

Validity of pleural lactate dehydrogenase measurements in assessment of pleural effusions

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ABSTRACT

BACKGROUND

Pleural effusions are classified into transudates and exudates based on Light's criteria, but the main disadvantage of Light's criteria is the misclassification of transudates as exudates in about 20% of cases. The aim of this study was to determine the validity of various biochemical parameters to differentiate pleural exudates and transudates.

METHODS

An observational study to evaluate diagnostics tests was conducted at the emergency department of Persahabatan Hospital, Jakarta, from September 2010 until December 2011. In total, 119 patients with pleural effusion were evaluated. Simultaneous pleural effusion and blood samples were examined for lactate dehydrogenase (LDH), total protein, cholesterol and albumin, with the clinical diagnosis as the gold standard.

RESULTS

There were 104 exudative and 15 transudative pleural effusions. Light's criteria achieved a higher overall accuracy (sensitivity 97%, specificity 80%, accuracy 95%). The optimum cut off values were pleural fluid to serum ratio of LDH 0.4 (sensitivity 95%, specificity 87%, accuracy 94%) and pleural fluid LDH of 178 IU/L (sensitivity 92%, specificity 87%, accuracy 92%). Pleural fluid cholesterol was 50 mg/dL (sensitivity 89%, specificity 53%, accuracy 85%), pleural fluid to serum cholesterol ratio 0.41 (sensitivity 75%, specificity 53%, accuracy 72%) and serum-effusion albumin gradient 1.3 g/dL (sensitivity 91%, specificity 73%, accuracy 89%). Combination of biochemical tests did not improve sensitivity or accuracy.

CONCLUSIONS

Light's criteria remain superior to other biochemical tests, but the new cut off values of LDH pleural fluid to serum ratio of 0.4 and pleural fluid LDH of 178 IU/L appears to yield a slight improvement in diagnostic accuracy.

Keywords: Lactate dehydrogenase, Light's criteria, albumin, pleural effusion

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Validitas laktat dehidrogenase pleura sebagai uji tambahan untuk menilai efusi pleura

ABSTRAK

LATAR BELAKANG

Efusi pleura diklasifikasikan menjadi eksudat dan transudat berdasarkan kriteria Light. Kekurangan kriteria Light adalah kesalahan mengklasifikasi transudat sebagai eksudat sekitar 20%. Tujuan penelitian ini adalah menentukan parameter laboratorium yang valid untuk membedakan eksudat dan transudat pada efusi pleura.

METODE

Sebuah studi observasional untuk evaluasi uji diagnostik dilakukan di instalasi gawat darurat RS Persahabatan Jakarta antara bulan September 2010 – Desember 2011. Uji diagnostik dilakukan pada 119 pasien efusi pleura. Cairan pleura dan serum digunakan untuk memeriksa laktat dehidrogenase (LDH), protein total, kolesterol dan albumin. Diagnosis klinik penyebab efusi pleura digunakan sebagai baku emas.

HASIL

Terdapat 104 pasien efusi eksudatif dan 15 pasien transudatif. Kriteria Light mempunyai sensitivitas 97%, spesifisitas 80%, akurasi 95%. Titik potong optimum didapatkan pada rasio LDH cairan pleura/serum 0,4 (sensitivitas 95%, spesifisitas 87%, akurasi 94%) dan LDH cairan pleura 178 IU/L (sensitivitas 92%, spesifisitas 87%, akurasi 92%). Kolesterol cairan pleura 50 mg/dL (sensitivitas 89%, spesifisitas 53%, akurasi 85%), rasio kolesterol cairan pleura/serum 0,41 (sensitivitas 75%, spesifisitas 53%, akurasi 72%) dan gradien albumin serum-cairan pleura 1,3 gr/dL (sensitivitas 91%, spesifisitas 73%, akurasi 89%). Kombinasi ketiga parameter tidak meningkatkan sensitivitas ataupun akurasi diagnostik.

KESIMPULAN

Kriteria Light mempunyai akurasi diagnostik tertinggi tetapi rasio LDH cairan pleura/serum dengan titik potong 0,40 dan LDH cairan pleura dengan titik potong 178 IU/L memiliki akurasi yang lebih tinggi dibandingkan dengan titik potong yang digunakan pada kriteria Light.

Kata kunci: Laktat dehidrogenase, kriteria Light, albumin, efusi pleura

INTRODUCTION

Pleural effusion is the abnormal accumulation of fluid in the pleural cavities caused by excessive transudation or exudation from the pleural surfaces. Pleural effusion may appear in the course of a known disease, or it may present without associated symptoms or previously known cause.⁽¹⁾ However, regardless of presentation, pleural effusion is always abnormal and indicates the presence of an underlying disease.⁽²⁾ The most frequent causes of pleural effusions are cardiac failure,

pneumonia, and malignant neoplasm. The diagnosis of a pleural effusion is based on the clinical history and physical examination, followed by chest radiography, analysis of pleural fluid,⁽³⁾ and optionally by other investigations, such as computed tomography (CT) of the thorax, pleural biopsy, thoracoscopy, and bronchoscopy.

The initial step in the search for the etiology of a pleural effusion is to categorize it as a transudate or an exudate. For this purpose, the criteria formulated by Light⁽⁴⁾ have been extensively used. According to Light's criteria,

pleural fluid is classified as an exudate if it meets at least one of the following conditions: pleural fluid-serum protein ratio of >0.5 ; pleural fluid-serum lactate dehydrogenase (LDH) ratio of >0.6 ; and pleural fluid LDH concentration of minimally 200 U/L. Light's criteria have a high sensitivity (almost 100%) for diagnosing exudates, but have a lower specificity, and may therefore misclassify a transudate as an exudate. In a prospective comparative study of pleural effusions involving 172 patients, Porcel et al.⁽⁵⁾ found that approximately 20% of the patients with heart failure who were taking diuretics also met Light criteria for an exudate. Exudates require more diagnostic tests to determine their etiology, thus misclassification of a transudate can have serious consequences by unnecessarily subjecting the patient to invasive procedures and increasing the morbidity of concomitant diseases, such as cardiac, renal or hepatic disorders. A number of investigations have been evaluated for differentiating exudates from transudates, e.g. a pleural fluid cholesterol concentration of >60 mg/dL (1.55 mmol/L) or a pleural fluid protein concentration of >3 g/dL are considered as indicating an exudate,⁽⁶⁾ whereas a pleural fluid cholesterol concentration of <60 mg/dL, and an serum-pleural fluid albumin gradient (i.e. the difference between serum and pleural fluid albumin levels) of ≤ 1.2 g/dL are deemed to indicate a transudate.⁽⁷⁾

The use of Light's criteria for categorizing pleural effusions into exudates and transudates, as an initial step in establishing the etiological diagnosis, suffers from the disadvantage of misclassification, making it necessary to apply additional investigations.^(8,9) The aim of the present study was to identify an optimal combination of markers for differentiating between exudates and transudates, namely by measuring LDH and albumin concentrations in the pleural fluid, in addition to the traditional (or standard) Light criteria.

METHODS

Design of the study

An observational study to evaluate diagnostics tests was conducted at the emergency department of Persahabatan Hospital, Jakarta, from September 2010 until December 2011.

Study subjects

As study subjects were taken all patients attending the emergency department at Persahabatan Hospital and meeting the inclusion and exclusion criteria. The inclusion criteria were patients with pulmonary and non-pulmonary disorders presenting with pleural effusion, who agreed to participate in the study and give written informed consent. Patients who were pregnant or in the postpartum period, who had a history of thoracic or abdominal laparotomy, or had coagulation disorders (a platelet count of $< 50,000$ per mm^3), were excluded from the study. The optimal sample size of 83 subjects was determined from a diagnostic sensitivity of exudates of 0.82, a significance level of 0.05, and a pleural effusion prevalence of 0.75.⁽¹⁰⁾ The sample was selected by non-random consecutive sampling, followed by clinical and radiological examinations. If the posteroanterior chest radiograph showed the presence of fluid in the pleural cavities, the subject underwent pleural puncture.

Pleural fluid biochemical analysis

Ten milliliter samples of pleural fluid and 5 milliliter of venous blood without added anticoagulant were collected for analysis at the 24-hour laboratory of Persahabatan Hospital. Pleural fluid was examined by macroscopy (fluid color), biochemical investigations (protein, glucose, LDH, cholesterol, and albumin), and microscopy (number of cells and differential count), while serum biochemistry comprised the same parameters as pleural fluid, viz. protein, LDH, cholesterol, and albumin.

Laboratory instruments used were a Hitachi 911 and a Fuchs Rosenthal counting chamber.

Statistical analysis

To determine the cutoff points for the diagnostic tests a receiver operator characteristic (ROC) curve was used based on the results of the pleural fluid and serum analyses. Subsequently using these cutoff points, the sensitivity, specificity, positive and negative predictive values, and accuracy (proportion of all correctly diagnosed cases: $(TP + TN) / (TP + FP + FN + TN)$) of each parameter were calculated. The data analysis was performed by means of the Statistical Program for Social Sciences version 17.0.

RESULTS

A total of 119 patients with pleural effusion were recruited into this study, with a mean age of 47.36 ± 16.43 years. The majority (55.5%) of the subjects were males, 40.3% had graduated from senior high school, and 47.1% were employees in the private business sector.

Among the pleural effusions of the subjects there were exudates in 104 (87%) and transudates in 15 (13%) patients. Tuberculosis was the main cause of the pleural effusions, followed by pulmonary cancers. Regarding the latter, 42 patients had adenocarcinoma, 2 patients

Table 1. Etiology of pleural effusions (n=119)

Etiology	n	%
Exudates		
Tuberculosis	50	42.0
Pulmonary cancers	46	38.7
Mediastinal tumors	3	2.5
Non-tuberculous infections	3	2.5
Metastatic tumors in lungs	2	1.7
Transudates		
Heart failure	8	6.7
Hepatic cirrhosis	4	3.3
Renal failure	3	2.5

had atypical carcinoid tumors and 2 patients squamous cell carcinoma. Mediastinal tumors were found in 3 patients, viz. lymphomas in 2 patients and teratomas in 1 patient. Transudates were mainly caused by heart failure, followed by hepatic cirrhosis and renal failure (Table 1).

ROC curves were constructed from serum and pleural fluid laboratory parameters, comprising protein, LDH, cholesterol and albumin, and used to determine the area under the curve (AUC) using a 95% confidence interval (CI), and optimal cutoff points for Light's criteria, cholesterol, and albumin (Table 2). The three parameters in Light's criteria had AUC values above 90%. Pleural fluid cholesterol (PF CHOL) and pleural fluid-serum cholesterol ratio (PF/S CHOL) had an AUC of

Table 2. Area under the curve (AUC), AUC 95% confidence interval (CI) and optimum cutoff points for each parameter, for differentiation of exudates and transudates

Criterion	AUC	SE	95% CI	Cutoff point
PF/S PROT	0.93	0.04	0.84 - 1	0.46
S-PF PROT	0.81	0.076	0.72 - 0.9	3.1 g/dL
PF LDH	0.90	0.052	0.80 - 1	178 IU/L
PF/S LDH	0.92	0.046	0.81 - 1	0.4
PF CHOL	0.66	0.095	0.47 - 0.85	50 mg/dL
PF/S CHOL	0.62	0.098	0.43 - 0.81	0.4
S-PF ALB	0.81	0.076	0.66 - 0.96	1.3 g/L
PF/S ALB	0.82	0.081	0.66 - 0.98	0.6

PF/S PROT=pleural fluid-serum protein ratio; S-PF PROT=serum-pleural fluid protein gradient; PF LDH=pleural fluid lactate dehydrogenase; PF/S LDH=pleural fluid-serum lactate dehydrogenase ratio; PF CHOL=pleural fluid cholesterol; PF/S CHOL=pleural fluid-serum cholesterol ratio; S-PF ALB=serum-pleural fluid albumin gradient; PF/S ALB=pleural fluid-serum albumin ratio; CI=confidence interval

66% and 62%, respectively. The serum-pleural fluid protein gradient (S-PF PROT), serum-pleural fluid albumin gradient (S-PF ALB) and pleural fluid-serum albumin ratio (PF/S ALB) had AUC values of approximately 80%.

On the ROC curve of each parameter, the cutoff point was selected with the best sensitivity and specificity, and the corresponding sensitivity, specificity, positive and negative predictive values, and diagnostic accuracy calculated (Table 3).

From the three parameters in the Light criteria, the pleural fluid LDH value of >200 u/L had the highest sensitivity (92%), but by combining these parameters, their combined sensitivity increased to 97%. The pleural fluid-serum LDH ratio of >0.6 had the highest specificity (93%), exceeding the 80% of the three Light criteria. The highest positive predictive value was found to be 99% for the pleural fluid-serum LDH ratio of >0.6. This was slightly higher than that of Light's criteria (97%). The highest negative predictive value was found to be 80% for pleural fluid LDH, but this was far lower than that of Light's criteria. The diagnostic accuracy of pleural

fluid LDH was the highest among Light's criteria but lower than their combined value.

The Light criteria parameters with their new cutoff point, i.e. the pleural fluid-serum LDH ratio of >0.4, had the highest sensitivity, highest negative predictive value, and highest diagnostic accuracy in comparison with other parameters. On the other hand, the specificity and positive predictive values of the three parameters with the new cutoff point were the same. In comparison with the standard Light criteria parameters, the pleural fluid-serum LDH ratio of 0.4 had a higher sensitivity, negative predictive values, and diagnostic accuracy than other parameters, while the specificity and positive predictive values of the three new parameters were the same.

On the ROC curve a cutoff point was found with the best sensitivity and specificity for the cholesterol parameter, i.e. a pleural fluid cholesterol value of 50 mg/dL and a pleural fluid-serum cholesterol ratio of 0.4.

The results of the ROC curve analysis yielded a cutoff point with the best sensitivity and specificity for a pleural fluid-serum albumin gradient parameter value of 1.3 g/dL

Table 3. Diagnostic test results for parameters for classification of exudates, expressed in percentages

Parameter	TP	FP	FN	TN	Sensitivity	Specificity	PPV	NPV	Accuracy
PF/S PROT >0.5	84	20	2	13	81	87	98	39	81
PF/S LDH >0.6	86	18	1	14	83	93	99	44	84
PF LDH >200	96	8	2	13	92	87	98	62	91
Light's criteria	101	3	3	12	97	80	97	80	95
PF/S PROT >0.46	93	11	2	13	89	87	98	54	89
S-PF PROT <3.1	84	20	4	11	81	73	95	35	80
PF/S LDH >0.4	99	5	2	13	95	87	98	72	94
PF LDH >178	96	8	2	13	92	87	98	62	91
PF CHOL >50	93	11	7	8	89	53	93	42	85
PF/S CHOL >0.41	78	26	7	8	75	53	92	25	72
S-PF ALB <1.3	95	9	4	11	91	73	96	55	89
PF/S ALB >0.6	94	10	3	12	90	80	97	55	89

TP=true positive; FP=false positive; TN=true negative; FN=false negative; PPV=positive predictive value; NPV=negative predictive value; PF/S PROT=pleural fluid-serum protein ratio; S-PF PROT=serum-pleural fluid protein gradient; PF LDH=pleural fluid lactate dehydrogenase; PF/S LDH=pleural fluid-serum lactate dehydrogenase ratio; PF CHOL=pleural fluid cholesterol; PF/S CHOL=pleural fluid-serum cholesterol ratio; S-PF ALB=serum-pleural fluid albumin gradient; PF/S ALB=pleural fluid-serum albumin ratio

and a pleural fluid-serum albumin ratio of 0.6. The specificity and positive predictive values of the pleural fluid-serum albumin ratio parameter were higher than that of the serum-pleural albumin gradient parameter.

DISCUSSION

This study found that the majority of pleural effusions (87%) were exudates caused by local disease of the thoracic cavity, and that the remaining 13 % were caused by systemic diseases. Similar results were reported by Afful et al.,⁽¹¹⁾ where 84% of patients had exudative effusions. Studies performed in countries with a high TB prevalence found that exudative effusions were more frequent than transudative effusions. A similar result was reported by Leers et al.,⁽¹²⁾ who found that exudative effusions accounted for approximately 75% of all effusions. In our study 38.7% of the effusions were exudates due to malignancy. Essentially the same results were obtained in a US study involving 44 subjects with pleural effusion, with mean age of 46 ± 11.1 years, which showed that the proportion of exudates due to malignancy was 55.0%.⁽¹³⁾ The first step in the diagnosis of patients with pleural effusion is to differentiate between exudates and transudates. In this connection, numerous studies have been conducted to evaluate the use of biochemical markers for differentiating exudates and transudates. The markers commonly used are the Light criteria, comprising determination of pleural fluid-serum protein ratio, pleural fluid LDH concentration, and pleural fluid-serum LDH ratio. Our study found sensitivity and specificity values of 97% and 80%, respectively, for Light's criteria, while the diagnostic accuracy was 95%. Similar results were obtained in the study conducted by Gonlugur et al.,⁽¹⁴⁾ who reported a sensitivity of 96% for Light's criteria. However, for the specificity and diagnostic accuracy of these criteria these authors found values of 59% and 88%, respectively. A study conducted with 249

subjects, with mean age of 61 ± 17 years, obtained a value 93% for the accuracy of the Light criteria, which is consistent with our results.⁽¹⁵⁾

In addition to the use of the standard Light criteria, several studies attempted to find new cutoff points for the Light criteria parameters. In these studies the ROC curve was used to obtain lower cutoff points for pleural fluid LDH concentration, namely 178 IU/L, with 92% sensitivity, 87% specificity, and 92% diagnostic accuracy. This new cutoff point was similar to the standard cutoff point of 200 IU/L. Gonlugur et al.⁽¹⁴⁾ obtained a higher cutoff point for pleural fluid LDH (377 IU/L), with sensitivity of 75%, specificity of 83%, and diagnostic accuracy of 77%. In the present study, at the cutoff point of 0.4 for the pleural fluid LDH ratio, a sensitivity of 95%, specificity of 87% and diagnostic accuracy of 94% were found. In comparison with the cutoff point of 0.6 for the Light criteria, our study obtained a higher sensitivity and diagnostic accuracy with the new cutoff point. The Light criteria as modified by the new cutoff point did not result in an increased sensitivity, specificity, and diagnostic accuracy.

In addition to abovementioned criteria, other frequently used parameters are pleural fluid cholesterol, pleural fluid-serum cholesterol ratio, and serum-pleural fluid albumin gradient.⁽⁷⁾ The pleural fluid cholesterol concentration has been used in cases of heart or renal failure treated with diuretics, where a value of >60 mg/dL (1.55 mmol/L) suggests the presence of an exudate.⁽¹⁶⁾ In our study, the pleural fluid cholesterol concentration and the pleural fluid-serum cholesterol ratio had low AUC values (66% and 62%, respectively). At a cutoff point for pleural fluid cholesterol of 50 mg/dl we found the sensitivity to be 89%, with the substantially lower specificity of 53%. The pleural fluid-serum cholesterol ratio with a cutoff point of 0.41 had a sensitivity of 75% and a specificity of only 53%. Differing results were obtained by Leers et al.,⁽¹²⁾ who found that pleural fluid cholesterol at a cutoff point of 60

mg/dl had a sensitivity of 75.7% and a specificity of 98.1%, the latter being higher than that found in our study. A high specificity for pleural fluid cholesterol was also obtained in the study conducted by Guleria et al.⁽¹⁷⁾ Leers et al.⁽¹²⁾ conclude that pleural fluid cholesterol and LDH measurements may be used to differentiate exudates from transudates with a higher diagnostic accuracy. Determination of pleural fluid cholesterol and LDH do not require the simultaneous collection of serum samples, thus reducing the number of examinations.

Several studies found that the serum-pleural fluid albumin gradient may also be used in the differentiation of exudates and transudates. In cases where the clinical evaluation indicates the presence of a transudate, whereas pleural fluid analysis indicates an exudate, then it becomes necessary to determine this parameter. In nearly all patients in whom the serum albumin has a value of 1.2 g/dL above the pleural fluid albumin, the effusion will be transudative in nature. Our study shows a cutoff point of 1.3 g/dL for the serum-pleural fluid albumin gradient, with 91% sensitivity, 73% specificity, and 89% diagnostic accuracy. These values differ from those obtained in the study conducted by Leers et al.,⁽¹²⁾ with a cutoff point of 14.5 g/L for the serum-pleural fluid albumin gradient, having a lower sensitivity (44.0%), a higher specificity (88.9%) and a far lower diagnostic accuracy (55.9%). The serum-pleural fluid albumin gradient at the cutoff point of 1.2 g/dL has been found to be capable of correctly classifying 95% of transudates and exudates.⁽⁷⁾ Singh et al.⁽¹⁸⁾ also found that the use of the serum-pleural fluid albumin gradient correctly identified all cases of transudative pleural effusion with 97.2% sensitivity and 100% specificity, with only one case from 36 cases of exudative pleural effusion being misclassified. Therefore the serum-pleural fluid albumin gradient may be regarded as an effective discriminator between exudates and transudates, except in patients with hypoalbuminemia.

The pleural fluid albumin fraction originates from serum by a process of diffusion. Increases in albumin production frequently results in adjustments in the pulmonary microvascular endothelium, which lead to increased fluid leakage, raised protein level, and lowered serum-pleural fluid albumin gradients. The highest serum-pleural fluid albumin gradient occurs in transudative effusions, since there is a low albumin filtration rate through the relatively normal pleural microvasculature. In exudative effusions, the microvasculature is damaged, allowing progressively higher amounts of albumin to enter the pleural cavity, depending on the severity of the lesion. The etiology of exudative effusions involves inflammation, changes in the pulmonary and pleural microvasculature leading to a high fluid leakage rate, high protein levels and a lowered serum-pleural fluid albumin gradient.⁽⁷⁾


By combining the pleural fluid LDH parameters of the Light criteria with pleural fluid cholesterol values, a sensitivity of 86%, a specificity of 87% and a diagnostic accuracy of 86% was obtained in the present study. By combining a pleural fluid LDH concentration of >207 IU/L or a serum-pleural fluid albumin gradient of <1.3 g/dL, Gonlugur et al.⁽¹⁴⁾ obtained a sensitivity of 95%, a specificity of 69% and a diagnostic accuracy of 89%. Thus it turns out that combining the three Light criteria parameters did not increase either their sensitivity, specificity, or diagnostic accuracy. In most cases of pleural effusion, pleural fluid analysis yields important diagnostic information, and in certain cases, the use of Light's criteria alone is enough for etiological diagnosis. However, to overcome the limitation of misclassification by using the criteria of Light et al.,⁽⁴⁾ the new cut-off values of LDH pleural fluid to serum ratio of 0.4 and pleural fluid LDH of 178 IU/l appears should be used, to yield an improvement in diagnostic accuracy in the differentiation of exudates and transudates in clinical practice.

The cost of performing pleural fluid LDH determinations is affordable and provides essential diagnostic support to the clinicians, enabling them to avoid misclassification of transudates as exudates that may lead to unnecessary and costly investigations, thus obviating the need to order bronchoscopic procedures and computed tomography scans.

CONCLUSIONS

The Light criteria have a high sensitivity and diagnostic accuracy. Determination of pleural fluid LDH concentration is a valid means for distinguishing exudates from transudates. Further studies of prospective design are necessary to test the validity of various parameters with newer cutoff points.

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REFERENCES

- Maskell NA, Butland RJA. BTS guidelines for the investigation of unilateral pleural effusion in adults. *Thorax* 2003;58:8-17.
- Rahman NM, Chapman SJ, Davies RJ. Pleural effusion: a structured approach to care. *Br Med Bull* 2004;72:31-47.
- McGrath EE, Paul B, Anderson PB. Diagnosis of pleural effusion: a systematic approach. *Am J Critical Care* 2011;20:119-28.
- Light RW. Pleural effusion. *N Engl J Med* 2002;346:1971-7.
- Porcel JM, Vives M, Vicente de Vera MC, Cao G, Rubio M, Rivas MC. Useful tests on pleural fluid that distinguish transudates from exudates. *Ann Clin Biochem* 2001;38:671-5.
- Cragun WH. Pleural effusion prediction failure. *Chest* 2002;122:1505-6.
- Mangaraj M, Kumari S, Nanda R, Pattnaik MR, Mohapatra PC. Pleural fluid MDA and serum-effusion albumin gradient in pleural effusion. *Indian J Clin Biochem* 2008;23:81-4.
- Light RW. Pleural effusions: the separation of transudates and exudates. *EJB* 2007;1:8-11.
- Heffner JE, Highland K, Brown LK. A meta-analysis derivation of continuous likelihood ratios for diagnosing pleural fluid exudates. *Am J Respir Crit Care Med* 2003;167:1591-9.
- Bachmann LM, Puhan MA, Riet G, Bossuyt PM. Sample sizes of studies on diagnostic accuracy: literature survey. *BMJ* 2006;332:1127-9.
- Afful B, Murphy S, Antunes G, Dudzevicius V. The characteristics and causes of pleural effusion in Kumasi Ghana: a prospective study. *Tropical Doctor* 2008;38:219-20.
- Leers MP, Kleinveld HA, Scharnhorst. Differentiating transudative from exudative pleural effusion: should we measure effusion cholesterol dehydrogenase? *Clin Chem Lab Med* 2007;45:1332-8.
- Abouzgheib W, Bartter T, Dagher H, Pratter M, Klump W. A prospective study of the volume of pleural fluid required for accurate diagnosis of malignant pleural effusion. *Chest* 2009;135:999-1001.
- Gonlugur U, Gonlugur TE. The distinction between transudates and exudates. *J Biomed Sci* 2005;12:985-90.
- Candeira-Romero S, Hernandez L, Romero-Brufao S, Orts D, Fernadex C, Martin C. Is it meaningful to use biochemical parameters to discriminate between transudative and exudative pleural effusions? *Chest* 2002;122:1524-9.
- Froudarakis ME. Diagnostic work-up of pleural effusions. *Respir* 2008;75:4-13. DOI:10.1159/000112221.
- Guleria R, Agarwal SR, Sinha S, Pande JN, Ball WC. Role of pleural fluid cholesterol in differentiating transudative from exudative pleural effusion. *Nat Med J India* 2003;16:64-9.
- Singh G, Kajal NC, Kaur A, Singh M, Bhatia AS. Diagnostic value of serum-effusion albumin gradient in differentiating exudative and transudative pleural effusions. *Chest* 2003;124:4.