Original
ISSN 2521-8492

The Pleural Fluid Lactate Dehydrogenase/Adenosine Deaminase and Pleural Fluid Adenosine Deaminase/Serum C - Reactive Protein Ratios for Differentiating between Tuberculous and Other Causes in a Sample of Iraqi Patients

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(Submitted: 23 June 2021 – Revised version received: 19 July 2021 – Accepted: 12 September 2021 – Published online: 26 December 2021)

Abstract
Objectives: This study aim is to evaluate the importance of pleural fluid LDH/ADA ratio and pleural fluid ADA/serum CRP ratio in differentiating tuberculous pleural effusion from other causes in a sample of Iraqi patients.
Methods: A prospective study of 100 patients with pleural effusion whom age ranges from 18–70 years where admitted at medical department at Al-Imamein Kadhimein medical city in Bagdad and in Marjan and Al-Sadik hospitals at Babylon province. Out of 61 (61%) are males and 39 (39%) are females. The study period was 9 months started from 1st of February to End of October 2019.
Results: In this study the result of comparison of mean level of pleural fluid LDH/ADA ratio and pleural fluid ADA/Serum CRP ratio between tuberculous and para pneumonic pleural effusions were significant = 0.025 and 0.002 respectively. Also the comparison of pleural fluid LDH/ADA ratio and pleural fluid ADA/Serum CRP ratio between tuberculous and malignant pleural effusions were significant = 0.005 in both.
Conclusion: Pleural fluid LDH/ADA ratio is of great value in differentiation tuberculous pleural effusion from malignant pleural effusion with predominant lymphocytes, pleural fluid ADA/serum CRP ratio is of great value in differentiation tuberculous pleural effusion from para pneumonic pleural effusion with elevated pleural fluid ADA and elevated serum CRP.
Keywords: Pleural fluid lactate dehydrogenase/adenosine deaminase, pleural fluid adenosine deaminase/serum C - reactive protein, ratios, tuberculous, Iraq

Introduction

Pleural fluid acts as a lubricant to minimize friction between chest wall and lung as they move against each other during inspiration and expiration. There is a continual movement of the fluid into and out pleural surface. The flux of fluid depend on the oncotic and hydrostatic pressure within parietal and visceral pleura as well as the pressure with pleural surface itself.[1] Pleural fluid accumulates when pleural fluid formation exceeds pleural fluid absorption. Normally, fluid enters the pleural space from the capillaries in the parietal pleura and is removed via the lymphatics in the parietal pleura. Fluid also can enter the pleural space from the interstitial spaces of the lung via the visceral pleura or from the peritoneal cavity via small holes in the diaphragm.[2] Parts of the world, the most common cause of an exudative pleural effusion is tuberculosis (TB). Tuberculous pleural effusions usually are associated with primary TB and are thought to be due primarily to a hypersensitivity reaction to tuberculous protein in the pleural space. Depending on the extent of reactivity, the effusion may be small, remain unnoticed, and resolve spontaneously or may be sufficiently large to cause symptoms such as fever, pleuritic chest pain, and dyspnea. Physical findings are those of pleural effusion: dullness to percussion and absence of breath sounds. A chest radiograph reveals the effusion and, in up to one-third of cases shows a parenchymal lesion. Thoracentesis is required to ascertain the nature of the effusion and to differentiate it from manifestations of other etiologies.[3,4] The fluid is straw colored and at times hemorrhagic; it is an exudate with a protein concentration >50% of that in serum (usually ~4–6 g/dL), a normal to low glucose concentration, a pH of ~7.3 (occasionally <7.2), and detectable white blood cells (usually 500–6000/μL). Neutrophils may predominate in the early stage, but lymphocyte predominance is the typical finding later. Mesothelial cells are generally rare or absent. Tuberculous pleural effusions resolve spontaneously in the majority of cases, but two-thirds of untreated patients go on to develop pulmonary TB within 5y, and so treatment is recommended. Treatment is the same as for pulmonary TB.[5] Adenosine deaminase has been more commonly preferred for the diagnostic algorithms in the countries with a moderate to the high incidence of tuberculosis because it is an inexpensive method that can be accessed more quickly.[5] C-reactive protein is an acute-phase protein that serves as an early marker of inflammation or infection. The protein is synthesized in the liver and is normally found at concentrations of less than 10 mg/L in the blood. During infectious or inflammatory disease states, CRP levels rise rapidly within the first 6 to 8 hours and peak at levels of up to 350–400 mg/L after 48 hours.[6,7] LDH is released from the cells when cells are damaged or destroyed. Because of this, the LDH test can be used as a general marker of injury to cells. Elevations of LDH may be measured either as a total LDH or as LDH isoenzymes. A total LDH level is an overall measurement of five different LDH isoenzymes.[8] The aim of study is evaluate the importance of pleural fluid LDH/ADA ratio and pleural fluid ADA/serum CRP ratio in differentiating tuberculous pleural effusion from other causes in a sample of Iraqi patients.

Method

A prospective study of 100 patients with exudative pleural effusion whom age ranges from 30–70 years where admitted at medical department at Al-Imamein Kadhimein medical city in Bagdad and in Marjan and Al-Sadik hospitals at Babylon city. From them 61 (61%) are males and 39 (39%) are females. The study period is 9 months started from first of February 2019 to thirty of October 2019. In this study we firstly use light criteria in differentiation of transudative from exudative pleural effusion and according this criteria some transudative cases diagnosed as heart failure when we do echo and other cases diagnosed as liver cirrhosis by ultrasound of abdomen and ascetic fluid analysis. Also we do pleural biopsy for some cases of exudative pleural effusion and some cases diagnosed as tuberculous pleural effusion and other as malignant pleural effusion specially in elderly with massive and lymphocytic predominant pleural effusion.

Inclusion Criteria

1. Patient age more than 18 years.
2. Patients with definite diagnosis of pleural effusion on clinical, radiological imaging and laboratory.

Exclusion Criteria

1. Age less than 18 years.
2. Patients without definitive diagnosis of pleural effusion.
3. Patients previously diagnosed and already on treatment.

Post detailed history and clinical examination, chest X-ray was done to confirm and localize the pleural effusion. Diagnostic tapping of pleural fluid was done under ultrasonography guide of the chest to localize effusion in some cases. All pleural fluid samples where tested for cell count and differentiation, cytology, protein, sugar, LDH, ADA, gram stain, AFB, Gen expert study and even pleural biopsy and serum CRP. Further study such as computed tomography scan of chest, bronchoscopy, where done to determine etiology of pleural effusion when needed. The samples of pleural fluid obtained in each patients was considered for analysis using standard laboratory methods:

1. CXR for diagnosis of pleural effusion and exclude other pathology like lung mass and cardiomegaly.
2. Ultrasound of chest for differentiation between pleural effusion and pleural thickening and for detect optimal site of aspiration of pleural effusion and also ultrasound of abdomen to assess is there is ascites and liver size in case of liver disease and renal state like size of kidney in case of chronic renal failure or obstructive uoropathy.
3. CT-scan of the chest with or without contrast to assess the pleural effusion if there suspicion of malignant pleural effusion or empyema.
4. Protein was measured by the biuret method.
5. LDH measured by Ultra-violet spectrophotometry method
6. ADA by colorimetric method of Guisti and Galanti, normal value in my study <30 IU/L (11).
7. Serum CRP by titration test.
8. Pleural biopsy by Abraham needle and pleuroscopy.
9. Peural fluid sugar by spectrophotometry.
10. Echo to exclude heart failure.
11. Ascitic fluid analysis to assess the cause of ascites when it associated with pleural effusion.
12. Thyroid function test to exclude hypothyroidism as a cause of pleural effusion.
13. Blood urea and serum creatinine to exclude renal failure as a cause of pleural effusion.

The Statistical study of differences between means was estimated by chi-squared test. A *P*-value of less than 0.05 where considered significant.

Results

This prospective study include 100 patients. 50 patients had Tuberculous pleural effusion with mean age of 49 years, 31 (62%) were males, and 19 (38%) were female; 25 patients had Para pneumonic effusion with mean age of 50 years from them 13 (52%) patients were males and 12 (48%) were females; 25 patients with Malignant pleural effusion with mean age of 63 years from them 17 (68%) were males and 8 (32%) were females as had been shown in Table 1.

In this study we compare the meaning level of pleural fluid protein, LDH, ADA and serum CRP between tuberculous and Para pneumonic pleural effusions the result of study was not statically significant but the pleural fluid LDH/ADA and pleural fluid ADA/serum CRP ratios were statically significant as shown in Table 2.

Table 3 shows comparison the mean level of pleural fluid protein, ADA, LDH and serum CRP between tuberculous and malignant pleural effusions and the result of study was statically not significant but the pleural fluid LDH/ADA and pleural fluid ADA/serum CRP ratios were statically significant.

Table 1. **The causes of pleural effusions according to the sex and age for demographic**

Type of pleural effusion	No. (%)	Male No. (%)	Female No. (%)	Age years
Tuberculous pleural effusion	50 (50%)	31 (62%)	19 (38%)	49
Parapneuomonic effusion	25 (25%)	13 (52%)	12 (48%)	50
Malignant pleural effusion	25 (25%)	17 (68%)	8 (32%)	63
Total	100 (100%)	61 (61%)	39 (39%)	

Table 2. **Comparison of biochemical results between patients with Tuberculous and Para pneumonic effusions**

Parameters	Tuberculous pleural effusion	Parapneoumonic effusion	*P*-value
Protein g/dl	53.8 (±9.74)	56.1 (±8.19)	**0.95**
LDH U/L	377.5 (±68.97)	500.8 (±58.18)	**0.20**
ADA U/L	35 (±7.82)	21.7 (±4.68)	**0.10**
LDH/ADA ratio	10.7 (±2.61)	23.08 (±6.42)	**0.025**
S-CRP mg/dL	1.7 (±0.43)	3.7 (±0.98)	**0.20**
ADA/CRP ratio	20.5 (±5.01)	5.8 (±1.52)	**0.002**

P-value ≤ 0.05 (Significant)

Table 3. **Comparison biochemical results between patients with Tuberculous and Malignant pleural effusions**

Parameters	Tuberculous pleural effusion	Malignant pleural effusion	*P*-value
Protein g/dl	53.8 (±9.74)	54.0 (±7.82)	**0.95**
LDH U/L	377.5 (±68.97)	559 (±48.14)	**0.995**
ADA U/L	35 (±7.82)	20 (±4.04)	**0.20**
LDH/ADA ratio	10.7 (±2.61)	27.95 (±8.75)	**0.005**
S-CRP mg/dL	1.7 (±0.43)	3.5 (±0.45)	**0.10**
ADA/CRP ratio	20.5 (±5.01)	5.7 (±1.15)	**0.005**

P-value ≤ 0.05 (significant)

Discussion

This prospective study include 100 patients. 50 patients had Tuberculous pleural effusion with mean age of 49 years, 31 (62%) were males, and 19 (38%) were female; 25 patients had Para pneumonic effusion with mean age of 50 years from them 13 (52%) patients were males and 12 (48%) were females; 25 patients with Malignant pleural effusion with mean age of 63 years from them 17 (68%) were males and 8 (32%) were female.In comparison between tuberculous with para pneumonic pleural effusions the mean level of protein in Tuberculous pleural effusion was 53.8 gm/dl, and the mean level of protein in Para pneumonic pleural effusion was 56.1 gm/dl with no significant difference. The LDH mean level in Tuberculous pleural effusion was 377.5 U/L, and its mean level in Parapneumonic effusion was 500.8 U/L with no significant statistically difference. Adenosine deaminase had been taken as parameter and we found that its level in Tuberculous pleural effusion was 35 U/L and its level in Para pneumonic effusion was 21.7 U/L, the comparison between them was not significant. The ratio of LDH/ADA in Tuberculous pleural effusion was 10.7 and in Para pneumonic effusion was 23.08. The comparison between the two results were significant. These two parameters were in agreement with Wang et al. study[9] which conclude that absolute level of ADA in TB and para pneumonic effusion not useful to differentiate between TB and para pneumonic effusions but the ratio between LDH/ADA helpful to differentiate TB from para pneumonic effusion in Wang et al. study the level of protein was 50 gm/dl in tuberculous effusion and in para pneumonic effusion was 47.6 gm/dl with no significant difference. LDH in tuberculous effusion was 364.5 U/L and in para pneumonic effusion was 4037 U/L, the result of *P* -value was significant. ADA mean level in tuberculous pleural effusion was 33.5 U/L and in para pneumonic effusion was 43.3 U/L with no significant, which in agreement with this study. The ratio of pleural fluid LDH/ADA of tuberculosis was 10.88, and in para pneumonia pleural effusion was 66.91, with significant, which in agreement with this study. The protein mean level in tuberculous pleural effusion was 53.8 gm/dl and its level in Malignant pleural effusion was 54 gm/dl whiteout significant difference. LDH mean level in tuberculous pleural effusion was 377.5 U/L, in Malignant, pleural effusion was 559 U/L, and the result of comparison was not significant. These two results agreed Liu Y. C. et al. study[10] which confirmed that both protein and LDH levels were not useful in differentiate TB from malignant effusion. Since in Liu Y. C. et al. study 24 patients with tuberculous pleural effusion and 42 patients with malignant pleural effusions and there were no statically significant differences between these two groups in regard to protein level, LDH and glucose levels, in which the protein level in tuberculous pleural effusion was 4.50 g/dl and its level in malignant pleural effusion was 4.28 g/dl with no significant difference and this in agreement with this study. Since LDH in tuberculous pleural effusion was 368 IU/L and in malignant pleural effusion was 282.5 IU/L so the result of comparison not significant which is in agreement with this study. Other studies that in agreement of my study like Verma A. et al. study[11] and Darooei R. et al. study[12], since in first study total number was 118, malignant pleural effusion was 84 and tuberculous pleural effusion was 34, mean level of LDH in malignant pleural effusion was 525 IU/L in malignant pleural effusion and 494 IU/L in tuberculous pleural effusion so the *P* -value was 0.08 which statically not significant. The mean ADA level in Tuberculous pleural effusion was 35 U/L, and its mean level in Malignant pleural effusion was 20 U/L with no significant difference, and this result not in agreement with Verma et al. study[11] which conclude that ADA level in malignant pleural effusion = 9 U/L and its level in tuberculous pleural effusion was 42 U/L, so the *P* value was significant which equal to was 0.001 which is useful in differentiate tuberculous from malignant pleural effusion but in this study the result of ADA level in tuberculous pleural effusion and malignant pleural effusion may be of no benefit in regions where tuberculosis is highly prevalent; arising value is very sensitive for tuberculous pleural effusion but is not specific as its level can increase in pleural fluid of both malignancy and para pneumonic effusion so we cannot depend on its level alone to differentiate between the tuberculous from malignant pleural effusions.[13] The ratio between LDH/ADA in Tuberculous pleural effusion was 10.7 and in Malignant, pleural effusion was 27.95, with significant value. The mean level of serum CRP in tuberculous pleural effusion was 1.7 mg/dl and in the para pneumonic effusion was 3.7 mg/dL the result of P-value was not significant. This result is in agreement with Fiona Mendelson et al. study[13] which confirmed that the serum CRP is not useful in differentiate TB from para pneumonic effusions which included the serum CRP and procalcitonin level, since the CRP was 131 mg/l in tuberculosis and was 60 mg/l in pneumonia with no significant *P* -value = 1 which in agreement with this study. The ratio of pleural fluid ADA/ Serum CRP was 20.5 in tuberculous pleural effusion was 5.8 in para pneumonic effusion so the result of comparison between them was significant, with p value equal to 0.002. This result in agreement with Lee J., et al. study[14] which include 36 patients with tuberculosis and 41 patients with para pneumonic effusion and the ratio of pleural fluid ADA/serum CRP is best useful parameter in differentiate tuberculous pleural effusion from para pneumonic effusion. Serum CRP mean level in tuberculous pleural effusion was 1.7 mg/dl and in malignant pleural effusion was 3.5 mg/dl and the result of comparison between them was not significant And this result is in agreement with Mohamed et al. study[15] which include two groups of patients in their study, first group which include 29 patients with tuberculous pleural effusion and the level of serum CRP in these patients was 2.834 mg/dl and the second group was patients with malignant pleural effusion and its mean level of serum CRP was 2.787 mg/dl with no significant difference but the result of

pleural fluid CRP in tuberculous pleural effusion was 3.651 mg/dl and in malignant effusion was 2.693 mg/dl, so the result of comparison between two groups was significant. The ratio of pleural fluid ADA/serum CRP in tuberculous pleural effusion was 20.5 and in malignant pleural effusion was 5.7 with significant *P*-value so the ratio of pleural fluid ADA to serum CRP is useful to differentiate tuberculous from malignant pleural effusions.

Conclusion

Pleural fluid LDH/ADA ratio is of great value in differentiation tuberculous pleural effusion from malignant pleural effusion with predominant lymphocytes, pleural fluid ADA/serum CRP ratio is of great value in differentiation tuberculous pleural effusion from para pneumonic pleural effusion with elevated pleural fluid ADA and elevated serum CRP.

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