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Original Research Article

Diagnostic utility of cancer ratio in differentiating malignant from non-malignant pleural effusions in a tertiary care centre in central Kerala

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ABSTRACT

Background: Malignant pleural effusion (MPE) is a common clinical condition observed in patients suffering from malignant diseases. None of the tumour markers have both high sensitivity and specificity. A retrospective study on patients with pleural effusion was done to evaluate the diagnostic accuracy of Cancer ratio (CR) in diagnosing MPE.
Methods: A retrospective analysis of patients with undiagnosed exudative pleural effusion was done. Results of serum Lactate dehydrogenase (LDH), pleural fluid Adenosine deaminase (ADA), pleural fluid analysis such as cytology and histopathology reports of pleural biopsy were analyzed. Serum LDH: pleural fluid ADA ratio (CR) was calculated and compared with histopathology report. Data were analyzed statistically.
Results: A total of 102 patients were enrolled in the study (56 males and 46 females). The sensitivity and specificity of CR at the cut off level of >20 were 57.14% and 75.47% respectively. The positive predictive value was 68.29% and the negative predictive value was 65.57%. CR>20 ($p<0.001$) is statistically significant in predicting malignancy in undiagnosed exudative pleural effusions.
Conclusions: CR has a high sensitivity and specificity and is a novel tool in differentiating malignant from nonmalignant pleural effusions. Patients with unconfirmed diagnosis but higher CR will identify the need for early biopsy, follow-up and frequent or repeat chest imaging to assess the progression.

Keywords: Cancer ratio, Malignant pleural effusion, Tubercular pleural effusion, Parapneumonic effusion

INTRODUCTION

Exudative effusion is commonly seen in three conditions namely cancer, tuberculosis and parapneumonic effusion. Malignant pleural effusion (MPE) is associated with unfavorable prognosis and is a common clinical condition observed in patients suffering from malignant diseases, such as primary thoracic cancer, pleural mesothelioma, metastatic cancer, etc.[1-3] It is associated with unfavorable prognosis and a median survival time of 3-12 months.[4,5] Assessment and comparison of serum Lactate dehydrogenase (LDH) and protein with the pleural fluid LDH and protein (based on Light's criteria) is the first step determine the exudative or transudative nature of the effusion associated with the management of pleural effusion.[6-9]

Once an exudative effusion is identified, further work-up entails its analysis for cell count, glucose, pH, Adenosine deaminase (ADA), cytology and TB culture. If the biochemical results are inconclusive then invasive techniques closed pleural biopsy or thoracoscopy is done to confirm the diagnosis.

Low diagnostic yield of pleural fluid cytology (~60%), and the invasive nature of closed or thoracoscopic pleural biopsy are a significant limitation in detecting MPE.[10-12] Often the low levels of ADA are used as a surrogate indicator of malignant effusion while waiting for the cytology result.

Among the routinely performed tests for investigating pleural effusion, serum LDH, pleural ADA and pleural

lymphocyte count change in reciprocal manner in patients with MPE and TPE.

Serum LDH is raised in MPE whereas pleural ADA and pleural fluid lymphocyte count remain comparatively low. Conversely, serum LDH is low in TPE whereas pleural ADA and pleural fluid lymphocyte count are raised. This reciprocal change presents an opportunity to combine these test results developing a ratio with the diagnostic power to differentiate MPE from non-malignant pleural effusions in a cost-effective manner. Such a marker not only may provide an early signal toward malignant nature of pleural effusion, but can potentially serve as a 'forewarning' for patients with negative cytology that are subsequently found to have MPE.

Initial treatment decisions are based on changes in the biochemical markers, such as high levels of LDH, low levels of pH and glucose, and neutrophil predominance that aid in the diagnosis of pyogenic effusion (parapneumonic, empyema) and guide regarding the need for antibiotics, drainage or surgical decortications.[13]

Similarly, a raised level of 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.[14] In recent years, a number of tumour markers have been used for the diagnosis of MPE, including vascular endothelial growth factor, carcinoembryonic antigen, Carbohydrate antigen (CA) 125, CA 15-3, CA 19-9, and CYFRA 21-1.[15-17] However, none of these markers has shown both high sensitivity and high specificity.

The aim of the study was to find a marker and to confirm its diagnostic utility for differentiating MPE from non-malignant effusions in a tertiary health care facility in the district of Thrissur in Central Kerala.

METHODS

Study design and sample collection

A retrospective analysis was designed among patients hospitalized for the management of undiagnosed exudative pleural effusion from January 2020 to June 2021 under department of pulmonary medicine in Amala Institute of Medical Sciences, Thrissur. The study was started after receiving approval from the institutional research committee and ethical clearance.

Study procedure

We collected data on serum LDH, pleural fluid analysis results such as cytology and histopathology of pleural biopsy. We analyzed the serum LDH: pleural fluid ADA ratio as a predictor of malignant pleural effusion and described it as 'Cancer ratio' (CR).

Sample size calculation

Random sampling technique was used to include all the patients who full fill the inclusion criteria andhospitalized for the management of undiagnosed exudative pleural effusion during the study period.

Statistical analysis

Data were analysed using SPSS software version 23(IBM Statistics, Chicago, USA) and Microsoft office 2007. Chi-square (χ^2) test was used for association between two categorical variables. $P<0.05$ was considered to be statistically significant.

RESULTS

A total of 102 patients with exudative pleural effusion enrolled in the study. There were 56 males and 46 females. The age group 60-80 years showed the maximum incidence of undiagnosed pleural effusion in our study (Table 1). The mean age was found to be 58.6 years. The lowest age enrolled in our study was 22 years and oldest was 84 years.

Among the total, 74 cases were malignant effusion, 32 cases of tubercular effusion and 6 cases of parapneumonic effusion from histopathology analysis of pleural biopsy specimen. The distribution of cases according to cytology, histopathology and CR is given in Figure 1.

The CR and histopathology reports were compared in Table 2. For serum LDH: pleural fluid ADA ratio, at the cut off level of >20, the sensitivity and specificity were 57.14% and 75.47%, respectively (Table 3).

Out of the total 49 cases which were detected as malignant by histopathological examination, 28 cases had CR>20, but subtyping of cancer was not done owing to decreased sample size. The diagnostic accuracy of CR in detecting MPE was 66.67%.

The Positive predictive value (PPV) was 68.29% and the negative predictive value was 65.57%. CR>20 has a p value<0.001, which is statistically significant in predicting malignancy in undiagnosed exudative pleural effusions. The lowest measured CR was 0.13 and highest was 124.47. The positive predictive value and negative predictive value of cancer ratio was 68.29% and 65.57% in diagnosing MPE.

In our study lowest measured pleural fluid ADA was 2.39 and the highest measured value was 1594 and, in serum LDH measured the lowest measured value was 125 and the highest was 1061.

We also observed that higher values of pleural fluid ADA was seen in Tubercular pleural effusion (TPE) and higher serum LDH was seen in MPE.

Table 1: Distribution of cases according to background parameters.

Parameters	N	%
Age (years)		
20-40	14	13.7
40-60	35	34.3
60-80	48	47.1
>80	5	4.9
Sex		
Male	56	54.9
Female	46	45.1
Total	102	100

Table 2: Distribution of cancer ratio according to HPE.

Cancer ratio	HPE				P value
	Malignant		Benign		
	N	%	N	%	
>20	28	57.1	13	24.5	0.001*
<20	21	42.9	40	75.5	
Total	49	100.0	53	100.0	

Note: *-p value significant at 5% level of significance (p<0.05).

Table 3: Sensitivity analysis of cancer ratio compared to HPE.

Parameters	Cancer ratio
TP (true positive)	28
FN (false negative)	21
FP (false positive)	13
TN (true negative)	40
Sensitivity	57.14%
Specificity	75.47%
PPV	68.29%
NPV	65.57%
Accuracy	66.67%

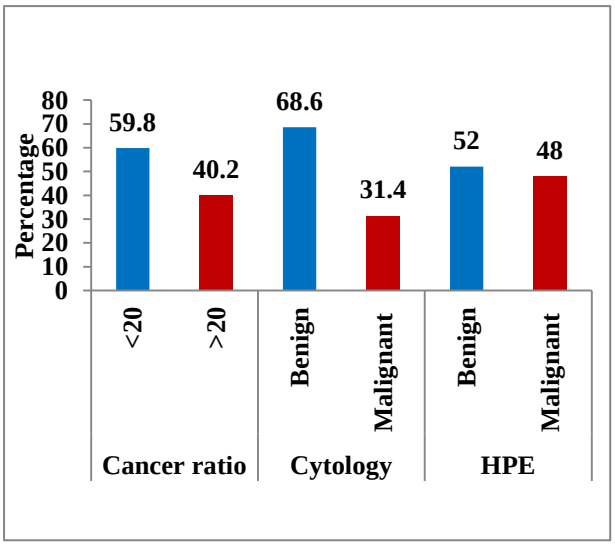

Figure 1: Distribution of cases according to study parameters.

DISCUSSION

For undiagnosed exudative pleural effusion, the clinical utility of CR for the diagnosis of MPE is that it can help guide treatment plans: patients with high CR values (>20) must be treated with caution, and further diagnostic examinations such as repeated cytologic test, invasive procedures such as medical thoracoscopy and pleural biopsy should be considered. In our study, CR showed a sensitivity and specificity of 57.14% and 75.47% respectively. These findings were similar to Verma et al reported that CR at the cut-off level of more than 20, the CR showed high sensitivity and specificity for identifying patients with MPE.[18,19] The high diagnostic performance of this parameter is based on the observations that MPE is usually associated with high serum LDH levels, while TP-with high pleural fluid ADA levels.

In a retrospective analysis of patients 163 hospitalized with exudative pleural effusion in 2013 by Verma et al found that at the cut-off level of 20, the Positive likely hood ratio (PLR) value was 32.6 suggesting that patients with cancer have about 32 fold higher chance of having CR (serum LDH: pleural fluid ADA ratio) of >20 compared with patients without cancer.[18,19] This high probability would be considered high enough to consider an effusion very likely to be malignant. On the other hand, Negative likely hood ratio (NLR) at this cut-off was found to be 0.03 which suggests that if the cancer ratio is <20, the probability that this patient has cancer is 3%, which is low enough to make the diagnosis of cancer highly unlikely. Serum LDH is a ubiquitous cellular enzyme, which rises in response to tissue injury.[20] Elevated serum LDH is found in numerous clinical conditions very high and isolated serum LDH might be a marker of specific diagnostic groups. Its diagnostic and prognostic role has previously been studied and reported as a poor prognostic marker in sepsis and cancer patients.[21-23]

Serum LDH is raised in cancer as the cancer cells don't depend on oxidative phosphorylation for energy utilization, instead preferential use of glycolysis for energy by tumour cells, a switch in the ATP generation pathway which is mediated by LDH.[24,25] High rate of glycolysis is advantageous to growing cells because it is capable of producing ATP considerably faster than oxidative phosphorylation. Glycolysis is best suited for meeting increased ATP demands of cancer cells to aid their growth. ADA is a known biomarker of tuberculous pleural effusion.[16-17] ADA plays an important role in purine nucleoside metabolism and is secreted by mononuclear cells, lymphocytes, neutrophils and RBCs.[26,27] It is of two types, ADA-1 and ADA-2, however, only total ADA is measured in the routine clinical practice. High levels correlate with infective conditions such as TB (ADA-2) and empyema (ADA-1).[28] MPE patients typically show low levels of ADA, but whether this can aid MPE diagnosis is unclear. Carcinoembryonic antigen (CEA) has been widely used

in the diagnosis of MPE. A meta-analysis based on 45 studies showed low pooled sensitivity (0.54) and high pooled specificity (0.94) for CEA when diagnosing MPE, the low sensitivity of CEA limited its role in screening MPE.[29]

Limitations

Our study has several First, it was a single-center retrospective study. Second, it included only patients with MPE, TPE, and PPE but no patients with other causes of exudative pleural effusion, such as pulmonary embolism or drug-induced pleural effusion. Patients with other underlying diseases were not included because their number was relatively low and they formed a highly heterogeneous group. Third, our analysis was limited to patients with MPE as a whole group, with no sub-analysis of patients with different tumor types and stages. We could not perform such an analysis due to a small number of patients in different subgroups defined by tumor type and the stage of the disease.

CONCLUSION

The study showed that serum LDH: pleural fluid ADA (CR) has a sensitivity and specificity of 57.14% and 75.47% respectively and is a novel tool in differentiating malignant from nonmalignant pleural effusions. For patients with unconfirmed diagnosis but higher cancer ratio, it will identify the need for early follow-up and frequent or repeat chest imaging to assess for progression and early biopsy. Studies with greater number of subjects and more types of control including all other etiologies of exudative PE, such as chylothorax, chemical pleurisy or connective tissue disease should be performed to rigorously evaluate the diagnostic accuracy of CR.

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