could be due to referral bias, ours being a tertiary care center as most of the tuberculosis cases are managed at primary care centers. The higher prevalence of malignant effusion is similar to Western studies where malignancy is a common cause of effusions. Our study findings are in concordance with the study by Akash Verma (29) et al where the incidence of malignant pleural effusions was 61.3%.

Among the malignant pleural effusions, the adenocarcinoma of the lung was the most common etiology (62.3%) followed by lymphoma/leukemia and carcinoma of the breast. In 16% of malignant cases, the primary origin of the malignant effusion could not be found. This is different from the study conducted by AkashVerma et al (29) where lung malignancy was the cause in 95% of malignant effusions.

Table 2: Ratio of Serum LDH/ Pleural fluid ADA among study population

Cancer Ratio		N(sample size)	Mean	Std. Deviation
	Malignant	57	25.134	12.553
	Non malignant	43	20.451	32.936
	P value	<0.0000		

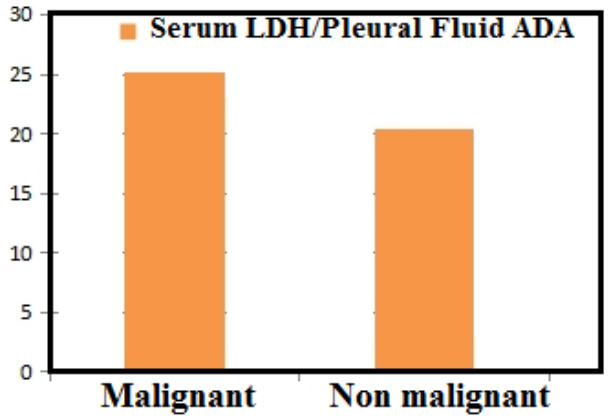

Figure 1: Ratio of Serum LDH/Pleural fluid ADA in malignant and non-malignant pleural effusion.

Regardless of the etiology, cough and dyspnea were observed to be the most common presenting symptoms in our study. The most common symptom encountered by patients with pleural effusions related to nonmalignant variants is a dry cough, followed by breathlessness, fever, and chest pain.In a study by ArunGopi et al. (31) the most common symptom was chest pain followed by dry cough. We had a yield of 80% in pleural fluid cytology when compared to 48.5% in the study by ONG Kc (14) et al. In tubercular pleural effusion, the pleural fluid ADA level has good diagnostic sensitivity. In our study, if pleural fluid ADA ≥ 33 IU/L is taken as a diagnostic cut-off, it yields a sensitivity of 85%, the specificity of 84.4%, a positive predictive value of 80.3%, a negative predictive value of 95%.

In the present study, we have observed that the serum LDH is significantly higher among the malignant causes of effusion when compared to other etiologies. This is in concordance with the study conducted by Akash Verma et al (29). Cancer ratio with a cut-off level of ≥20 is highly predictive of malignancy in patients with exudative pleural effusion with high sensitivity (98%) and specificity (94%) (29). our study had a sensitivity and specificity of 70.17 % and 76.74% respectively. We had low sensitivity and specificity in comparison to the above study. If the cancer ratio cut-off is decreased to 15, the sensitivity increases to 92.98%. With specificity falling to 70 %.Thus as per our study, the diagnostic cut-off of 15 gives a better diagnostic prediction and would help in differentiating between malignant and nonmalignant etiologies and also guide us to look for malignancy elsewhere if the cancer ratio is more than 15.

Conclusion

Cancer ratio could help in predicting the underlying etiology while awaiting cytological diagnosis or who have a high index of suspicion of malignancy and cytologically negative, with a diagnostic cutoff of 20 has a sensitivity and specificity of 70.17 % and 76.74% respectively. A cutoff value of 15 has a sensitivity of 92.98% and a specificity of 70%. In conclusion, the cancer ratio is a valuable diagnostic tool in differentiating malignant from nonmalignant causes, so that further diagnostic workup

can be targeted with tumor markers, thoracoscopy, etc.

Limitations

Limitations of this study include its small sample size and single-center study. The non-availability of thoracoscopy and PET scan made it difficult to get a final diagnosis in cases of unknown primary malignancies.

Conflicts of interest

The authors have declared no conflict of interest.

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