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Comparison between serum pleural effusion albumin gradient, total protein, lactate dehydrogenase, and erythrocyte count in malignant and non-malignant pleural effusion

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ABSTRACT

Background: Malignant pleural effusion carries a bad prognosis. Pathologic examination as the gold-standard diagnosis of malignant pleural effusion has sensitivity limitations and may cause delayed diagnosis. Several affordable examinations, such as serum pleural effusion albumin gradient, total protein, lactate dehydrogenase (LDH), and erythrocyte count, might be useful as malignant pleural effusion diagnostic tools.

Methods: This is an observational analytic study with a cross-sectional design conducted at Sanglah Central General Hospital in Denpasar from December 2021 to July 2022. Pleural effusion fluid and blood were taken from subjects with malignant and non-malignant pleural effusion. Data were analyzed with SPSS version 25 software for Windows.

Results: Total subjects were 47 persons consisting of 26 subjects with malignant pleural effusion and 21 subjects with non-malignant pleural effusion. Results from statistical analysis of malignant and non-malignant pleural effusion were serum pleural effusion albumin gradient median (IQR) 0.91 (0.65) g/dL vs. 1.22 (1.2) g/dL (p=0.129), total protein mean 3.92±0.95 g/dL vs. 3.52±1.67 g/dL (p=0.334), LDH median 535 (840) IU/L vs. 187 (1,016) IU/L (p=0.057), and erythrocyte count median 23,500 (109,250) cells/mm^3 vs. 3,000 (11,000) cells/mm^3 (p=0.004). The AUC of erythrocyte count from the ROC method was 0.745 (95%CI=0.599-0.890; p=0.004). Using a cut-off point ≥ 4,500 cells/mm^3, it had a sensitivity of 80.8%, specificity of 61.9%, and Odds Ratio (OR) of 6.8 (95%CI=1.8-25.4).

Conclusion: Erythrocyte count as routine examination showed good validity for diagnosing malignant pleural effusion and expected to reduce diagnosis delay. Meanwhile, albumin gradient, total protein, and LDH delivered no difference.

Keywords: Malignant Pleural Effusion, Albumin Gradient, Total Protein, LDH, Erythrocyte Count.

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INTRODUCTION

Pleural effusion is an excessive fluid accumulation in pleural space due to transudation or exudation process. Exudate pleura effusion is often caused by malignancy, tuberculosis (TB), and parapneumonic effusion. On the other hand, transudative pleural effusion is often caused by heart failure, liver cirrhosis, and nephrotic.[1] The incidence of malignant pleural effusion (MPE) in the United States of America is approximately 150,000-175,000 per year and becomes the main cause of exudate pleura effusion. Most of the pleural effusion in Persahabatan General Hospital Jakarta and Sanglah General Hospital Bali was exudate and mainly caused by malignancy and TB.[2] Patients with EPM have a bad prognosis with *overall survival* (OS) of 3-12 months. More than half of patients with pleural metastasis have MPE.[3]

Diagnostic investigation of MPE has difficulties. Pleural fluid cytology examination has limitations because it has low sensitivity (11,6-71%). Closed pleural biopsy only increases detection yield by about 8% and is limited by patient clinical status and healthcare facility.[4] Delay in MPE diagnosis may postpone treatment and aggravate the patient's prognosis. Malignancy diagnosis was delayed around 3-6 months in western countries due to low disease awareness, limited healthcare accessibility, and low diagnostic investigation aggressivity.[5,6]

Several studies showed significant results of laboratory examinations for identifying malignant and non-malignant pleural effusion (NMPE). These examinations were feasible and routinely used in most healthcare facilities. Based on those mentioned above, this study aims to compare serum pleural effusion albumin

gradient, total protein, LDH level, and erythrocyte count in MPE and NMPE.

METHODS

This cross-sectional observational study was conducted at Sanglah General Hospital Denpasar from December 2021 to July 2022. Data collection was done consecutively from patients who met inclusion criteria as follows adult patients (≥ 18 years old) with thoracocentesis indication readily gave informed consent for thoracocentesis and venous blood drawing and were not under any medication for pleural effusion yet. Subjects with contraindications for thoracocentesis, who had more than one pleural effusion etiology, chest trauma, or were under diuretic medication were excluded. Malignant pleural effusion was defined as pleural effusion associated with malignancy and proven by malignant cells found in cytology or biopsy examination or pleural effusion that occur in a patient with malignancy in the lung or other organ. No other cause was proven.

Non-malignant pleural effusion included exudative or transudative pleural effusion besides than malignancy process. Classification of pleural effusion using Light's criteria showed as exudate or transudate. According to Light's criteria, exudative pleural effusions meet at least one of the following criteria: pleural fluid protein divided by serum protein greater than 0.5, pleural fluid LDH divided by serum LDH greater than 0.6, pleural fluid LDH greater than two-thirds of the upper limit of normal serum LDH. Transudative pleural effusions meet none of the above. Blood and pleural fluid samples were processed with Sysmex XN-1000 Automated Haematology Analyser for erythrocyte count and Abbott Alinity c for protein, albumin, and LDH measurement. Data were analyzed with SPSS version 25 software for Windows. Independent t-test, parametric *Mann-Whitney* test, and Receiver Operating Curve (ROC) method were used for calculation.

RESULTS

The total number of participants was 47, divided into 26 subjects in the MPE group and 21 in the NMPE group. There were 57.7% female subjects in the MPE group and 71.4% male subjects in the NMPE group. Subjects with MPE were older than NMPE with a mean age of 54.9±11.8 and 52.4±15.1 years old. Subject characteristics are shown below in Table 1 and Table 2.

Comparison of variables between MPE and NMPE showed serum pleural effusion albumin gradient median (IQR) 0.91 (0.65) g/dL and 1.22 (1.2) g/dL (p=0.129), total protein mean±SD 3.92±0.95 g/dL and 3.52±1.67 g/dL (p=0.334), and LDH median (IQR) 535 (840) IU/L and 187 (1,016) IU/L (p=0.057). Meanwhile, pleural fluid erythrocyte count showed a significant difference (p=0.004) with a median (IQR) was 23,500 (109,250) cells/mm^3 and 3,000 (11,000) cells/mm^3 (Table 3).

Figure 1 shows the receiver operating curve (ROC) analysis. Erythrocyte count had a valid diagnostic value for the cause of pleural effusion with the area under the curve (AUC) 0.745 (95%CI 0.599-0.890, p=0.004). AUC values are shown in Table 4. The calculation of the erythrocyte count cut-off point was ≥ 4,500 cells/mm^3.

Table 1. Demographic characteristics of subjects.

Variables	Diagnosis (N=47)	
	Malignant pleural effusion (N=26)	Non-malignant pleural effusion (N=21)
Sex, n (%)		
Male	11 (42.3)	15 (71.4)
Female	15 (57.7)	6 (26.6)
Age (years old) (mean±SD)	54.9±11.8	52.4±15.1
Nutritional status, n (%)		
Low (BMI < 18.5)	13 (50)	8 (38.1)
Normal (BMI 18.5-22.9)	6 (23,1)	9 (42.9)
Overweight (BMI ≥ 23)	7 (26.9)	4 (19)
Smoker, n (%)		
Yes	6 (23.1)	5 (23.8)
No	20 (76.9)	16 (76.2)
Etiology, n (%)		
Lung cancer	15 (57.7)	0 (0)
Breast cancer	2 (7.7)	0 (0)
Gastrointestinal cancer	2 (7.7)	0 (0)
Ovarium cancer	2 (7.7)	0 (0)
Cervix uteri cancer	2 (7.7)	0 (0)
Nasopharynx cancer	2 (7.7)	0 (0)
Spinal cord cancer	1 (3.8)	0 (0)
Tuberculosis infection	0 (0)	7 (33.3)
Bacterial infection	0 (0)	3 (14.3)
Heart disease	0 (0)	8 (38.1)
Renal disease	0 (0)	3 (14.3)

BMI=Body Mass Index, SD=Standard Deviation.

Erythrocyte count ≥ 4,500 cells/mm^3 showed a sensitivity of 80.8% (95%CI 60.7-93.5) and specificity of 61.9% (95%CI=38.4-81.9%) for diagnosing MPE. Other statistical values were Positive Predictive Value (PPV) 72.4% (95%CI=59.6-82.4), Negative Predictive Value (NPV) 72.2% (95%CI 52.5-85.9), Positive Likelihood Ratio (LR+) 2.1 (95%CI 1.2-3.8), Negative Likelihood Ratio (LR-) 0.31 (95%CI=0.1-0.7), accuracy 72.3% (95%CI=57.4-84.4), and Odds Ratio (OR) 6.8.

DISCUSSION

Malignant pleural effusion occurred most in females (57.7%), while non-malignant had a male preponderance (71.4%). Singgih et al., reported a similar result, 61.3% of the subject of MPE was female and the mean age of the MPE subject was 71±8.38 years old.[7] There was a substantial number of female subjects with breast, ovarium, and cervix uteri cancer in this study, which could explain this result. According to Deniz et al., malignancy associated with pleural effusion usually occurs in patients older than 50 years old.[8] The mean age in this study was 54.9±11.8 years old for MPE and 52.4±15.1 years old for NMPE. Aunan et al., stated that the mechanism of aging and malignancy process is similar, including genomic instability, telomere attrition, epigenetic change, proteostasis loss, nutrition deregulation, metabolism disturbance, cellular senescence, and stem cell function.[9]

Half of the MPE subjects were found to have low nutritional status (BMI < 18 kg/m^2). Grober et al., stated that 30-90% of patients had inadequate diets and may develop cachexia.[10] MPE group was dominated by patients with lung cancer (57.7%). Cardiac disease and tuberculosis were the majority in the NMPE group (38.1% and 33.3%, subsequently). Similar to our study, a descriptive study by Khairani et al., in Persahabatan Hospital Jakarta reported lung cancer occurred considerably as the cause of MPE as well tuberculosis in the NMPE group.[11] MPE often occurred in the right hemithorax (46.2%). This could be related to the anatomy of thoracic lymphatic drainage having propensity in the right hemithorax.[8]

Exudative pleural effusion was in all MPE but only in 61.9% of NMPE, which was caused by tuberculosis and bacterial infection. Skok et al., declared exudative pleural effusion is often caused by malignancy, tuberculosis, and parapneumonic effusion.[1] Inflammation and malignant tumor infiltration lead to pleural tissue and capillary vessel damage in the exudation process. Exudate fluid contains higher protein levels because

Table 2. Clinical characteristics of subjects.

Variables	Diagnosis (N=47)	
	Malignant Pleural Effusion (N=26)	Non-malignant pleural effusion (N=21)
Location of effusion, n (%)		
Right hemithorax	12 (46.2)	7 (33.3)
Left hemithorax	8 (30.8)	5 (23.8)
Bilateral	6 (23.1)	9 (42.9)
Classification, n (%)		
Exudate	26 (100)	13 (61.9)
Transudate	0 (0)	8 (38.1)
Pleural fluid color, n (%)		
Hemorrhagic	16 (61.5)	5 (23.8)
Non-hemorrhagic	10 (38.5)	16 (76.2)
Dyspnea, n (%)		
Yes	24 (92.3)	19 (90.5)
No	2 (7.7)	2 (9.5)
Chest pain, n (%)		
Yes	12 (46.2)	6 (28.6)
No	14 (53.8)	15 (71.4)
Cough, n (%)		
Yes	19 (73.1)	17 (81)
No	7 (26.9)	4 (19)
Fever, n (%)		
Yes	0 (0)	7 (33.3)
No	26 (100)	14 (66.7)
Weight loss, n (%)		
Yes	24 (92.3)	6 (28.6)
No	2 (7.7)	15 (71.4)

Table 3. Comparison of albumin gradient, total protein, LDH, and erythrocyte count.

Variables	Diagnosis (N=47)		p
	Malignant Pleural Effusion (N=26)	Non-malignant Pleural effusion (N=21)	
Albumin gradient (g/dL) Median (IQR)	0.91 (0.65)	1.22 (1.2)	0.129
Total protein (g/dL)			
Mean±SD	3.92±0.95	3.52±1.67	0.334
LDH (IU/L)			
Median (IQR)	535 (840)	187 (1,016)	0.057
Erythrocyte count (cells/mm^3)			
Median (IQR)	23,500 (109,250)	3,000 (11,000)	0.004*

IQR=Interquartile Range; LDH=Lactate Dehydrogenase; SD=Standard Deviation; *Statistically significant if p-value less than 0.05

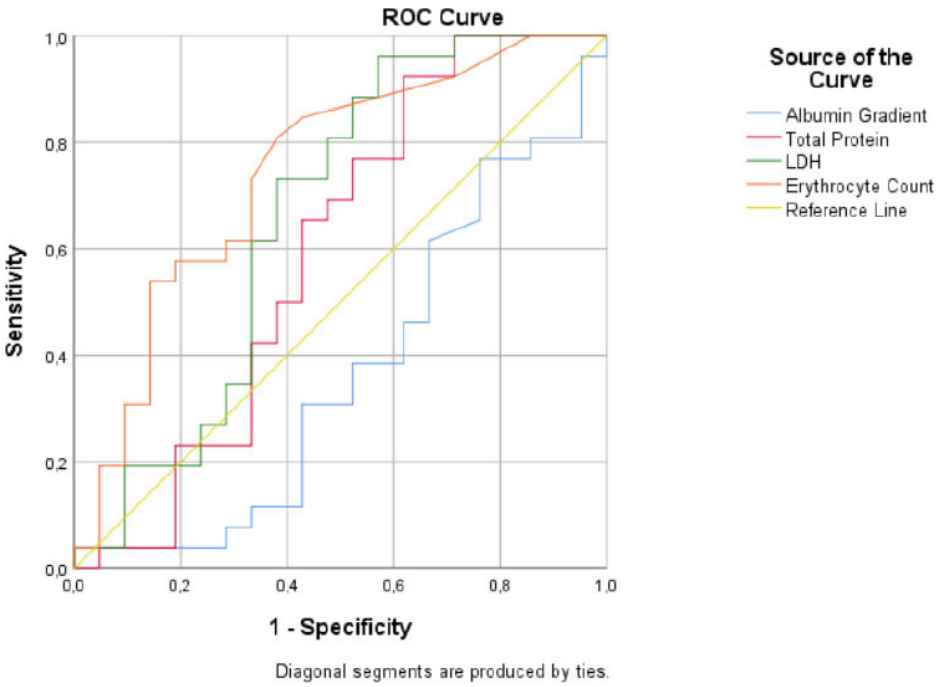

Figure 1. ROC curves for analysis of albumin gradient, total protein, LDH, and erythrocyte count.

Table 4. Threshold values of albumin gradient, total protein, LDH, and erythrocyte count.

Variables	AUC	SE	p	95% CI	
				Lower Bound	Upper Bound
Albumin gradient	0.370	0.084	0.129	0.205	0.535
Total protein	0.593	0.090	0.275	0.417	0.770
LDH	0.663	0.086	0.057	0.494	0.832
Erythrocyte count	0.745	0.074	0.004	0.599	0.890

AUC=Area Under Curve; LDH = Lactate Dehydrogenase; SE: Standard Error; CI: Confidence Interval

of the increased protein permeability of capillary vessels.[12]

As much as 61.5% of MPE was hemorrhagic pleural effusion. On the opposite, 76,2% of EPNM was non-hemorrhagic. Deniz et al., agreed macroscopic appearance gives diagnostic information. Hemorrhagic and exudate pleural fluid had a preponderance of MPE.[8] Bloody color may be caused by tumor invasion to blood vessels or angiogenesis induction from the tumor itself.[13] One milliliter blood leakage to the pleural cavity in a patient with a pleural fluid volume of 500 mL and serum erythrocyte count $5x10^6/mm^3$ could bring redness in pleural fluid color. The quantitative measurement should be added to the qualitative method because even in non-hemorrhagic pleural fluid, erythrocyte cells still counted as many as 1,000-11,000 cells/mm^3.[12]

Clinical manifestations in subjects with MPE and NMPE were dyspnea and cough predominantly. There was no fever in MPE, but it occurred in one-third of NMPE subjects with tuberculosis or bacterial infection. The pleural infection triggers pyrogenic cytokines such as IL-6, IL-1, and TNF-α.[14] Chest pain was more prevalent in MPE subjects. Pleural inflammation and cancer pain are responsible for it.[15]

Serum pleural effusion albumin gradient in MPE subjects did not significantly different than NMPE in this study (p=0.129). It may be caused by a variety of etiology in the NMPE group. Samanta et al., showed albumin gradient was significantly higher in tuberculous pleural effusion than in malignant one (0.7±0.135 vs. 0.626±0.136 g/dL; p≤0.002).[16] The albumin gradient was influenced by the transudation or exudation mechanism.

Transudative pleural effusion occurs with intact microvascular endothelium condition; therefore, the albumin gradient is maintained. On the contrary, inflammation in exudative pleural effusion yields plasma leakage from blood vessels into the pleural cavity and results in a low albumin gradient.[17] Albumin gradient > 1.2 g/dL may distinguish cardiac failure associated with transudative pleural effusion in patients with diuretic medication from exudate misclassification.[12]

Total protein in the MPE group was 3.92 ± 0.95 g/dL and in the NMPE group was 3.52 ± 1.67 g/dL (p=0.334). Deniz et al., found a significant difference in total protein (p=0.018) between MPE and NMPE (4.2±1 vs. 3.7±1.4 g/dL, p=0.018).[8] NMPE groups in their study defined secondary pleural effusion without pleural involvement in lung cancer patients and excluded exudative pleural effusion and empyema. The difference in inclusion criteria with our NMPE group may contribute to our result. According to a previous study, total protein is generally higher in exudative than transudative pleural effusion. The malignancy process may lower the pleural fluid protein absorption rate compared to a non-malignant condition such as tuberculosis, pulmonary embolism, or congestive heart failure.[12]

There was no significant difference in LDH parameters between MPE and NMPE, median (IQR) 535 (840) IU/L vs. 187 (1,016) IU/L (p=0.057), subsequently. A study by Singgih et al., revealed no significant difference between MPE and tuberculous PE (1,037 (41-34,012) IU/L vs. 583.5 (189-11,469) IU/L; p=0.448).[7] However, Antonagelo et al., showed a significant difference between malignant and tuberculous PE (1,177±675 vs. 1,030±788 IU/L; p=0.003).[18] NMPE groups in our study consisted of exudate and transudate. LDH levels in transudative pleural effusion are usually low and may increase in exudate. LDH is a non-specific inflammatory marker. Higher LDH levels in MPE may be related to the extent of pleural damage or blood in the pleural cavity. The higher level of LDH, the higher the pleura inflammation. However, the

LDH level could not differentiate MPE from NMPE.[12,18]

Pleural fluid erythrocyte count showed a significant difference between MPE and NMPE (median (IQR) 23,500 (109,250) cells/mm^3 vs. EPNM 3,000 (11,000) cells/mm^3, p=0.004). Previous studies also reported similar results.[8,19] A previous study stated bloody pleural fluid color has an erythrocyte count estimation of more than 100,000 cells/mm^3 and gives a clue for pleural malignancy. However, about 30-50% of MPE have an erythrocyte count of fewer than 10,000 cells/mm^3 and no bloody color.[12] Hemorrhagic pleural effusion is a sign of direct pleural involvement. Malignancy induces pleural inflammation, angiogenesis, and vascular hyperpermeability.[1,20] These mechanisms support high erythrocyte count in MPE.[1]

The AUC of erythrocyte count was 0.745 (95%CI 0.599-0.890) and statistically significant (p=0.004). The optimal cut-off of erythrocyte count was ≥ 4,500 cells/mm^3. It obtained a sensitivity of 80.8% (95%CI=60.7-93.5), specificity of 61.9% (95%CI=38.4-81.9), Odds Ratio (OR) 6.8 (95%CI=1.8-25.4), Positive Predictive Value (PPV) 72.4% (95%CI=59.6-82.4), and Negative Predictive Value (NPV) 72.2% (95%CI=52.5-85.9). A study by Deniz et al., showed an erythrocyte count cut-off of 300,000 cells/mm^3 with a sensitivity of 70.59%, specificity of 6.25%, and OR of 6.25.[8] However, their value could not be used for diagnostic purposes. Our result showed erythrocyte count ≥ 4,500 cells/mm^3 had good diagnostic validity for diagnosing MPE, particularly for screening and early detection of MPE. Erythrocyte count is a simple laboratory examination and may be used widely in every healthcare facility. This was the first study done in Bali, Indonesia.

The limitations of our study were there was a variation of exudate and transudate in the NMPE group and this study was only conducted at one site.

CONCLUSION

Pleural fluid erythrocyte count had a diagnosis validity of MPE. There was no difference in albumin gradient, total protein, and LDH pleural fluid level between MPE and NMPE. The result of this study may be used as a simple additional parameter along with other clinical parameters in diagnosing malignant pleural effusion.

CONFLICT OF INTEREST

All authors stated no conflict of interest.

ETHICAL CLEARANCE

This study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Udayana with number 95/UN14.2.2.VII.14/LT/2022.

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AUTHOR CONTRIBUTION

All authors contributed equally to conducting the study and preparing the manuscript.

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