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EVALUATION OF PLEURAL EFFUSION TYPE DETERMINATION BASED ON LIGHT'S AND HEFFNER'S CRITERIA

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ABSTRACT

Pleural effusion is an abnormal accumulation of pleural fluid in the pleural cavity due to excessive transudation or exudation. Light's criteria is used as the standard method to distinguish between exudates and transudates. Some recent studies reported misclassifications which led to development of several alternative criteria, such as Heffner's criteria. The purpose of this study was to determine the sensitivity and specificity of Heffner's criteria to determine the type of pleural effusion. This research was an observational study with a cross-sectional method using a pleural effusion of patients at the Clinical Pathology Laboratory Installation at the Wahidin Sudirohusodo Hospital in July 2018. Total protein, LDH, and cholesterol levels were measured in all samples that met the inclusion and exclusion criteria. There were 45 pleural effusion samples that consisted of 30 transudate and 15 exudate samples. Based on clinical diagnosis, the Light's criteria showed 3 misclassifications and Heffner's criteria obtained showed 2 misclassifications. Based on the data above, the statistical data showed that Light's criteria had a sensitivity of 96.7% and specificity of 86.7%. Heffner's criteria had a sensitivity of 100% and specificity of 86.7%. Heffner's criteria can be used an alternative method to determine the type of pleural effusion because it showed a better sensitivity and specificity than Light's criteria.

Key words: Heffner's criteria, Light's criteria, transudate, exudate, pleural effusion

INTRODUCTION

Pleural effusion is an abnormal accumulation of pleural fluid in the pleural cavity due to excessive transudation or exudation. Based on its type, pleural effusion is classified into namely transudative effusion and exudative effusion. This classification of pleural effusion is important to recognize the causes of the condition.[1]

Transudates are found in various systemic disorders that interfere with fluid filtration and/or fluid reabsorption. Transudates are usually caused by an imbalance between hydrostatic pressure and colloid osmotic pressure. Transudative effusion are found in congestive heart failure, liver cirrhosis, nephrotic syndrome, or hypoalbuminemia (hypoproteinemia) triggered by various conditions. Exudates, on the other hand, are commonly found during an inflammatory process causing damage to the blood vessel walls and cavity membrane, or decreased reabsorption by the lymphatic system. Generally, exudates are found in infection, inflammation, trauma, neoplasm, or malignancy. Thus, determination of the types of pleural effusion is considered as an important first step to identify the etiology of pleural effusion.[1,2]

Light's criteria (1972), have become the standard method to distinguish between exudative effusion and transudative effusion. Based on Light's criteria, pleural exudative effusion has one or more of the following criteria: a ratio of pleural protein fluid to serum protein > 0.5; a ratio of serum lactate dehydrogenase (LDH) to pleural fluid > 0.6; and pleural fluid LDH is greater than $\frac{2}{3}$ of the upper limit of the normal serum LDH.[3] Previous research by Chakko *et al*. and Porcel *et al*. found adequately high sensitivity of Light's criteria. Its specificity; however, was not satisfactorily good since the criteria incorrectly classified 25% of transudates as exudates, especially in patients with heart failure.[4,5] Unfortunately, determination of the criteria requires the results of LDH level, total serum protein, and pleural fluid analysis; therefore, alternative criteria to determine the types of pleural effusion were needed.[3-5]

A meta-analysis by Heffner found an alternative criteria to identify the types of pleural effusion. Based on Heffner's criteria, exudative effusion has one or

more of the following criteria: a pleural fluid protein level > 2.9 g/dL; a pleural fluid cholesterol level > 45 mg/dL; and a pleural LDH level > ⅔ of the upper limit of the normal serum LDH.[6] Based on previous research by Hamal *et al.*, pleural fluid cholesterol test according to Light's criteria had sensitivity and specificity of 97.7% and 100%, respectively.[7] Patel and Choundry *et al*. also suggested that the combination of cholesterol and pleural fluid total protein in identification of exudates based on clinical diagnosis and compared to Light's criteria had sensitivity and specificity of 100% and 100%, respectively.[8] Similarly, Guntur *et al*. found that a combination of two or more than three parameters (protein, LDH, and pleural fluid cholesterol) based on clinical diagnosis has a sensitivity and a specificity of 94.6% and 100%, respectively.[6-9]

Based on the Heffner's criteria above, as a result, this research was aimed to find a faster, easier and more affordable alternative diagnosis to determine the types of pleural effusion as transudates or exudates. This research was expected to be a reference for clinicians to choose an effective and efficient examination.

METHODS

This research was a diagnostic study with a cross-sectional design. This research was conducted at the Clinical Pathology Laboratory Installation of the Dr. Wahidin Sudirohusodo General Hospital in Makassar started in July 2018 and ended until the minimum number of samples was obtained. Sampling was consecutively carried out on all subjects that met the research criteria. The inclusion criteria in this research were patients with a clinical diagnosis of pleural effusion and had undergone pleural effusion analysis. Contrastingly, patients with an undetermined diagnosis of pleural effusion were excluded. Pleural fluid specimens were collected and the total protein, LDH, and cholesterol levels were measured by chemical autoanalyzer (ABX Pentra 400) with colorimetric method at the clinical pathology laboratory installation.

The samples were subsequently classified into two transudates or exudates based on clinical diagnosis according to Light's and Heffner's criteria. The clinical diagnosis was established based on the results of physical examination and other additional tests, such as radiology/ultrasonography (USG), chest radiograph, histopathology, pleural fluid culture, identification of acid-fast bacillus, etc. This research has been approved (ethical clearance) by the Health Research Ethics Committee of University of Hassanudin/Dr. Wahidin Sudirohusodo General Hospital No. UH18080447. Data were statistically analyzed using Statistical Package for Social Sciences (SPSS) software version 22 to determine sensitivity, specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV).

RESULTS AND DISCUSSION

This research was performed conducted in July 2018. 56 samples that consisted of 35 males (62.5%) and 21 females (37.5%) were obtained . It showed that the distribution of male samples was greater than that of female. In addition, the age distribution of the patients ranged from 17 to 87 years. The largest percentage was the age group of 46-55 years (30.3%) followed by the age group of more than 65 years about (25.2%) (Table 1). Similarly, previous research by Khairani *et al.* at the Persahabatan Hospital in Jakarta and Dwianggita *et al*. at the Sanglah Hospital in Denpasar reported that the number of patients with pleural effusion was more commonly found in males with the most age group of 40-79 years.[10,11]

Table 1. Characteristics of the research subjects

Subject characteristics	n = 56	%
Sex		
Male	35	62.5
Female	21	37.5
Age		
17 – 25 years old	1	1.8
26 – 35 years old	9	16.0
36 – 45 years old	6	10.7
46 – 55 years old	17	30.3
56 – 65 years old	9	16.0
>65 years old	14	25.0
Transudative Effusion	18	32.1
Congestive heart failure	11	19.6
Kidney disease	6	10.7
Hepatic cirrhosis	1	1.8
Exudative Effusion	38	67.9
Malignancy	16	28.6
Infection	22	39.3

Source: Primary data

Based on the diagnosis of pleural effusion, 38 of 56 pleural fluid samples were classified into exudative effusion (67.9%), while the other 18 samples were classified into transudative effusion (32.1%). Samples diagnosed with transudative pleural effusion consisted of 11 cases of congestive heart failure (19.6%), 6 cases of kidney disease

Table 2. Distribution of pleural effusion types based on clinical diagnosis and Light's criteria

		Clinical Diagnosis		Total
		Exudates	Transudates	
Light's criteria	Exudates	36	3	39
	Transudates	2	15	17
Total		38	18	56

Source: primary data

Table 3. Distribution of pleural effusion types based on clinical diagnosis and Heffner's criteria

		Clinical Diagnosis		Total
		Exudates	Transudates	
Heffner's criteria	Exudates	37	2	39
	Transudates	1	16	17
Total		38	18	56

Source: primary data

Table 4. Comparison of Light's and Heffner's criteria in determination of pleural effusion types

Criteria	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Light	94.7	83.3	92.3	88.2
Heffner	97.4	88.9	94.9	94.1

Note: PPV: Positive Predictive Value; NPV: Negative Predictive Value

(10.7%) including chronic renal failure and nephrotic syndrome, and 1 case of liver disease (liver cirrhosis) (1.8%). On the other hand, samples with the diagnosis of exudative pleural effusion consisted of 16 malignancy cases (28.6%) with lung tumors as the most exudative pleural effusion-causing tumor. The infection by *Mycobacterium tuberculosis*, lung abscess, bacterial pneumonia or other bacteria was then considered as the second most common cause of 22 (39.3%) exudative pleural effusions, caused by both tuberculosis and other bacterial infections.

Classification of the pleural effusion type by the clinical diagnosis was used as the standard to distinguish between transudative and exudative pleural effusions based on Light's and Heffner's criteria. Based on Light's criteria, 17 of 56 pleural effusion samples were classified into transudative pleural effusion, while the other 39 samples were classified into exudative pleural effusion (Table 2).

Based on clinical diagnosis, there were 17 samples of transudative pleural effusion and 39 samples of exudative pleural effusion identified with Heffner's criteria (see Table 3).

The results of the research in Table 2 and Table 3 showed that there were several misclassifications for both Light's and Heffner's criteria. There were 3 patients with congestive heart failure and were categorized as transudates based on clinical diagnosis. Similarly, based on Heffner's criteria, the 3 patients were classified into transudative pleural effusion. Contrastingly, based on Light's criteria, those 3 patients were classified into exudative pleural effusion.

There was also a misclassification found in patients with dextra lung tumors. Based on clinical diagnosis, this patient was categorized as exudates. Similarly, based on Heffner's criteria this patient was classified into exudative pleural effusion. Contrastingly, based on Light's criteria, this patient was classified into transudative pleural effusion.

Subsequently, the data were statistically analyzed. The results revealed that Light's criteria had a sensitivity, specificity, PPV, and NPV of 94.7%, 83.3%, 92.3%, and 88.2%, respectively. Meanwhile, Heffner's criteria had a sensitivity, specificity, PPV, and NPV of 97.4%, 88.9%, 94.9%, and 94.1%, respectively (Table 4).

The results of this research then showed that Light's and Heffner's criteria had almost the same sensitivity and specificity, but Heffner's criteria had better ones than Light's criteria had.

The results of this research showed that the number of exudate was higher than the number of transudates. Various diseases actually can cause pleural effusion. Exudate is an accumulation of fluid that occurs due to the inflammatory process in the

serous cavity that increases the capillary permeability of the pleural arteries and fluid is discharged into the pleural cavity. The results of this research found 38 exudative pleural effusions with 22 samples of infectious diseases as the highest cause based on clinical diagnosis. The inflammatory process by bacterial infection causes activated neutrophils to damage the endothelium which will release oxygen metabolites, constituents of granules, and phospholipase products thereby increase capillary permeability. The resultant pulmonary extravascular fluid subsequently increases the gradient of pleural interstitial pressure and pushes fluid from the mesothelial cells into the pleural cavity which causes the formation of pleural effusions.[2,12]

The second most common cause was malignancy which was found in 16 samples. Malignancy found in this research were tumor/lung cancer, mammary carcinoma, malignant lymphoma, and ovarian carcinoma. In 2000, the American Thoracic Society (ATS) reported that most malignancies that were considered as the cause of exudative pleural effusions were tumors/lung cancer, breast cancer, and lymphoma. Tumor cells spread along the parietal pleural membrane and clog intrapleural lymphatic flow. In addition, tumor cells also stimulate the release of chemokine which increases the permeability of the pleural membrane and blood vessels leading to the accumulation of fluid in the pleural space. [1,2,13,14]

Increased protein levels both in serum and pleural fluid indicate a capillary permeability due to pleural effusion. The higher LDH values indicate the higher the degree of inflammation that occurs. Cholesterol in pleural fluid is a new parameter that is widely studied today. Increase of pleural fluid cholesterol in exudates is triggered by exudation processes, such as infection/inflammation/ malignancy causing cell degeneration, increased pleural membrane permeability and increased vascular permeability. This subsequently triggers a vascular leak allowing cholesterol to enter the pleural cavity.[6,15]

The results of this research found several misclassifications. For instance, a patient with congestive heart failure based on Light's criteria was identified as exudative pleural effusion type, while based on Heffner's criteria the patient was categorized as transudate. Thus, this patient received diuretic therapy, namely furosemide and spironolactone. This result could be considered as a weakness of Light's criteria. Chakko *et al*. reported that patients receiving diuretic therapy can have a diuresis process that the fluid will come out of the pleural cavity faster than other molecules.[4] Porcel *et al*. also reported that the sensitivity of Light's criteria was adequately high, but its specificity was still not satisfactory since the criteria incorrectly classified 25% of transudates as exudates, especially patients with heart failure.[5] Similarly, Ekpe *et al.* found that 25% exudate cases were reported among patients with heart failure.[17] Seth *et al*. also reported that there were 25% exudative pleural effusion in patients with congestive heart failure as much as. Therefore, Heffner's criteria can be used as an alternative.[4,16-18]

Another misclassification was found when a patient with right lung tumor and Community Acquired Pneumonia (CAP) was classified into transudative pleural effusion based on Light's criteria, while based on Heffner's criteria the patient was identified as transudate. In addition, this patient also had hypoproteinemia and hypoalbuminemia, and received antibiotic therapy and methylprednisolone. In fact, Hypoalbuminemia and hypoproteinemia can trigger a decrease of oncotic pressure, causing transudative pleural effusions. This was thought to be the cause of transudate. Unfortunately, this research did not get any information about the patient's disease record. As the result, the further patient's condition could not be identified. The patient only received further therapy and was asked for re-control of the pleural fluid analysis after the therapy.

This research showed that Light's and Heffner's criteria had almost the equal sensitivity and specificity. However, Heffner's criteria were better than the Light's criteria. Heffner's criteria could be used as an alternative in determination of the types of pleural effusion.

CONCLUSION AND SUGGESTION

Light's and Heffner's criteria can be used as methods to determine transudative and exudative pleural effusion. Nevertheless, Heffner's criteria gave better results with higher sensitivity and specificity. Heffner's criteria was also able to determine the types of effusion more easily with a lower cost than Light's criteria. In addition, the process of sample analysis was able to be accelerated and was comfortable for the patients. Therefore, Heffner's criteria can be considered as an alternative to determine the types of pleural effusion. However, it was recommended for further research to focus on

hypoproteinemia or hypoalbuminemia population which can cause misclassification for both Light's and Heffner's criteria.

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