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# DIAGNOSTIC VALUE OF URIC ACID IN PLEURAL EFFUSION

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## ABSTRACT

Pleural effusion is excessive pleural fluid accumulation in the aimed pleural cavity, are categorized into exudate and transudate. Light's criteria (1972) has become a classic criteria to distinguish pleural effusion types. Other criteria were evaluated such as pleural fluid uric acid. The aimed of this study was to analyze the difference of uric acid level between transudate and exudate and to compare it with Light's criteria. A cross-sectional study was conducted in Clinical Pathology Laboratory of the Dr. Wahidin Sudirohusodo Hospital Makassar in September 2016. Uric acid level of pleural effusion samples was measured by ABX Pentra 400. Statistical analysis used Mann-Whitney U test, significance was indicated if $p<0.05$. Cut-off, sensitivity and specificity of uric acid used ROC curve. Total subjects were 56 patients, mean age 49.54$\pm$13.63 years-old, 31 males (55.4%) and 25 females (44.6%). Most cases were exudative effusion (58.9%) with 19 malignancy cases (33.9%). Uric acid level median was 6.6 mg/dL (3.24-17.50 mg/dL) higher in transudate than exudate 5.01 mg/dL (0.6-9.40 mg/dL) (p=0.001). The cut-off point for pleural fluid uric acid was 5.845 mg/dL, with a sensitivity of 78.3% and specificity of 66.7%. Sensitivity and specificity of Light's criteria was 97% and 60.9%. There was a significant difference between pleural fluid uric acid level in transudate and exudate, higher in transudate than exudate. Light's criteria were higher in sensitivity than uric acid, but lower in specificity. Further research is needed with better sampling method to reduce bias.

**Key words:** Uric acid, pleural effusion, Light's criteria

## INTRODUCTION

Pleural cavity located between the visceral and parietal pleura is, normally filled with thin fluid approximately 1-10 mL. The pleural fluid serves as a lubricant between the two pleural surfaces in respiration. The balance of fluid in the pleural cavity is maintained by colloid osmotic pressure, capillary permeability and hydrostatic pressure. Pleural fluid in normal circumstances is formed slowly as plasma filtration through capillaries and then reabsorbed via the lymph vessels around the pleura.[1,2]

Pleural effusion is excessive pleural fluid accumulation in the pleural cavity, caused by excessive production or an absorption disorder, or both of them. Pleural effusion is a common manifestation of pleural abnormalities that caused by a variety of diseases, ranging from cardiovascular disease, inflammatory or malignant diseases that require further evaluation and therapy.[3] Pleural effusion can be categorized into exudate or transudate based on the pathogenesis. Transudate occurs due to changes in hydrostatic pressure or oncotic systemic, without pathological abnormalities in the structure of the pleura or the walls of blood vessels. Exudate is caused by a local pathology disorder or structural damage to the pleura.[4,5]

Uric acid is a product of catabolism of nitrogen-containing products especially purines, either from diet or endogenous nucleic acids which are Deoxyribonucleic Acid (DNA) and Ribonucleic Acid (RNA). Uric acid in the circulation derived from the degradation of a normal dietary source and dead body cells.[6] Uric acid with low molecular weight (168 g/mol) based on studies can be found in the pleural fluid.[2,7,8] Increasing uric acid levels can be found in clinical conditions that cause oxidative stress and tissue hypoxia, such as obstructive lung disease, congestive heart failure and others. Depletion of cellular oxygen results in Adenosine Triphospate (ATP) degradation into hypoxanthine, xanthine and uric acid.[2,7]

Light's criteria introduced in 1972, has become a classic criteria to distinguish exudate from transudate. Fluid is considered exudative if it meets one or more of the following criteria: pleural/serum protein ratio of > 0.5; the pleural/serum LDH ratio of > 0.6; and/or the pleural fluid Lactate Dehydrogenase (LDH) greater than 200 U/l).[7,9] In a recent article, Porcel reported that Light's criteria had a very high sensitivity (98%) but lower specificity (73%).[10]

Several recent articles have evaluated alternative criteria for the distinction of transudate and exudate, such as a pleural fluid uric acid level. Hazarika *et al.* Found that pleural fluid uric acid levels were higher in transudate than exudate with a cut-off 5.35 mg/dL, sensitivity of 89.32% and specificity of 92.60%.[5] Jain *et al.* Also found pleural fluid uric acid level higher in transudate than exudate with a cut-off 5.5 mg/dL, sensitivity of 94% and specificity of 83%.[2]

Considering these alternative criteria, resecrhers are interested in comparing the two criteria mentioned above in determining the type of pleural fluid, to find a more accurate, applicable and inexpensive test. Thus, the result of this study can be used as a reference to the clinicians in selecting an effective and efficient test.

The aimed of this study was to evaluate the difference of pleural fluid uric acid level between transudate and exudate and to compare it with Light's criteria.

## METHODS

A cross-sectional study of 56 pleural fluid specimens was conducted in Clinical Pathology Laboratory of the Dr. Wahidin Sudirohusodo Hospital Makassar in September 2016. Pleural fluid specimens were obtained from thoracocentesis procedure by Pulmonologist on the ward and then the analysis was performed in the Clinical Pathology Laboratory. Patients having pleural effusion secondary to trauma, were excluded from this study. Uric acid pleural fluid levels were analyzed using a chemical autoanalyzer (ABX Pentra 400), colorimetric method.

Samples were therefore divided into two groups as transudative effusion or exudative effusion based on standard methods of diagnosis and Light's criteria. Malignancies were confirmed by cytology examination. Infections were confirmed by positive microbial culture and acid-fast bacilli smear. Congestive heart failure, chronic kidney disease and liver cirrhosis were confirmed by clinical examination, radiological examination and others. Exudates were separated from transudates by Light's criteria if one of the following three criteria was met: pleural/serum protein ratio of > 0.5; the pleural/serum LDH ratio of > 0.6; and/or the pleural fluid lactate dehydrogenase (LDH) greater than 200 U/l).

From normality test using Shapiro-Wilk Test, data were found not normally distributed, then data was reported in median (minimum-maximum). Statistical analysis was done with Mann-Whitney U test, p-value less than 0.05 was considered statistically significant with confidence interval 95%. Receiver Operating Characteristic (ROC) curves were calculated for evaluating the optimum cut-off points, sensitivity and specificity of uric acid levels. Sensitivity and specificity of Light's criteria were calculated by 2x2 table.

## RESULTS AND DISCUSSION

Fifty-six specimens of pleural fluid from 56 patients were obtained, 31 patients were males (55.4%) and 25 were females (44.6%), with a mean age of 49.54 $\pm$ 13.63 years (range 14-76 years). Most specimens was from the age group of 40-59 years, consisting of 31 patients (55.4%) as seen in Table 1. This result was relevant with Surjanto *et al.,*[11] study at the Dr. Moewardi Hospital (RSDM) Surakarta during the period January 1 until December 31 2012, that the number of patients with pleural effusion was more in males, with the largest age group between 41-60 years.[11]

Patients with transudative pleural effusion were 23 (41.1%), 10 of them were males (43.5%) and 13 females (56.5%), with a mean age of 53.43 $\pm$ 13.66 years (26 -76 years). Exudative pleural effusion with a total of 33 (58.9%), 21 of them were males (63.6%) and 12 females (36.4%), with a mean age of 46.82 $\pm$ 13.13 years (14 -71 years) (Table 2).

Most cases was exudative pleural effusion (58.9%). This was in line with Hazarika *et al.,*[5] who found exudate as the largest case (79.24%).[5] Based on this study, most of the transudative pleural effusion was caused by chronic renal failure in 13 cases (23.2%). Most of the exudative pleural effusion caused by malignancy in 19 cases (33.9%). This was in line with Surjanto *et al.* Study that malignancy was the most cause of pleural effusion.[11] Etiology of pleural effusion is shown in Table 3.

Increases in uric acid level in transudate may be found in clinical conditions associated with tissue hypoxia and oxidative stress.[7] Oxidative stress hap-

**Table 1.** Sex and age distribution characteristic of pleural effusion patients

| Variables | n (%) |
|---|---|
| Sex | |
| Male | 31 (55.4) |
| Female | 25 (44.6) |
| Age distribution | |
| < 20 years | 1 (1.8) |
| 20-39 years | 11 (19.6) |
| 40-59 years | 31 (55.4) |
| $\geq$ 60 years | 13 (23.2) |

**Table 2.** Age distribution and sex of patients based on the type of effusion by diagnosis

| Variables | Transudate (n=23) | Exudate (n=33) |
|---|---|---|
| Age mean (years) | 53.43 $\pm$ 13.66 | 46.82 $\pm$ 13.13 |
| Sex | | |
| Male | 10 (43.5%) | 21 (63.6%) |
| Female | 13 (56.5%) | 12 (36.4%) |

**Table 3.** Sample distribution based on diagnosis and mean of uric acid levels

| Diagnosis | n (%) | Mean of uric acid levels (mg/dL) |
|---|---|---|
| **Transudates** n=23 (41.1%) | | |
| Congestive heart failure | 8 (14.3) | 8.32$\pm$3.01 |
| Chronic kidney disease | 13 (23.2) | 6.68$\pm$2.25 |
| Liver cirrhosis | 2 (3.6) | 10.95$\pm$9.26 |
| **Exudates** n=33 (58.9%) | | |
| Malignancy | 19 (33.9) | 4.62$\pm$2.19 |
| Infection | 14 (25) | 5.63$\pm$1.15 |

pened in patients with chronic renal failure. Patients with chronic renal failure receiving hemodialysis experienced hypoxemia during routine dialysis.[12] The same applied to patients with congestive heart failure who turn hypoxemic. Similarly, liver cirrhosis is often associated with oxidative stress. A variety of cytokines like TNF-α can be produced in Kupffer cells induced by oxidative stress, which might increase inflammation and apoptosis. With regard to hepatic stellate cells, the proliferation and collagen synthesis of hepatic stellate cells are triggered by oxidative stress.[5,13] Depletion of cellular oxygen results in Adenosine Triphosphate (ATP) degradation into hypoxanthine, xanthine and uric acid.[2,7]

**Table 4.** Pleural fluid uric acid levels

| Variable | Transudate Median (min -max) | Exudate Median (min-max) | p-value |
|---|---|---|---|
| Uric Acid | 6.6 (3.24-17.50) | 5.01 (0.6-9.40) | 0.001* |

Normality test, Shapiro-Wilk test: p<0.05; data distribution not normal
*Mann-Whitney U test: p<0.05; significant

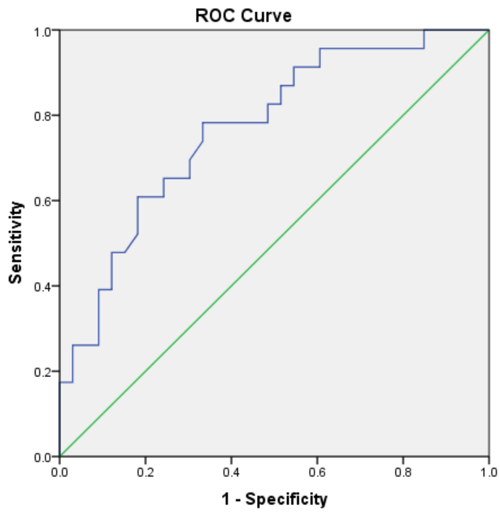


**Figure 1.** ROC curve of pleural fluid uric acid levels

A Receiver Operating Characteristic (ROC) curve of pleural uric acid (Figure 1), has been done to determine the demarcating cut-off value between exudates as compared to transudates. The optimum cut-off level for pleural uric acid was more than 5.845 mg/dL in transudate, with a sensitivity and specificity of pleural uric acid in differentiating between transudate and exudate pleural effusion of 78.3% and 66.7%, respectively. These results were different from Jain *et al.,*[2] study who stated that the cut-off level was 5.5 mg/dL with higher sensitivity and specificity of 94% and 83%, also Hazarika *et al.* Study wich stated that the cut-off level was 5.35 mg/dL, sensitivity 89.32% and specificity 92.60%.[2,5]

In this study there were 5 cases based on diagnosis categorized as transudate (3 cases chronic kidney disease, 1 case liver cirrhosis and 1 case congestive heart failure) but, had the uric acid level below 5.845 mg/dL (exudate). There were 11 cases based on diagnosis categorized as exudate (4 cases lung tumor, 1 case endometrium carcinoma metastases to lung, 1 case sepsis, 2 cases lung tuberculosis and 3 cases pneumonia) but, had the uric acid level higher than 5.845 mg/dL (transudate). It was assumed that was due to the limitation of this study because of uses of previous treatment which can influence uric acid level, such as uricosuric drugs, diuretic and chemotherapy were not controlled. Uricosuric drugs used in chronic kidney disease can decrease uric acid level. Diuretic therapy in pleura effusion patient can increase uric acid levels. Chemotherapy can increase uric acid level since degradation of dead tumor cells will be converted into uric acid.[7,9]

**Table 5.** Exudate and transudate categorized based on diagnosis and uric acid level (cut-off 5.845 mg/dL)

| | | Diagnosis | | Total |
|---|---|---|---|---|
| | | Transudate | Exudate | |
| Uric acid cut-off 5.845 mg/dL | Transudate | 18 | 11 | 29 |
| | Exudate | 5 | 22 | 27 |
| Total | | 23 | 33 | 56 |

**Table 6.** Exudate and transudate categorized based on diagnosis and Light's criteria

| | | Diagnosis | | Total |
|---|---|---|---|---|
| | | Exudate | Transudate | |
| Light's criteria | Exudate | 32 | 9 | 41 |
| | Transudate | 1 | 14 | 15 |
| Total | | 33 | 23 | 56 |

Sensitivity and specificity of Light's criteria in differentiating between transudate and exudate pleural effusion using 2x2 table were 97% and 60.9%, respectively (Table 6). One case based on diagnosis categorized as exudate (mediastinum tumor metastases to lung) was by Light's criteria categorized as transudate. Nine cases based on diagnosis categorized as transudate (6 cases chronic kidney disease, 3 cases congestive heart failure) were (Light's criteria) categorized as exudate.

**Table 7.** Sensitivity and specificity of each criteria comparing with the diagnosis

| Criteria | Sensitivity (%) | Specificity (%) |
|---|---|---|
| Pleural fluid uric acid (cut-off 5.845 mg/dL)* | 78.3 | 66.7 |
| Pleural fluid uric acid (cut-off 4.63 mg/dL) | 91.3 | 45.5 |
| Pleural fluid uric acid (cut-off 7.525 mg/dL) | 39.1 | 90.9 |
| Light's criteria | 97 | 60.9 |

* optimum cut-off level

## CONCLUSION AND SUGGESTION

This study indicated that there was a significant difference between pleural fluid uric acid level in transudate and exudate, which was higher in transudate than exudate. The sensitivity of Light's criteria (97%) was higher than uric acid pleural fluid level (78.3%), but, its specificity (60.9%) was lower than uric acid pleural fluid level (66.7%). However, the limitation of this study that there was no control in uses of previous treatment which could influence uric acid level. Further studies are needed with better sampling method to reduce bias.

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## REFERENCES

1. Nurahmi, Wibawa SY, Badji A, Hardjoeno. Tes dan Interpretasi Pleural fluid. Dalam: Hardjoeno, Fitriani, editors. Substansi dan Cairan Tubuh. Makassar, Lembaga Penerbi-

tan Universitas Hasanuddin, 2011; 67-84.

2. Jain A, Jain R, Petkar SB, Gupta SK, Khare N, Dutta J. A Study of Uric Acid - A New Biochemical Marker for The Differentiation between Exudates and Transudates in Pleural Effusion Cases. NJCM. 2014; 5(2): 204-8.
3. Rubins J. Pleural Effusion. 2014 [accesed September 4, 2014]; Available from: http://emedicine.medscape.com/article/299959-overview#showall.
4. Sato T. Differential Diagnosis of Pleural Effusions. JMAJ. 2006; 49(9-10): 315-9.
5. Hazarika B, Raghavendra MK, Sarma J, Sarmah KR. Role of Pleural Fluid Uric Acid Estimation In Differentiation Between Transudative and Exudative Pleural Effusion. The Pulmo-Face. 2015; 15(2): 55-60.
6. Wilson DD. Uric Acid, Blood. Manual of Laboratory and Diagnostic Tests. Illinois, McGraw-Hill, 2006; 579-80.
7. Uzun K, Vural H, Ozer F, Imecik O. Diagnostic Value of Uric Acid to Differentiate Transudates and Exudates. Clin Chem Lab Med. 2000; 38(7): 661-5.
8. National Center for Biotechnology Information. PubChem Compound Database CID1175; [accessed June 15, 2016]; Available from: https://pubchem.ncbi.nlm.nih.gov/compound/1175.
9. Light RW. Disorders of The Pleura and Mediastinum. In: Loscalzo J, editor. Harrisons's Pulmonary and Critical Care Medicine. 17th Ed., San Fransisco, McGraw Hill Medical, 2010; 215-9.
10. Porcel JM. Identifying misclassified by Light's criteria. Curr Opin Pulm Med. 2013; 19(4): 362-367.
11. Surjanto E, Sutanto YS, Aphridasari J, Leonardo. Penyebab Efusi Pleura pada Pasien Rawat Inap di Rumah Sakit. J Respir Indo. 2014; 34(2): 102-8.
12. Alfakir M, Moammar MQ, Ali MI, Alhatem E, Curran RD, Saoud RM, *et al*. Pulmonary Gas Exchange During Hemodialysis: A Comparison of Subjects with and without COPD on Bicarbonate Hemodialysis. Ann Clin Lab Sci. 2011; 41 (4): 315-20.
13. Li S, Tan HY, Wang N, Zhang ZJ, Lao L, Wong CW, et al. The Role of Oxidative Stress and Antioxidants in Liver Diseases. Int J Mol Sci. 2015; 16(11): 26087-90.