The diagnostic utility of pleural fluid viscosity in lymphocytic pleural effusion

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Context The first step in the diagnostic work up of pleural effusion is the distinction between transudative and exudative pleural effusions (TPEs and EPEs). This discrimination is based on some biochemical tests that are relatively costly and time consuming. Lymphocyte-predominant EPE is the result of many diseases with malignancy, tuberculosis being the most common among them.

Aims The aim of this study was to assess the role of pleural fluid viscosity in the differentiation between exudates and transudates and to identify the cause of pleural effusion.

Patients and methods The study comprised 10 patients with TPE and 48 patients with EPE: 18 of them had tuberculous (TB) effusion, 25 patients had malignant pleural effusion (MPE) (patients with MPE included 10 with lung cancer and 15 with other known or unknown cancers) and five patients had connective tissue disease (CTD)-associated effusion. Pleural fluid protein, albumin, lactic dehydrogenase, and viscosity were measured in all patients.

Results Pleural fluid viscosity was higher in patients with EPE with a highly significant difference ($P < 0.01$), and a cutoff value of 1.01 cP could distinguish between TPE and EPE with a sensitivity of 97.7%, a specificity of 93.9%, a positive predictive value of 97.5%, and a negative predictive value of 92.5%. It also showed significant positive correlation with protein, albumin, and lactic dehydrogenase. It was also higher in TB effusion than in MPE, with a highly significant difference ($P < 0.01$), and in CTD-associated effusion with a significant difference ($P < 0.05$). At a cutoff value of 1.5 cP, pleural fluid viscosity could discriminate between TB effusion and MPE with a sensitivity of 67%, a specificity of 84%, a positive predictive value of 75%, and a negative predictive value of 77%. There was also a nonsignificant difference between MPE secondary to lung cancer versus other known or unknown primary cancer ($P > 0.05$).

Conclusion Pleural fluid viscosity can reliably differentiate between TPE and EPE. It can also help in the discrimination between TB effusion and MPE with moderate sensitivity and high specificity. *Egypt J Broncho* 2015 9:73–78

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Introduction

Pleural effusion denotes abnormal accumulation of fluid within the pleural cavity. It may be caused by increased production, decreased drainage, or more commonly both. It is the most common manifestation of pleural disease, with etiologies ranging from cardiopulmonary disorders to systemic inflammatory or malignant diseases requiring urgent evaluation and treatment [1].

These effusions may be transudates needing only treatment of the cause or exudates requiring a definite diagnosis with specific treatment modalities. This classification was based on the criteria of Light *et al*. [2] and more recently, other tests such as protein and cholesterol levels in effusion and serum-effusion albumin gradient (SEAG) have been shown to have a statistically similar diagnostic accuracy [3,4].

Distinction between transudates and exudates to determine the origin of pleural effusions is an essential first step in the diagnostic work up. Other tests include radiologic and sonographic assessment, pleural fluid cytology, bacteriology, biochemistry, and blind pleural biopsy. However, after exhaustion of these tests, 20% of exudative pleural effusion (EPE) is still undiagnosed [5], and more advanced tests, such as image-guided pleural biopsy, pleuroscopy or video-assisted thoracoscopy, bronchoscopy, and open pleural biopsy are needed in individual patients [6].

Lymphocytic pleural effusion (lymphocytes constitute >50% of the white cell population) indicates that the patient probably has a malignant pleural effusion (MPE) or a tuberculous (TB) pleural effusion [7,8].

Viscosity means the resistance of fluid to flow; in other words, the viscosity of any type of fluid is the expression of the ratio of shear stress to the shear rate of the particles in that fluid. Plasma viscosity is related to the concentration of plasma proteins (especially fibrinogen) and lipoproteins. Other factors affecting plasma viscosity include their molecular weights, rigidity, and the shape of individual molecules [9].

The same could apply to pleural fluid in patients with pleural effusion as shown by Yektin *et al*. [10], who found that pleural exudates have a higher fluid viscosity. The cellular content of pleural fluid as well as the size and the rigidity of cells also cause increased fluid viscosity [11]; hence, diseases with a relatively high cellular content in the pleural space, such as TB pleural effusions and MPEs, could have a higher viscosity.

Aim of the work

The study aimed to assess the role of pleural fluid viscosity measurement in the differentiation between exudates and transudates and the identification of the cause of exudative lymphocytic pleural effusion.

Patients and methods

This cross-sectional comparative study was conducted in the Chest Unit, Suez Canal University Hospital, Ismailia, Egypt, and the Chest Department, Ain Shams University Hospitals, Cairo, Egypt. The study population included 58 patients with pleural effusion: 10 of them had transudative pleural effusion (TPE) and 48 patients had EPE with lymphocytic predominance (i.e. lymphocytes constituted more than 50% of cells in the pleural fluid). Transudates were defined by a negative test for all items of the Light criteria as well as by a SEAG greater than 1.2, and the reverse is true regarding EPE.

Patients with eosinophilic and neutrophilic pleural effusions as well as patients with lymphocyte-predominant effusion with unknown cause were excluded. All patients gave an informed written consent to be involved in the study.

All patients were subjected to the following: complete medical history and careful clinical examination, radiological assessment, diagnostic thoracentesis, routine blood investigations, measurement of pleural fluid viscosity, serum and pleural fluid proteins, albumin, lactic dehydrogenase (LDH), and glucose. Other investigations were performed in patients with EPE, which included pleural fluid cytology, differential cell count, pleural biopsies with histopathological examination, adenosine deaminase when TB pleural effusion was suspected, and antinuclear antibody and rheumatoid factor when connective tissue disease (CTD) was suspected. Further investigations were dictated by the clinical presentation of each patient. MPE was suggested in patients with a known malignancy and diagnosed by positive cytology and/or pleural biopsy specimens for malignancy. TB pleural effusion was diagnosed by positive tuberculin skin testing, lymphocytic predominance, and the presence of caseating granuloma in biopsy specimens; otherwise, the diagnosis was confirmed by the presence of adenosine deaminase level higher than 43 IU/l [12], in patients younger than 40 years of age, with a highly suggestive clinical picture and with good response to anti-TB medications.

Patients with CTD were diagnosed by the rheumatologist on the basis of specific criteria [13,14]. Rheumatoid pleural effusion was suggested by a glucose level in pleural fluid less than 30 mg/dl and rheumatoid factor of at least 1 : 320 with values higher than the serum titer [15], and lupus pleuritis was diagnosed if the antinuclear antibody in the pleural fluid was higher than in the serum in the proper clinical setting with good response to corticosteroids [16].

Measurement of pleural fluid viscosity

Ten milliliters of pleural fluid mixed with EDTA were used for the measurement of viscosity using a portable viscometer (Viscolite 100; Hydramotion, Malton/York, UK) before and after centrifugation with digital expression of the viscosity (η) readings in centipoises (cP) units.

Statistical analysis

Data were analyzed using Statistical Program for Social Science (SPSS version 20, 2009, Echosoft Corporation, USA). Quantitative data were expressed as mean ± SD. Qualitative data were expressed as frequency and percentage.

The following tests were performed:

(1) Independent-sample *t*-test of significance was used when comparing between two means.
(2) A one-way analysis of variance was used when comparing between more than two means.
(3) The χ^2-test of significance was used to compare proportions between two qualitative parameters.
(4) Pearson's correlation coefficient (*r*) test was used for correlating data.
(5) Probability (*P*-value)
    (a) *P*-value less than 0.05 was considered significant.
    (b) *P*-value less than 0.01 was considered as highly significant.
    (c) *P*-value greater than 0.05 was considered insignificant.

Results

The study comprised 58 patients with pleural effusion: 10 of them had TPE, three men and seven women with a mean age of 59.2 ± 10.2 years (Table

1) (two with hepatic hydrothorax, two with nephrotic syndrome, and six with congestive heart failure), and 48 patients had EPE with lymphocyte predominance, 32 men and 16 women with a mean age of 55.15 ± 12.72 years; 25 patients with exudative pleural effusion (EPE) received a diagnosis of MPE (10 with bronchogenic carcinoma, five with cancer breast, three with lymphoma, two with cancer cervix, and five with unknown primary cancer) (Figs. 1-4). Eighteen patients with EPE were diagnosed as TB pleural effusion and five were diagnosed as pleural effusion associated with CTD (three with rheumatoid arthritis and two with systemic lupus erythematosus) (Tables 2–6).

Discussion

Although there are more than 50 recognized causes of pleural effusion, malignancy, infections including tuberculosis, congestive heart failure and venous thromboembolism are the most common underlying etiologies [17,18]. Pleural fluid exudate is identified by any of the following criteria [19,20]:

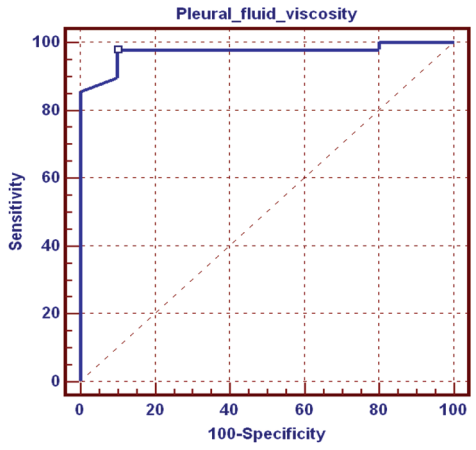
(1) The ratio of pleural fluid protein to serum protein is greater than 0.5.
(2) The pleural fluid LDH to serum LDH is greater than 0.6 or two-third of the upper limit of the normal of serum LDH.

However, in some patients with TPE receiving diuretics, serum effusion protein or albumin gradients can be used [21,22]. EPEs with lymphocytes greater than 50% of the total cell population are caused by many diseases with malignancy, tuberculosis being the most common among them [23].

In the present study, pleural fluid viscosity was measured in 10 patients with TPEs and 48 patients with lymphocytic EPEs. It revealed significantly higher values in EPEs than in TPEs, and a significant positive correlation with pleural fluid protein, albumin, LDH, and the SEAG. Using the receiver operating characteristics curve, it was found that a cutoff value of 1.01 cP could discriminate between both types of effusions, with a sensitivity of 97.7%, a specificity of 93.9%, a positive predictive value (PPV) of 97.5%, and a negative predictive value (NPV) of 92.8% with a diagnostic accuracy of 98%. These results are consistent with those of Hurth *et al.* [24] who demonstrated that an EPE had a viscosity around 1.39 ± 0.08 cP, whereas a TPE measured at 0.89±0.09 cP, and those of Yetkin *et al.* [10] who found that using a cutoff value of 1 Cp for pleural fluid viscosity could differentiate between both types of effusions with a sensitivity of 94%, a specificity of 93%, and PPV and NPV of 97%.

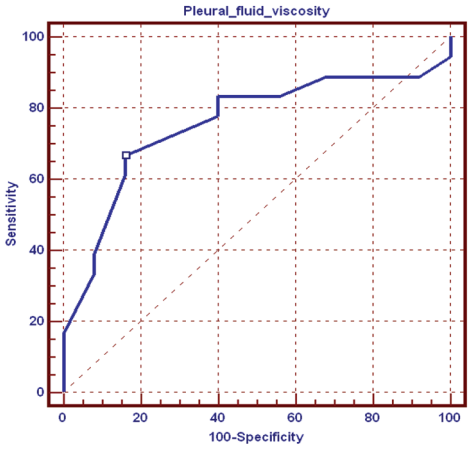
Plasma viscosity is almost twice as high as that of water, which is due to dissolved macromolecules, mainly fibrinogen, immunoglobulins, albumin, and lipoproteins [25]. Pleural fluid transudate results from diseases that do not directly involve the pleural, but instead produce an imbalance of Starling's forces, resulting in the movement of fluid into the pleural space [26]. It is expected for a transudate, which is a

Fig. 1



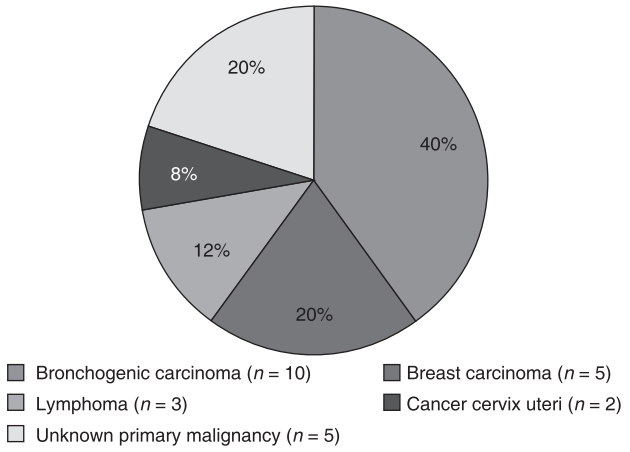
A receiver operating characteristics curve was used to differentiate between transudative and exudative pleural effusion viscosities; the best cutoff value of the pleural fluid viscosity was 1.01 cP, with a sensitivity of 97.7%, a specificity of 93.9%, a positive predictive value of 97.5%, and a negative predictive value of 92.8%, with a diagnostic accuracy of 98% with values of at least 1.01 cP in favor of exudative pleural effusion.

Fig. 2



A receiver operating characteristics curve was used to differentiate between malignant and tuberculous pleural effusions; the best cutoff value of the pleural fluid viscosity was 1.5 cP, with a sensitivity of 67%, a specificity of 84%, a positive predictive value of 75%, and a negative predictive value of 77%, a with diagnostic accuracy of 75.7%, with values of at least 1.5 cP in favor tuberculous pleural effusion.

Fig. 3



The number and the percent distribution of primary cancers in patients with malignant pleural effusion.

Table 1 A comparison between transudative and exudative pleural effusions with regard to age and sex

Sex and age	Groups			
	Transudative pleural effusion	Exudative pleural effusion	*t*-test/ χ^{2a}	*P*-value
Age (mean ± SD) (years)	59.20 ± 10.20	55.15 ± 12.72	2.110	0.394
Sex [*n* (%)]				
Male	3 (30.00)	32 (66.67)		
Female	7 (70.00)	16 (33.33)	4.650	0.106*
Total	10 (100.00)	48 (100.00)		

There is a nonsignificant statistical difference between both types of effusions with regard to age and sex; $^{a}\chi^{2}$, χ^{2}-test; *t*-test, independent-sample *t*-test; *P*-value > 0.05, nonsignificant.

Table 2 A comparison between transudative and exudative pleural effusions with regard to protein, albumin, LDH, and SEAG

Laboratory parameters	Transudative pleural effusion (*n* = 10) (mean ± SD)	Exudative pleural effusion (*n* = 48) (mean ± SD)	*t*-test	
			t	*P*-value
Protein (g/dl)	1.74 ± 0.80	4.94 ± 0.80	−11.585	<0.01
Albumin (g/dl)	1.29 ± 0.47	3.84 ± 0.49	−14.959	<0.01
LDH (IU/l)	149.44 ± 44.16	387.56 ± 108.29	−6.458	<0.01
SEAG (g/dl)	1.48 ± 0.18	0.49 ± 0.33	9.087	<0.01

There is a highly significant statistical difference between both types of effusions with regard to all chemistry parameters; LDH, lactic dehydrogenase; SEAG, serum-effusion albumin gradient; *t*-test, independent-sample *t*-test; *P*-value < 0.01, highly significant.

Table 3 A comparison between transudative and exudative pleural effusions with regard to the pleural fluid viscosity

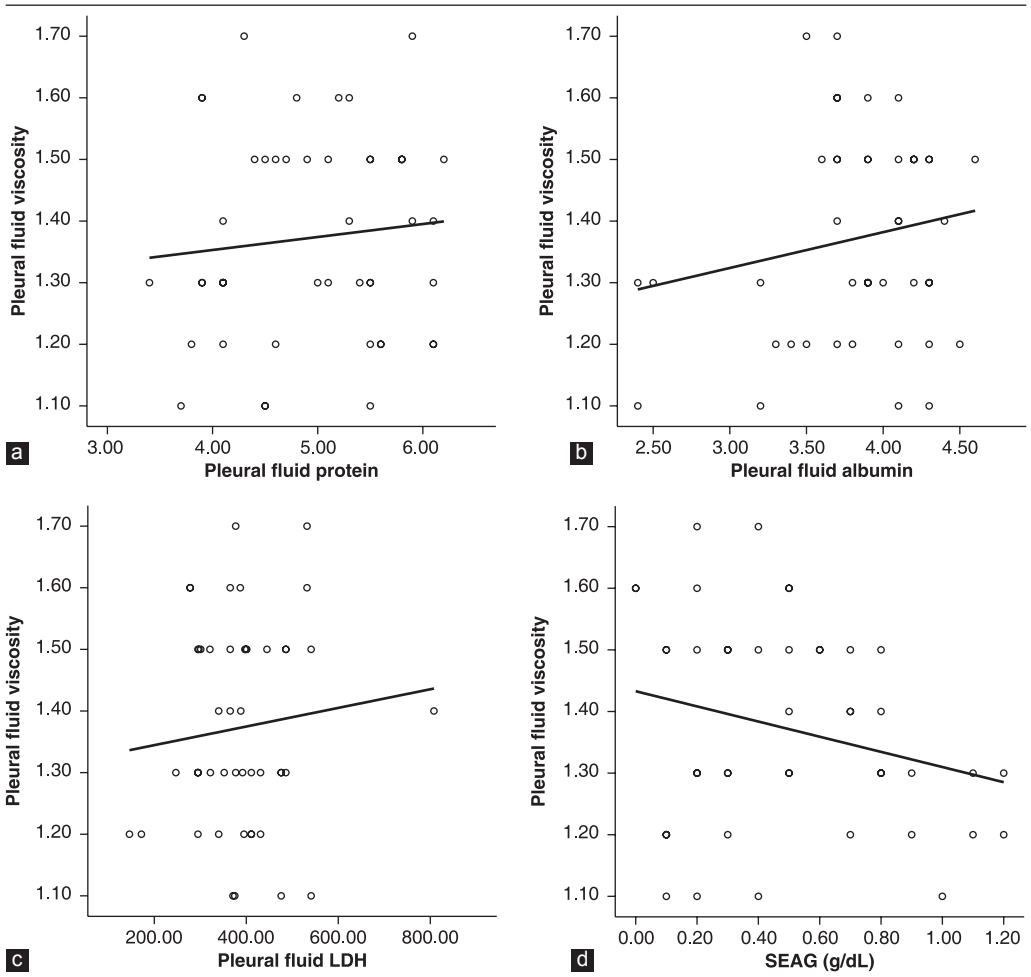
Pleural fluid viscosity (cP)	Transudative pleural effusion (*n* = 10) (mean ± SD)	Exudative pleural effusion (*n* = 48) (mean ± SD)	*t*-test	
			t	*P*-value
Precentrifugation	0.75 ± 0.11	1.70 ± 0.18	−15.663	<0.01
Postcentrifugation	0.63 ± 0.08	1.37 ± 0.16	−13.838	<0.01

There is a highly significant statistical difference between both types of effusions with regard to the pleural fluid viscosity; *t*-test, independent-sample *t*-test; *P*-value < 0.01, highly significant.

simple ultrafiltrate of the plasma, to have low viscosity approaching that of water.

In contrast, EPEs result from local or systemic diseases that directly involve the pleural surface [26], leading to increased permeability and influx of cells and macromolecules into the pleural space, with subsequent increased viscosity. Our study revealed that the precentrifugation pleural viscosity showed nonsignificant differences among malignant, TB, and CTD-associated effusions. However, postcentrifugation pleural fluid viscosity was higher in both TB and CTD-associated effusions compared with MPEs, with a highly significant statistical difference (0.01). We also found nonsignificant differences in the viscosity in MPE with regard to cases secondary to bronchogenic carcinoma versus other cases with known and unknown primary cancer. TB pleural effusions had significantly higher viscosity than CTD-associated effusions ($P < 0.5$). Using receiver operating characteristic curve for the differentiation between MPEs and TB pleural effusions, it was shown that at a cutoff value of pleural fluid viscosity of 1.5 cP, values of at least 1.5 cP were in favor of TB pleural effusion with a sensitivity of 67%, a specificity of 84%, a PPV of 75%, and an NPV of 77%, with a diagnostic accuracy of 75.7%. Our results are in agreement with those of Yetkin *et al.* [27] who found that pleural viscosity of at least 1.57 mPa s indicates TB effusion with a sensitivity of 100% and a specificity of 95% and pleural fluid viscosity of less than 1.39 mPa s indicates malignancy with a sensitivity of 100% and a specificity of 94%. In contrast, Chang *et al.* [28] claimed that MPE, with positive fluid cytology for malignant cells, had a significantly higher pleural fluid viscosity than infectious causes. These results could be explained by the higher protein content frequently encountered in TB pleural effusion, and values above 5 g/dl suggest a TB effusion [29]. Moreover, the variability of protein composition between malignant and benign effusions might potentially explain the difference [30]. Even a more recent study by Ji *et al.* [31] disclosed different profiles of acute-phase proteins (C-reactive protein) and prealbumin between infections (TB and parapneumonic) and MPE, and this might be reflected in the pleural fluid viscosity. Actually, as suggested by Yetkin *et al.* [32] plasma viscosity could be considered as an acute-phase reactant surrogate in patients with pneumonia. Fibrinogen, because of its molecular size and shape, is a major determinant of plasma viscosity, and during an acute-phase reaction, the expression of this protein is increased in hepatocytes and may be also in lung epithelial cells [33]. However, it is not known as to how much fibrinogen in the pleural fluid can affect the pleural fluid viscosity. The higher precentrifugation pleural fluid viscosity in MPE, as suggested by Chang

Fig. 4



(a) A positive correlation between the postcentrifugation pleural fluid viscosity and pleural fluid protein in exudative lymphocytic pleural effusion. (b) A positive correlation between the postcentrifugation pleural fluid viscosity and pleural fluid albumin in exudative lymphocytic pleural effusion. (c) A positive correlation between the postcentrifugation pleural fluid viscosity and pleural fluid lactic dehydrogenase (LDH) in exudative lymphocytic pleural effusion. (d) A negative correlation between the postcentrifugation pleural fluid viscosity and the pleural fluid serum-effusion albumin gradient (SEAG) in exudative lymphocytic pleural effusion.

Table 4 A comparison among different causes of exudative lymphocytic pleural effusion with regard to laboratory parameters in the pleural fluid

Laboratory parameters	Malignant pleural effusion (n = 25) (mean ± SD)	Tuberculous pleural effusion (n = 18) (mean ± SD)	CTD-associated effusion (n = 5) (mean ± SD)	ANOVA	
				F	P-value
Protein (g/dl)	4.19 ± 0.88	4.88 ± 0.53	4.12 ± 0.11	2.112	0.071
Albumin (g/dl)	3.72 ± 0.61	4.02 ± 0.30	3.82 ± 0.11	1.913	0.159
LDH (IU/l)	391.44 ± 129.86	409.78 ± 71.71	288.20 ± 9.31	2.678	0.126
Viscosity (cP)					
Precentrifugation	1.71 ± 0.22	1.71 ± 0.16	1.64 ± 0.05	0.287	0.752
Postcentrifugation	1.26[a] ± 0.12	1.61[b] ± 0.11	1.42 ± 0.16	25.680	<0.01
SEAG (g/dl)	0.58 ± 0.37	0.37 ± 0.21	0.48 ± 0.44	2.154	0.128

ANOVA, analysis of variance; CTD, connective tissue diseases; LDH, lactic dehydrogenase; SEAG, serum-effusion albumin gradient; [a]The postcentrifugation viscosity shows a highly significant difference between malignant and (tuberculous and CTD-associated) pleural effusions; [b]A significant difference between tuberculous and CTD-associated pleural effusions. Other parameters show nonsignificant differences; *F*, ANOVA test.

et al. [28] could be explained by the contribution of cell rigidity and the size of malignant cells to pleural fluid viscosity in cases with a positive fluid cytology; however, in contrast to our results, they also found nonsignificantly lower values of pleural fluid viscosity in infectious pleural effusions than in MPE.

Table 5 A comparison between pleural effusion secondary to lung cancer versus other cancers or unknown primary cancer with regard to precentrifugation and postcentrifugation pleural fluid viscosities

Viscosity (cP)	Pleural effusion (primary lung cancer) (n = 10) (mean ± SD)	Pleural effusion (others cancers or unknown primary) (n = 15) (mean ± SD)	t-test	
			t	P-value
Precentrifugation	1.76 ± 0.19	1.68 ± 0.23	−0.923	0.367
Postcentrifugation	1.3 ± 0.15	1.24 ± 0.09	1.243	0.227

There is a nonsignificant difference between pleural effusion secondary to lung cancer versus other cancers or unknown primary cancer with regard to precentrifugation and postcentrifugation pleural fluid viscosities, with P-value > 0.05.

Table 6 The correlation between postcentrifugation viscosity and protein, albumin, LDH, and SEAG in exudative lymphocytic pleural effusions

Laboratory parameters	Postcentrifugation pleural fluid viscosity (cP)	
	r	P-value
Pleural fluid protein (g/dl)	0.202	0.023
Pleural fluid albumin (g/dl)	0.374	0.023
Pleural fluid LDH (IU/l)	0.499	0.014
SEAG (g/dl)	−0.350	0.017

There is a significant positive correlation between the postcentrifugation viscosity and other chemistry parameters in exudative lymphocytic pleural effusions, but a negative correlation with the serum-effusion albumin gradient; LDH, lactic dehydrogenase; r, Pearson's correlation coefficient; SEAG, serum-effusion albumin gradient; $P < 0.05$, significant; $P < 0.01$, highly significant.

Conclusion

The measurement of pleural viscosity is a simple, cheap, and accurate test, and it can be used as a bed-side test to reliably distinguish pleural fluid exudates from transudates. It can also help in differentiating TB pleural effusion from MPEs with moderate sensitivity and high specificity in lymphocytic EPE.

Acknowledgements

Conflicts of interest

None declared.

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