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The Diagnostic Potential of Cancer Ratio, Cancer Ratio Plus and Age/Pleural Fluid ADA in Identifying Malignant Pleural Effusion

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Abstract

Aim: We aimed to validate the diagnostic potential of previously reported cancer ratio (CR) and cancer ratio plus in identifying malignant pleural effusion (MPE); to test whether the newly proposed age/pleural fluid adenosine deaminase (ADA) ratio has an additive role in discriminating MPEs from other causes of exudative pleural effusion.

Methods: Prospective observational study of 103 patients with exudative pleural effusion malignant n=27, tuberculous n=48, parapneumonic n=16, others n=11(uraemic, chylothorax, pancreatic, systemic lupus erythematosus, nocardiosis, non-specific pleuritis)]. Univariate and multivariate analysis of clinical data, biochemical parameters of pleural fluid and serum, cancer ratio, cancer ratio plus was performed.

Results: Both cancer ratio and cancer ratio plus had lower sensitivity (59.3%,66%) and fair specificity (81.2%,76.3%) at the proposed cut-off value of >20 and >30 respectively. In multivariate logistic regression analysis, both ratios could not discriminate between MPE and non-malignant pleural effusion. However, age and pleural fluid ADA showed statistical significance (*P*=0.046, *P*=0.017 respectively) in identifying MPEs. The age/pleural fluid ADA ratio at a cut off value of 1.83 had a sensitivity, specificity, and AUC of 81.5%, 63.2% ,0.80 (95% CI= 0.70 -0.90) respectively.

Conclusion: In our study, both cancer ratio and cancer ratio had a lower diagnostic potential in identifying malignant pleural effusion when compared to age and pleural fluid ADA. The ratio of age/pleural fluid ADA had a better diagnostic performance. The various pleural fluid and/or serum biomarkers may be an attractive alternative to more invasive diagnostic procedures but needs further validation by large multicentric prospective studies.

Keywords: Cancer ratio, Cancer ratio plus, Malignant pleural effusion, Pleural fluid ADA

Introduction

Pleural effusion is the most common manifestation of pleural disease, and its etiology range in the spectrum from cardiopulmonary disorders, systemic inflammatory conditions to malignancy. Ninety percent of cases of pleural effusion in western countries are reported to result from only five diseases: CCF, pneumonia, malignancy, pulmonary embolism, and viral infection.[1] In India, unlike the western countries, tuberculous pleural effusion is common.

The initial workup of pleural effusion is aimed to classify effusion is exudative or transudative

based on Light´s criteria.[1-4] Once an exudative pleural effusion is identified, further analysis of the fluid is done to find out the etiology. The three commonly encountered etiology of an exudative pleural effusion are tuberculosis, parapneumonic and malignant effusion.[1] Biochemical, microbiological and pathological analysis of the pleural fluid for ph, glucose, protein, LDH, ADA, AFB smear, GeneXpert, Mycobacterial culture, gram stain, bacterial culture, and sensitivity, cell count, differential count aid in diagnosing TB and parapneumonic effusion.[4]

Raised level of adenosine deaminase (ADA) helps to diagnose tubercular pleural effusion with the sensitivity and specificity of 0.92 (95 % confidence interval 0.90–0.93) and 0.90 (95 % confidence interval 0.89–0.91), respectively.[5] Neutrophilic predominant pleural effusion usually suggests a parapneumonic effusion. However, in malignant pleural effusion (MPE) the diagnostic yield of pleural fluid cytology is low (50% to 60%) and requires invasive procedures like a closed or thoracoscopic pleural biopsy to establish the diagnosis.[6,7] MPE is probably the second leading cause of exudative effusion (next to tuberculous effusion) subjected to thoracentesis and accounts for 24% of all pleural effusion.[1]

In recent years a plethora of different tumor markers expressed by cancer cells in pleural fluid-like CEA, CA15-3, CA125, cyfra 21-1, and protein microassay (osteopontin,fibulin-3) has been established in diagnosing malignant pleural effusion.[8,9]The majority of these tumor markers have not yet gained acceptance in clinical practice due to their low potential, cost, inadequate validation of their results, and lack of availability in many centres. Promising tumor markers are emerging but future research with larger studies and prospective validation before the clinical application is required.

There is no reliable biochemical marker specific to aid in the diagnosis of malignant pleural effusion especially when the pleural fluid cytology is negative for malignant cells. Unlike tuberculous pleural effusion, where the pleural fluid lymphocyte count is high, lymphocyte count is comparatively low in malignant pleural effusion. Serum LDH is a ubiquitous cellular enzyme that is raised in response to tissue injury in a non-specific manner. Elevated serum LDH is present in hemolysis, cancer, sepsis, HIV infection, and many other conditions.[10] It has been reported as a marker of poor outcome in sepsis and cancer patients. The explanation for raised serum LDH in cancer is because of the preferential use of glycolysis for energy instead of oxidative phosphorylation by tumor cells which is mediated by LDH.[10-12]

The search for a reliable biochemical marker to diagnose malignant pleural effusion using these simple tests has led to the formation of ratios like cancer ratio (serum LDH and pleural fluid ADA) and cancer ratio plus (cancer ratio with pleural fluid lymphocyte count) in identifying malignant pleural effusion.[13,14] At the cut-off level of more than 20 and 30, the cancer ratio and cancer ratio plus showed high sensitivity and specificity in identifying MPE. The high diagnostic performance of this parameter is based on the observations that MPE is usually associated with high serum LDH levels, while tuberculous effusion with high pleural fluid ADA levels.

Most recently Richard W.Light, Piotr, Michal, Rafal, et al, studied the sensitivity and specificity of cancer ratio and suggested a newer ratio by comparing age/pleural fluid ADA as a positive predictor of MPEs.[15]These ratios can aid in planning the further choice of investigations in patients suspected to have malignant pleural effusion, as they are cost-effective, easily available, and can get results on time. Therefore in search of a useful index, in this study, we aimed at assessing the ability of cancer ratio and cancer ratio plus in identifying malignant pleural effusion from other exudative pleural effusion; to test whether age/pleural fluid ADA could serve as a biomarker in discriminating between MPEs and non–MPEs.

Patients and Methods:

The present study is a prospective observational study conducted in the Department of Pulmonary Medicine, Yashoda Hospitals, Hyderabad. A total of 103 patients presenting to the pulmonary medicine outpatient/ inpatient department with pleural effusion were included in the study.

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Inclusion Criteria:

1. Age above 12 years
2. Exudative pleural effusion as diagnosed by any one of the following

Light´s criteria

Serum protein to pleural fluid protein gradient

(< 3.1gm/dl)

Serum albumin to pleural fluid albumin gradient (<1.2gm/dl)

Exclusion Criteria:

1. Transudative pleural effusion
2. Effusion without a definitive diagnosis
3. Patients who denied to give consent for thoracentesis

Study Design:

Clinical data were obtained after getting informed consent and appropriate investigations were performed as mentioned below

Radiological And Laboratory Investigations:

Pleural effusion was quantified using chest x-ray and (USG chest when needed) and thoracentesis was done under USG guidance after written informed consent. Pleural fluid was subjected to biochemical (protein, glucose, ADA, LDH) microbiological (AFB smear, GeneXpert, MTB BACTEC) pathological (cell count, differential count, cell block, cytology) and other investigations depending on the clinical suspicion of etiology. In addition levels of serum protein, serum LDH was measured.

The cancer ratio and cancer ratio plus was derived from the above results as below

1. Cancer ratio (serum LDH: pleural fluid ADA) with cut-off >20
2. Cancer ratio plus (cancer ratio: pleural fluid lymphocytic count) with cut-off >30

Pleural Biopsy:

In patients with inconclusive pleural fluid results, thoracoscopic pleural biopsy after anesthetic fitness was performed under conscious sedation.

Other investigations like HRCT chest were performed when clinically indicated.

Diagnosis:

Tuberculous pleural effusion was diagnosed if any of the following criteria were met

1. Pleural fluid ADA >70 U/L.
2. Pleural fluid AFB smear or GeneXpert is positive for MTB.
3. Patients with lymphocytic rich pleural effusion with pleural fluid ADA levels of < 70U/L but with high clinical-radiological suspicion of tuberculosis and showing clinical response to anti-tuberculous therapy.
4. Pleural biopsy showing granulomatous necrotizing inflammation/AFB smear-positive or/GeneXpert positive for MTB.

Para pneumonic effusion was diagnosed if any of the following criteria were met

1. Neutrophilic rich exudative effusion
2. Pleural fluid culture and sensitivity grew any bacteria.
3. Sputum culture and sensitivity grew organism and response of pleural effusion to sensitive antimicrobial therapy.
4. Neutrophilic rich effusion, despite negative pleural fluid and sputum culture sensitivity, results in patients responding to antimicrobial therapy.

Malignant Pleural Effusion

1. Pleural fluid cytology positive for malignant cells
2. Pleural biopsy showing evidence for malignancy.

Data Analysis:

Continuous variables were presented as mean (SD) or median (quarterfinal range) based on data distribution. The difference in continuous measures between the two groups was assessed using Wilcoxon rank-sum test. The difference in proportion between the two groups was assessed using the chi-square test.

To know the independent predictors, multivariate analysis using logistic regression was performed and adjusted Odds ratios with 95% confidence interval and co-coefficients were estimated. A P value of <0.05 was considered statistically significant. Analysis was done in SPSS version 17.0

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Analysis and Results:

In our prospective observational study of 103 patients with exudative pleural effusion, 27 (26.2%) had malignant pleural effusion and 76 (73.8%) had non-malignant pleural effusion.The mean age of the population in the malignant effusion group was 52.9 ± 18.8 years and in non-malignant effusion was 43.8 ± 17.7 years. Sex distribution showed an equal incidence of MPE in males {n=15(55.6%)}and females {n=12(44.4%)} as compared to non-malignant effusion which had a male predominance{n=51(67.1%)}.

Etiological diagnosis of exudative pleural effusion: The etiology of exudative pleural effusion in patients with malignant pleural effusion (n=27) was lung cancer in 18(66.7%) patient (n=17 adenocarcinoma, n=1 squamous cell carcinoma) and in rest of the patients the underlying malignancy was as follows: ovarian cancer (n= 1), breast cancer (n=4), lymphoma (n= 3), synovial sarcoma (n=1). Among the 76 (73.8%) patients with non-malignant pleural effusion the etiology was as follows: 48 (63.2%) had tuberculous effusion, 16 (21.1%) had parapneumonic effusion, 11 (14.5%) had other causes (uraemia, chylothorax, systemic lupus erythromatosus, nocardiosis, non-specific pleuritis, pancreatic pleural effusion)[Table1].

Table 1: Etiological Diagnosis of Study Population

Malignant PE (n=27)	n (%)
Lung cancer	18(66.7%)
Others*	9(33.3%)
Non-malignant PE (n=76)	
Tuberculous	48(63.2%)
Parapneumonic	16(21.1%)
Others**	11(14.5%)

*** Ovarian, breast, lymphoma, spindle cell**

****Chylothorax, SLE, nocardiosis, pancreatic pleural effusion, non-specific pleuritis**

Pleural fluid / Serum biochemical parameters: Pleural fluid and serum biochemical parameters were compared between MPE and non-malignant pleural effusion.[Table.2]

Table.2: Pleural fluid biochemical parameters and Serum LDH of the study population

S.No.	Variable	Malignant PE (n=27)|*	Non-malignant PE (n=76)*	*P* value
1	Total leukocyte count (cells/mm³)	1128.2 ± 900.9	2040.6 ± 3427.8	0.176
2	Lymphocytes (%)	71.8 ± 24.3	72.2 ± 27.9	0.951
3	Polymorphs (%)	24.2 ± 23.9	26.2 ± 27.7	0.741
4	Protein (g/dl)	4.2 ± 1.0	4.7 ± 1.3	0.086
5	Sugar (mg/dl)	120.4 ± 54.8	105.2 ± 53.5	0.210

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S.No.	Variable	Malignant PE (n=27)*	Non-malignant PE (n=76)*	*P* value
6	LDH(U/L)	407.6 ± 447.4	600.1 ± 1087.3	0.375
7	ADA (U/L)	17.9 ± 19.9	40.4 ±36.5	0.003
8	Serum LDH(U/L)	265.5 ± 108.5	273.1 ± 343.5	0.910

***values expressed as mean ± standard deviation, #*P* value <0.05 is considered as statistically significant**

Among the various parameters analyzed, pleural fluid ADA (U/L) was statistically significant in discriminating MPE from other causes of exudative pleural effusion (*P*=0.003).

Cancer ratio and Cancer ratio plus:

The cancer ratio (serum LDH: pleural fluid ADA) and cancer ratio plus (cancer ratio: pleural fluid lymphocytic count) were derived using the pleural fluid and serum biochemical parameters. Univariate and multivariate analysis of age, biochemical parameters of serum and pleural fluid, pleural fluid lymphocytic count, cancer ratio, cancer ratio plus was performed [Table.3,4].

Table.3: Univariate analysis of age, biochemical parameters in patients with malignant and non –malignant pleural effusion

Parameter	Pleural effusion		*P* value
	Malignant	Non-malignant	
Age	52.9 (18.8)	43.8 (17.7)	0.04*
Pleural ADA	8 (6-23)	29.6 (13.7-57.8)	<0.001*
Serum LDH	233 (191-346)	212.5 (163-266)	0.11
Pleural lymphocyte count (%)	71.8 (24.3)	72.2 (27.9)	0.9
Serum LDH: pleural ADA (cancer ratio)	8.6 (4.7-30.2)	10.3 (4.3-23.4)	0.802
Pleural LDH-Serum LDH ratio	1.1 (0.7-1.8)	1.2 (0.7-2.8)	0.2
Cancer ratio: Pleural fluid lymphocyte count (cancer ratio plus)	16.1 (5.6-55.3)	15.8 (4.9-51.1)	0.6

******P*-value <0.05 is considered as statistically significant**

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In univariate analysis, the mean age in patients with MPE was 52.9 years and pleural fluid ADA was low (8 U/L) as compared to patients with non-malignant PE. Both age (*P*=0.04) and pleural fluid ADA (*P* <0.001) were statistically significant in identifying MPEs. Whereas serum LDH, cancer ratio, and cancer ratio plus did not maintain statistical significance in distinguishing the effusions [Table.3]

Multivariate logistic regression analysis with malignancy as the outcome variable showed patient's age [95% CI 1.0 (1.00-1.06) *P*=0.046] and pleural fluid ADA [95% CI - 0.97 (0.94- 0.99) *P*=0.01] as predictors of MPEs. Other parameters including cancer ratio and cancer ratio plus had no statistical significance [Table.4]

Table.4: Multivariate logistic regression analysis with malignancy as the outcome variable

Variable	Coefficient	Odds (95% CI)	*P* value
Age (years)	0.029	1.0 (1.00-1.06)	0.046
Pleural ADA(U/L)	-0.035	0.97 (0.94-0.99)	0.017
Serum LDH(U/L)	-0.001	1.0 (0.99-1.01)	0.608
Pleural lymphocyte count (%)	0.005	1.0 (0.99-1.02)	0.619
Serum LDH : Pleural ADA (cancer ratio)	-0.011	1.00 (0.96-1.01)	0.431
Pleural LDH : serum LDH ratio	-0.068	0.93 (0.70-1.25)	0.648
Cancer ratio : Pleural fluid lymphocyte count (cancer ratio plus)	0.003	1.00 (1.00-1.01)	0.393

***P*-value <0.05 is considered as statistically significant**

We also analyzed the sensitivity and specificity of both the cancer ratio and cancer ratio plus at the proposed cut-off levels and the results are depicted in Table.5

Table.5: Cancer ratio, Cancer ratio plus, Pleural fluid ADA, Sensitivity, Specificity at the proposed cut off level for differentiating between malignant and non-malignant pleural effusion

Parameter	Cut off value	Sensitivity %	Specificity %	PPV	NPV	PLR	NLR
Cancer ratio	>20	59.3	81.2	53.3	84.9	3.22	0.50
Cancer ratio plus	>30	66	76.3	50	86.6	2.82	0.44
Pleural fluid ADA(U/L)	<40	93	46	38	95	1.72	0.16

PPV-positive predictive value, NPV-negative predictive value, PLR-positive likelihood ratio, NLR-negative likelihood ratio

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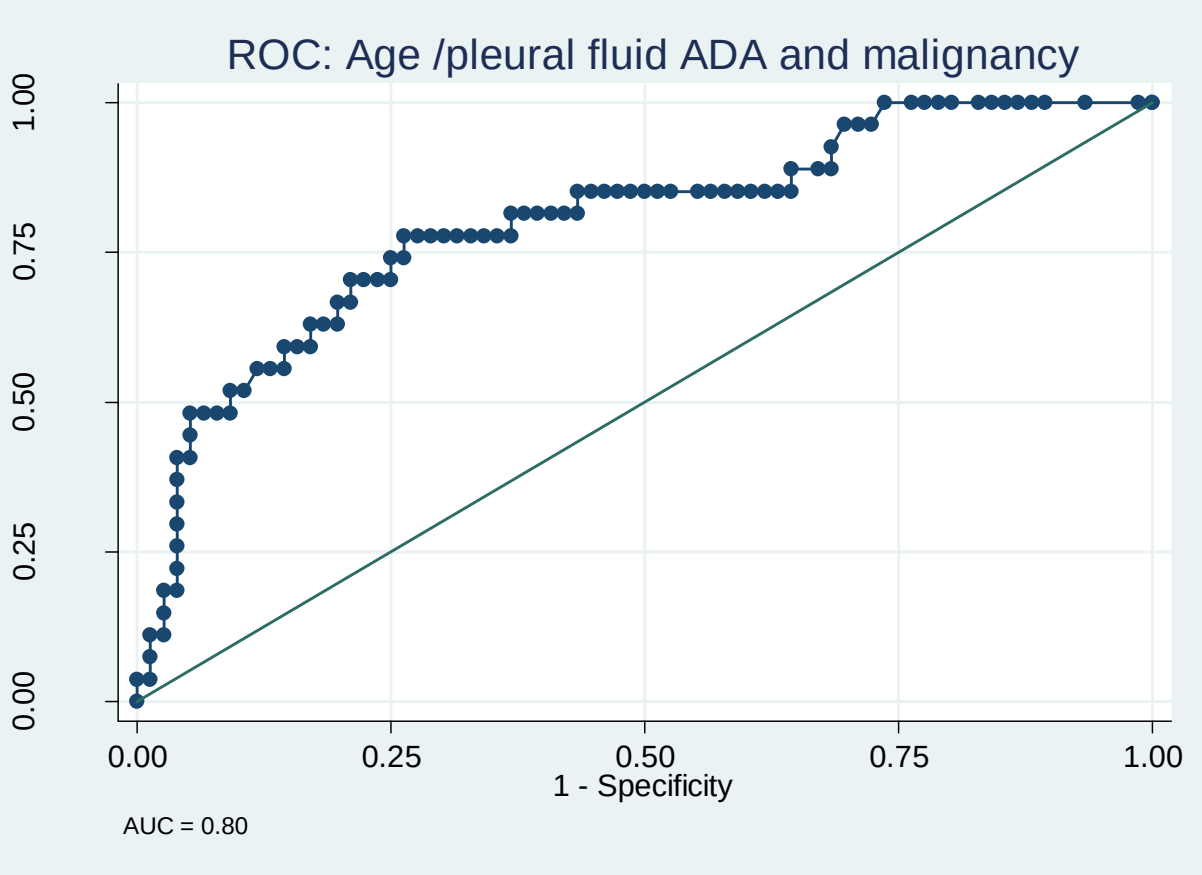
Both cancer ratio and cancer ratio plus showed lower sensitivity but better specificity in comparison with pleural fluid ADA. In addition, receiver operating characteristic (ROC) of age/pleural fluid ADA was performed and it showed AUC of 0.80, sensitivity and specificity of 81.5%,63.2% respectively with a positive likelihood ratio of 2.21 and negative likelihood ratio of 0.29 at a cut off value of 1.83 [Table.6].

Table.6: Area under the curve, cut off value, sensitivity, specificity of age/pleural fluid ADA

Parameter	AUC	95% CI	Cut off value	Sensitivity %	Specificity %	PPV	NPV	+LR (95%CI)	-LR (95%CI)
Age /pleural fluid ADA	0.80	0.70-0.90	1.83	81.5	63.2	44.0	90.6	2.21 (1.57-3.12)	0.29 (0.13-0.66)

Figure:1 Receiver operating characteristic (ROC) curve for age/ pleural fluid adenosine deaminase.



Discussion:

The current study was undertaken to test the diagnostic potential and validate the cancer ratio and cancer ratio plus in identifying malignant pleural effusion. Raised level of serum LDH in cancer has been postulated, as there is increased demand for ATP by the rapidly growing cells and there is a switch in the ATP generation pathway which is mediated by LDH(oxidative phosphorylation to glycolysis).[11,12] Thereby explaining the increased level of serum LDH in malignancy. But in our

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analysis serum, LDH was elevated in both malignant and other causes of exudative pleural effusion and was not statistically significant (*P*=0.910).

Cancer Ratio

In univariate and multivariate regression analysis cancer ratio at a cut-off level of >20 was not found to be statistically significant (*P* =0.802 and *P* =0.431) in identifying MPE (Table.3,4).

However the sensitivity and specificity at this cut off level was 59.3% and 81.2%, lower when compared to the sensitivity of 98%,95%, and specificity of 94%,85% respectively as reported by Verma et al.[13,14] In comparison with the recent article by Korczynski P, Mierzejewski M, Krenke R, Safianowska A, Light RW et al published in 2018, where they tested the diagnostic performance of cancer ratio in an external cohort, the specificity of cancer ratio in our study was higher (81.2% as compared to 68.2%).[15] The PLR (3.22) and NLR(0.50) at this cut-off level were also low.

A highly sensitive test is good for screening. It will, however, tend to give a greater number of false-positive results. This may lead to a false alarm for cancer and mental agony. High specificity makes the test more definitive for the diagnosis. As the cytology is negative in 50 % of the patients, previous studies focused on high specificity with reasonable sensitivity.[13] The reason for the lower sensitivity and specificity in our study can be explained, as the number of patients with malignant pleural effusion in our study population was only 26.2% as compared to 61.3% and 71.2% and 52.9% in the previous studies and we included other causes of exudative pleural effusion as compared to only TPE, PPE in these studies.[13,14,15] Raised level of serum LDH was seen in patients with both malignant and non-malignant effusion which could have falsely elevated the cancer ratio.

Cancer ratio plus (Cancer Ratio: Pleural Fluid Lymphocytic Count)

As similar to the cancer ratio, cancer ratio plus at a cut-off of >30 could not identify malignant pleural effusion (univariate analysis *P*=0.6 and multivariate analysis *P*=0.393) (Table.3,4). Like cancer ratio the sensitivity and specificity of cancer ratio plus was low (66% and 76.3% as compared to 97.6% and 94.1% respectively reported by R.W. Light et al.14 The PLR and NLR at this cut-off level were 2.82 and 0.44.The possible explanation for such lower yield would be a higher cancer ratio in the non- malignant effusion and low levels of pleural fluid lymphocytes as in parapneumonic, empyema, uraemic, CTD-related pleural effusion.

Thus, cancer ratio (>20) and cancer ratio plus (>30) when used as a diagnostic marker in identifying malignant pleural effusion from tuberculous and parapneumonic effusion may not yield promising results and be used as a biomarker.

In addition, both these ratios were elevated in other non-malignant causes of effusion apart from TPE and PPE like uraemic, connective tissue related effusion, chylothorax, pancreatic pleural effusion, non-specific pleuritis.

Pleural fluid ADA

Often the low level of ADA is used as a surrogate indicator of malignant effusion. In our study, pleural fluid ADA at a cut-off < 40 U/L was a positive predictor of MPEs. It showed a sensitivity of 93%, specificity of 46%, PLR of 1.72, and NLR of 0.16.As described earlier a test with higher sensitivity will give false-positive results but lowers the chances of false negative.

Thereby it can aid in selecting patients with exudative pleural effusion for further invasive investigations like thoracoscopic pleural biopsy for histopathological diagnosis.

Although MPEs can be diagnosed by simple pleural fluid cytology, it has significant limitations, including a highly variable sensitivity, ranging from as low as 11.6% to as high as 71%.[16,17] Therefore when there is high clinical suspicion of MPEs and pleural fluid cytology is negative for malignant cells, ADA at a cut-off value of <40 U/L can have an additive role in diagnosing MPEs.

Age / Pleural fluid ADA ratio

Lee et al, revealed that older patients may have low ADA levels with tuberculous pleural effusion (TPE).[18] Therefore, in elderly age group patients with tuberculous pleural effusion(TPE), low pleural fluid ADA levels should be interpreted with caution. The relationship between age and pleural fluid ADA level was also reported by Abrao et al, who found a significant moderate negative correlation between

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these two variables.[19] Hence, the authors concluded that the use of lower ADA cut-off value in older patients can reduce the number of false-negative results of ADA in TPE.

As in our study, both age and pleural fluid ADA could discriminate between MPEs and non-malignant pleural effusion, we tried to validate the recently proposed age/pleural fluid ADA by Piotr Korczyński et al. Though the proposed cut off level was >2.62 with a sensitivity and specificity of 93.2% and 71.2% respectively.[15]In our analysis age/pleural fluid ADA at a cut-off value of 1.83 had a sensitivity and specificity of 81.5%, 63.2% respectively, and a better diagnostic performance when compared to cancer ratio and cancer ratio plus in identifying malignant pleural effusions.

Conclusion:

All these ratios can be easily derived as they require the measurement of routinely performed biochemical parameters in the evaluation of pleural effusion. These ratios can be evaluated and may guide before performing an invasive procedure. But as their diagnostic performance is variable, the use of these ratios as a biomarker and alternative to the invasive diagnostic procedure is questionable. Thus, we need further prospective studies to incorporate these ratios into routine clinical practice.

Strengths of study:

1. Prospective observational data
2. In our study, we included diseases causing lymphocytic exudative effusions other than MPE, TPE, PPE such as connective tissue diseases, chylothorax, and pancreatic pleural effusion, uraemic effusion.
3. Patients with extrapulmonary malignancies causing MPE were included eg.,ovarian, breast, lymphoma. As lymphoma-related malignant pleural effusion can also have high ADA levels and can mimic TPE and give false-negative results.

Limitations:

1. Single centered study, small population studied.
2. Our analysis was limited to patients with MPE as a whole group, with no subgroup analysis of patients with different tumor types and stages due to a small number of patients in different subgroups.
3. Sub-group analysis of non-malignant pleural effusion was not done.
4. India being a developing country with a high burden of tuberculosis, our study had TPE as the most common diagnosis of exudative pleural effusion (43.7%) than MPE (26.2%) in the total study population.

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