Original Research Article

Role of pleural fluid interleukin-6, neutrophil-lymphocyte ratio, and monocyte-lymphocyte ratio in distinguishing tuberculous and malignant pleural effusions

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ABSTRACT

Background: Pleural effusion is caused by various disease, including tuberculosis infection and malignancy. To determine the etiology, immunologic parameters are needed to distinguish tuberculous and malignant pleural effusions, including pleural fluid interleukin-6 (IL-6), neutrophil-lymphocyte ratio (NLR), and monocyte-lymphocyte ratio (MLR).
Methods: This was a cross-sectional study, conducted at Sanglah General Hospital in Denpasar from March 2020 to September 2020. Pleural fluid IL-6 and leucocyte differential count were measured from subjects with tuberculous and malignant pleural effusions.
Results: There were 22 tuberculous pleural effusion subjects with mean pleural fluid IL-6 9269.017±902.211 pg/ml, median (range) pleural fluid NLR 0.123 (0.044-9.449), and MLR 0.065 (0.044-0.355). There were 31 subjects with malignant pleural effusions, with mean pleural fluid IL-6 8212.146±2022.350 pg/ml, median pleural fluid NLR 0.189 (0.015-2.599), and MLR 0.065 (0.010-0.254). Pleural fluid IL-6 in tuberculous pleural effusions were significantly higher (p=0.014). With a pleural fluid IL-6 cut-off ≥9147.959 pg/ml, sensitivity of 63.6% and specificity of 64.5% were obtained. Pleural fluid NLR and MLR of the two groups were not significantly different (p=0.807 and p=0.116).
Conclusions: Pleural fluid IL-6 in tuberculous pleural effusions is higher than malignant pleural effusions, with a cut-off of ≥9147.959 pg/ml, tuberculous pleural effusions can be diagnosed with sensitivity of 63.6% and specificity of 64.5%. There is no difference in pleural fluid NLR and MLR in tuberculous and malignant pleural effusions.

Keywords: Interleukin-6, Tuberculous pleural effusions, Malignant pleural effusions

INTRODUCTION

Pleural effusion is a common respiratory disorder and its presence increases morbidity. In the United States, an estimated 1.5 million people suffer from pleural effusions each year, with the most common causes being congestive heart disease, parapneumonic pleural effusions, and malignant pleural effusions.[1] In countries with high prevalence of tuberculosis, including Indonesia, tuberculous pleural effusion is one of the main causes of pleural effusion. Research by Surjanto et al in Surakarta in 2012, 57.01% of pleural effusion patients were unilateral pleural effusions, and the most common etiology was malignancy (33.64%) and followed by tuberculosis (30.84%).[2] At Sanglah General Hospital, Denpasar in 2013, the cause of pleural effusions were malignancy (34.6%), pneumonia (15%), and tuberculosis (10.3%).[3]

Determining the etiology of pleural effusion is still a challenge. Tuberculous pleural effusions often present

similar clinical manifestations and pleural fluid analysis to those of malignant pleural effusions. Symptoms that often arise are chronic cough, shortness of breath, chest pain and weight loss.[4] Tuberculous and malignant pleural effusions are characterized by exudative pleural fluid and are dominated by lymphocytes. In addition, lung cancer, which is the most common cause of malignant pleural effusions, is often diagnosed at a younger age. Ten percent of lung cancer patients are diagnosed in the age range of 20-46 years at the time of diagnosis, and the majority are female, histological type of adenocarcinoma, non-smokers, with advanced stage of disease.[5] Lung cancer patients with pleural effusions are often diagnosed as tuberculous pleural effusions, thus are not receiving the optimal treatment. In exudate pleural effusion, an inflammatory process occurs in the pleural cavity that involves various cells, including neutrophils, lymphocytes, and monocytes. In addition, pro-inflammatory cytokines are involved, including interleukin-6 (IL-6). Research by Kiropoulos et al stated that pleural fluid IL-6 levels were higher in tuberculous pleural effusions than in malignant pleural effusions.[6] Research by El Sayed et al gave different results. Pleural fluid IL-6 levels were higher in patients with mesothelioma and pulmonary adenocarcinoma than tuberculous and transudate pleural effusions.[7] According to the study of Akturk et al in 2016, pleural fluid neutrophil-lymphocyte ratios (NLR) were lower in tuberculous pleural effusions than in malignant pleural effusions.[8] Research conducted by Guadagnino et al in 2017 stated that serum monocyte-lymphocyte ratio (MLR) increased significantly in tuberculosis patients compared to healthy individuals.[9] From previous studies, further research is needed to determine the parameters that can be used to distinguish tuberculous and malignant pleural effusions. Therefore, a study was conducted using pleural fluid IL-6, NLR, and MLR to differentiate tuberculous pleural effusions from malignant pleural effusions. The results are expected to help the diagnosis of tuberculous and malignant pleural effusions, so that optimal management can be provided and mortality can be diminished.

METHODS

The research was conducted at Sanglah General Hospital, Denpasar, Bali from March 2020 to September 2020. It was an analytic observational study using a cross-sectional design. The research subjects were tuberculous pleural effusions and malignant pleural effusions patients, diagnosed in the polyclinic and inpatient room of Sanglah General Hospital, using consecutive sampling until the sample size was met.

Patients with tuberculous pleural effusions were patients who experienced pleural effusion due to tuberculosis infection, as evidenced by one of the criteria, namely pleural effusion with a positive bacteriological examination for tuberculosis, including examination of acid fast staining, culture, or polymerase chain reaction (PCR) of pleural fluid, sputum, pleural tissue, or a rapid

molecular test of sputum or pleural tissue; pleural tissue biopsy showing granulomatous tissue specific for tuberculosis; exudate pleural effusion with negative bacteriological examination but diagnosed clinically confirmed pulmonary tuberculosis and improved with anti-tuberculosis therapy; or exudate pleural effusion with negative bacteriological examination, pleural fluid analysis showed dominant lymphocytes and pleural fluid adenosine deaminase levels above 40 U/l. Patients with malignant pleural effusions were patients with pleural effusions due to primary or metastatic malignancy processes, as evidenced by one of the criteria, namely pleural fluid cytology obtained malignant cells; pleural biopsy found malignant cells; or exudate pleural effusion with malignancy in the lung or other organs and no other cause of pleural effusion.

The inclusion criteria were over 18 years of age, had not received chemotherapy or anti-tuberculosis therapy, and pleural puncture could be performed. Exclusion criteria were bacterial infection, empyema, severe infection and / or sepsis, and the presence of pleural puncture contraindications, namely extensive skin infection in the puncture area, and coagulopathy.

Patients with tuberculous and malignant pleural effusions who came to the polyclinic or inpatient room of Sanglah General Hospital underwent pleural punctures. Pleural fluid samples were examined for IL-6 levels with enzyme-linked immunosorbent assay (ELISA) method using the human IL-6 ELISA kit Elabscience, and leucocyte differential counts were examined using the cell-dyn hematology analyzer. From the pleural fluid leukocyte counts, the NLR and MLR were measured. Informed consent was obtained from all study subjects. Research ethics and permits are completed according to the provisions. The collected data was then processed using IBM statistical package for the social sciences (SPSS) statistics 2.0, namely the 2 independent sample t-test for the IL-6 mean, Mann Whitney test for NLR and MLR, and measuring area under curve (AUC) with receiver operating characteristic (ROC) curve.

RESULTS

In this study, 22 subjects with tuberculous pleural effusions and 31 subjects with malignant pleural effusions were found. The mean age of subjects with tuberculous pleural effusions was younger (31.18±16.68 years), while the mean age of those in malignant pleural effusions was 54, 71±8.38 years. The majority of tuberculous pleural effusion subjects were male (72.7%), while the majority of malignant pleural effusion subjects were female (61.3%). The most common complaints in both groups were shortness of breath, cough, and weight loss. Complaints of fever were more common in tuberculous pleural effusion subjects (40.9%) than in malignant pleural effusion subjects (12.9%). In 71% of malignant pleural effusion subjects, breathlessness occurred with grade 4 modified Medical Research Council (mMRC) scale, whereas most

tuberculous pleural effusion subjects experienced grade 2 (40.9%) and grade 3 (50%). The results of the sputum molecular rapid test in the tuberculous pleural effusion subjects detected *Mycobacterium tuberculosis* in 36.4% of the subjects. The most common cause of malignant pleural effusion was pulmonary adenocarcinoma (45.2%), and 42.9% of these subjects had epidermal growth factor receptor (EGFR) mutations (Table 1). Pleural fluid analysis in subjects with tuberculous and malignant pleural effusions showed no significant difference (Table 2). The mean pleural fluid IL-6 in tuberculous pleural effusion subjects was 9269.017±902.211 pg/ml, and the mean

pleural fluid IL-6 in subjects with malignant pleural effusions was 8212.146±2022.350 pg/ml. Using independent t-test, there was a significant difference between the two groups (p=0.014), with a mean difference of 1056.870 pg/ml. To diagnose tuberculous pleural effusion, using the ROC curve, an AUC of 66.6% (95% CI 51.9-81.4%) was obtained, p=0.04 (Figure 1). Using the ROC curve, the optimal cut-off point for pleural fluid IL-6 was obtained, which was the intersection of the sensitivity curve with the specificity curve. The optimal cut-off point was ≥9147.959 pg/ml, with sensitivity of 63.6% and specificity of 64.5% (Figure 2).

Table 1: Demographic characteristics of tuberculous and malignant pleural effusion subjects.

Characteristics	Tuberculous pleural effusions (n=22)	Malignant pleural effusions (n=31)	P value
Age (years), mean ± SD	37.18±16.68	54.71±8.38	0.000
Gender, n (%)			0.015
Male	16 (72.7)	12 (38.7)	
Female	6 (27.3)	19 (61.3)	
Body mass index (kg/m^2), mean±SD	19.54±2.90	20.94±3.20	0.111
Smoking, n (%)			0.553
Smoker	8 (36.4)	8 (25.8)	
Pack year, mean±SD	16.8±21.7	38.7±36.3	
Passive smoker	9 (40.9)	12 (38.7)	
Non-smoker	5 (22.7)	11 (35.5)	
Symptoms, n (%)			
Shortness of breath	22 (100)	31 (100)	
Cough	21 (95.5)	29 (93.5)	
Chest pain	7 (31.8)	12 (38.7)	
Fever	9 (40.9)	4 (12.9)	
Weight loss	19 (86.4)	27 (87.1)	
mMRC scale, n (%)			
Grade 1	1 (4.5)	0 (0)	
Grade 2	9 (40.9)	2 (6.5)	
Grade 3	11 (50)	7 (22.6)	
Grade 4	1 (4.5)	22 (71)	
Sputum rapid molecular test, n (%)			
MTB detected	8 (36.4)		
MTB not detected	14 (63.6)		
Tumor diagnosis, n (%)			
Lung adenocarcinoma		14 (45.2)	
EGFR mutation, n (%)		6 (42.9)	
Wild type		6 (42.9)	
Unknown		2 (14.3)	
Squamous cell lung carcinoma		5 (16.1)	
Breast carcinoma		3 (9.7)	
Ovarian carcinoma		2 (6.5)	
Non Hodgkin lymphoma		2 (6.5)	
Thyroid carcinoma		1 (3.2)	
Cervical carcinoma		1 (3.2)	
Endometrial carcinoma		1 (3.2)	
Non-small cell lung carcinoma		1 (3.2)	
Carcinoma with neuroendocrine feature		1 (3.2)	

SD=standard deviation; mMRC=modified Medical Research Council; MTB=*Mycobacterium tuberculosis*; EGFR=epidermal growth factor receptor

Table 2: Pleural fluid characteristics of tuberculous and malignant pleural effusion subjects.

Characteristics	Tuberculous pleural effusions (n=22)	Malignant pleural effusions (n=31)	P value
Pleural fluid pH, median (range)	8.0 (7.0-8.0)	8.0 (7.0-8.0)	0.963
Leucocyte count/mm, mean ± SD	2237±1663	1597±1390	0.135
Pleural fluid glucose (mg/dl), mean±SD	74.55±32.36	75.31±31.17	0.931
Pleural fluid total protein (g/dl), mean±SD	4.70±0.98	4.23±1.11	0.117
Pleural fluid LDH (U/L), median (range)	583.5 (189-11469)	1037 (41-34012)	0.448
Pleural fluid neutrophil count (10^3/ul), median (range)	0.101 (0.009-13.100)	0.218 (0.008-2.576)	0.594
Pleural fluid lymphocyte count (10^3/ul), median (range)	1.020 (0.155-6.850)	0.933 (0.227-3.530)	0.957
Pleural fluid monocyte count (10^3/ul), median (range)	0.069 (0.013-0.990)	0.058 (0.008-0.205)	0.216

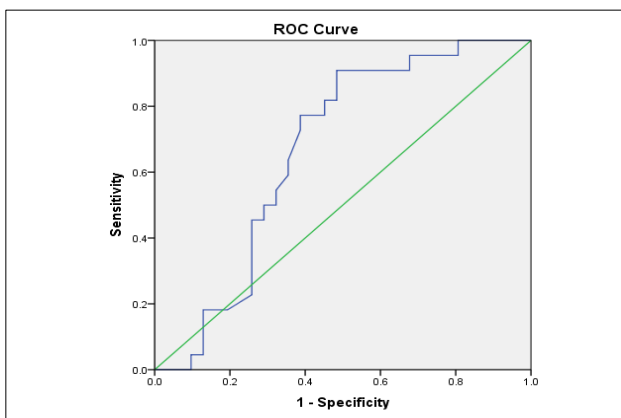SD = standard deviation; LDH = lactate dehydrogenase

Figure 1: ROC curve of pleural fluid interleukin-6, an area under curve (AUC) of 66.6% (95% CI 51.9-81.4%) was obtained, p=0.04.
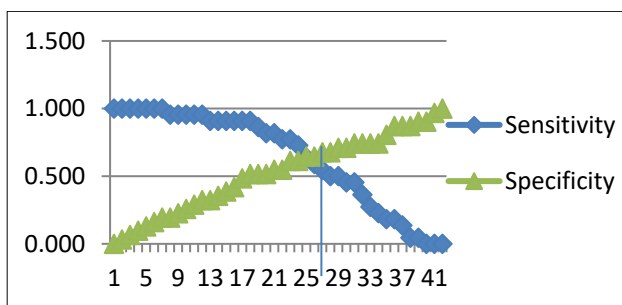

Figure 2: Cut-off point of sensitivity and specificity curve of pleural fluid Interleukin-6 to diagnose tuberculous pleural effusions. With pleural fluid IL-6 levels ≥ 9147.959 pg/ml, tuberculous pleural effusions can be diagnosed with a sensitivity of 63.6% and a specificity of 64.5%.

The median NLR of pleural fluid in tuberculous pleural effusion subjects was 0.123 (0.044-9.449), whereas in malignant pleural effusions was 0.189 (0.015-2.599). The median MLR of pleural fluid in tuberculous pleural effusion subjects was 0.065 (0.0044-0.355), whereas in malignant pleural effusion subjects was 0.065 (0.010-0.254). Median NLR and MLR of pleural fluid in both groups were not significantly different (p=0.807 and p=0.116, respectively).

DISCUSSION

In this study, the mean age of subjects with tuberculous pleural effusions was younger than the mean age of subjects with malignant pleural effusions. Malignant pleural effusion is more common in elderly, which is associated with higher prevalence of malignancy in elderly due to genomic instability, epigenetic changes, and loss of proteostasis.[10] Tuberculosis is frequent in young people due to more outdoor activities at productive age.[11]

The majority subjects with tuberculous pleural effusions were male, whereas the majority subjects with malignant pleural effusions were female. This is associated with higher tuberculosis infection in males, due to more outdoor activity, smoking habit and alcohol consumption. Moreover, there is worse stigma in women with tuberculosis, thereby reducing willingness to seek treatment.[12] Research by Hertz et al stated that in mice infected with tuberculosis, follicular B lymphocytes were smaller and interleukin-23 expression was lower in male mice, which had an effect on disease progression.[13] More malignant pleural effusions in women were associated with pulmonary adenocarcinoma as the highest cause. EGFR mutations are more common in women, and the estrogen receptor α (ERα) affects adenocarcinoma progression.[14] In this study, malignant pleural effusions were also caused by breast, ovarian, cervical, and endometrial tumors, thus affecting the high frequency of female subjects in this group.

The most common cause of malignant pleural effusion was pulmonary adenocarcinoma, with EGFR mutations detected in 42.9% of subjects with pulmonary adenocarcinoma. Research by Yang et al stated that EGFR mutations were detected in 70% of patients with pleural effusions due to pulmonary adenocarcinoma, and most were exon 19 deletions.[15]

In this study, mean pleural fluid IL-6 was significantly higher in subjects with tuberculous pleural effusions than in malignant pleural effusions. This is related to the significant role of IL-6 in tuberculosis infection which has pro-inflammatory and anti-inflammatory effects, especially in the early phase. *Mycobacterium tuberculosis*, which is phagocytized by macrophages and survives in macrophages, will induce the production of various inflammatory mediators, including IL-6. IL-6 is produced by T lymphocytes, B lymphocytes, phagocytes, fibroblasts, and endothelial cells. In a later stage, IL-6 plays a role in the formation and stability of granulomas. IL-6 also induces T and B lymphocyte responses, as well as hematopoiesis.[16] Mice that cannot produce IL-6 experience higher growth of *Mycobacterium tuberculosis*, especially in the early phase, and late induction of interferon gamma.[17]

Subjects with malignant pleural effusions had a fairly high range of IL-6 levels, namely 2438.776 pg/ml to 11137.755 pg/ml. This can be related to various mechanisms for malignant pleural effusions, including pleural metastases, mediastinal lymph node involvement, bronchial obstruction, pericardial involvement, hypoproteinemia, obstructive pneumonitis, and pulmonary embolism.[18] The second cause is different levels of IL-6 in various malignancies. In addition, pleural fluid IL-6 levels were associated with the progression of tumor infiltration in the pleural cavity. IL-6 plays a role in increasing the invasiveness of tumor cells, metastasis and angiogenesis by increasing the expression of matrix metalloproteinase-2 (MMP-2), vascular endothelial growth factor (VEGF), and fibroblast growth factor. Elevated IL-6 levels are associated with increased tumor staging, metastases, and poor prognosis. Therefore, varying levels of IL-6 pleural fluid in malignant pleural effusions can arise in varying tumor progression, stage, and metastases in the pleural space.[19]

NLR is the ratio of absolute neutrophils to lymphocytes, and generally neutrophil levels correlate with the degree of inflammation and disease progression, whereas lymphocytes correlate with the body's defence system against disease. Research by Akturk et al in 2016 stated that pleural fluid NLR was lower in tuberculous pleural effusions than malignant pleural effusions.[8] In this study, pleural fluid NLR was higher in subjects with malignant pleural effusions than tuberculosis pleural effusions, but not significantly different. This can be caused by an increase in pleural fluid neutrophils in tuberculous pleural effusions, especially in the early and late phases. Pleural fluid in tuberculous pleural effusions is generally lymphocyte dominant. In patients with symptoms less than 2 weeks, pleural fluid is dominated by polymorphonuclear cells. Over time, lymphocytes will increase with a lymphocyte-neutrophil ratio of 0.75. But at an advanced stage, especially when loculation and empyema arise, neutrophil will dominate in the pleural fluid.[20] In mice with tuberculosis infection, lung tissue neutrophils increase in 2 waves, namely on day 3 and day 23-56. Neutrophils have

2 opposite effects, namely in the initial phase increasing the movement of dendritic cells to the lymph nodes, increasing the initiation of CD4 T lymphocyte activation, and forming granulomas. Whereas in the advanced phase, the increase in neutrophils is associated with disease progression and tissue damage.[21]

There are several factors that influence pleural fluid neutrophil level; the first is a history of smoking. Pleural fluid neutrophil levels were increased in smokers (1-14%) compared to non-smokers (0-3%).[22] In this study, pleural fluid NLR levels were higher in the smoker group, but not significantly different. The second factor is the pleural drainage device which can play a role in the inflammatory process in the pleural cavity.[23] In this study, there were 3 subjects with a history of using indwelling pleural catheters (IPC) in malignant pleural effusion subjects, and 7 subjects with history of chest tube insertions in tuberculous pleural effusion subjects. The third factor is repeated pleural puncture. Research by Chung et al stated that the pleural fluid neutrophil levels in malignant pleural effusions increased with repeated pleural punctures, whereas the levels of lymphocytes and macrophages were not different.[24]

MLR is the ratio of absolute monocytes to lymphocytes. In this study, the median MLR of pleural fluid in subjects with tuberculous pleural effusions and malignant pleural effusions was not significantly different. No previous research used MLR as a parameter to differentiate tuberculous pleural effusions from malignant pleural effusions. Previous studies used MLR to determine immune deficiency status, the body's immune response to *Mycobacterium tuberculosis* infection, and to evaluate the prognosis for malignancy. Research by Guadagnino et al stated that blood MLR was significantly increased in tuberculosis patients compared to healthy individuals.[9] Another research by Sampath et al stated that the tuberculin test together with MLR could be used as a predictor of tuberculosis infection in individuals with a history of contact.[25] Whereas in malignancy, the research by Lim et al stated that in stage 4 non-small cell lung carcinoma with malignant pleural effusions, the combination of platelets and lymphocyte to monocyte ratio acted as a marker of inflammation and a predictor of poor prognosis.[26]

Monocytes have a role in the pleural inflammatory process in tuberculous pleural effusions and malignant pleural effusions. In tuberculous pleural effusions, monocytes that differentiate into macrophages become the first line of defence by differentiating into M1 macrophages, which play a role in producing pro-inflammatory cytokines and a bactericidal response to *Mycobacterium tuberculosis*, and forming granulomas in the advanced phase.[27] In malignant pleural effusions, macrophages modulate proliferation and T lymphocyte differentiation. Tumor associated macrophages (TAMs) decrease cytotoxicity, increase tumor cell growth and decrease immune response.[19]

Lymphocytes act as adaptive immunity to tuberculous and malignant pleural effusions. In tuberculous pleural effusions, there is a decrease in Th1 lymphocyte response, leading to decreased production of interferon gamma and interleukin-12 which exacerbates infection.[28] In malignant pleural effusions, the CD4+/CD8+ ratio increases more than 2.2 with an increase in CD4+ memory T cells and a decrease in T cells CD8+ effectors, which play a role in immune escape by tumor cells.[19]

The age and sex of subjects with tuberculous and malignant pleural effusions differed significantly between the two groups. To see the effect of gender on pleural fluid NLR and MLR of the two groups, an analysis of pleural fluid NLR and MLR was carried out in male and female subjects in both groups, and the results were that pleural fluid NLR and MLR were not significantly different between men and women in tuberculous pleural effusions and malignant pleural effusions. To see the effect of age on pleural fluid NLR and MLR in both groups, analyses of pleural fluid NLR and MLR were carried out in subjects with a homogeneous age range of 40-60 years in both groups, and the results stated that pleural fluid NLR and MLR of tuberculous and malignant pleural effusion subjects were not significantly different in this age range.

The weakness of this research was that the effect of interventions in the pleural cavity that cause changes in inflammatory parameters in the pleural cavity were not evaluated, namely the installation of pleural fluid drainage devices (chest tube and indwelling pleural catheter) and repeated pleural punctures.

CONCLUSION

In conclusion, pleural fluid IL-6 levels are significantly higher in tuberculous pleural effusions than in malignant pleural effusions. With pleural fluid IL-6 levels ≥9147.959 pg/ml, tuberculous pleural effusions can be diagnosed with a sensitivity of 63.6% and a specificity of 64.5%. There is no difference between RNL and RML pleural fluid in tuberculous pleural effusions and malignant pleural effusions. Future studies can use pleural fluid IL-6 levels in combination with other inflammatory parameters to differentiate tuberculous pleural effusions and malignant pleural effusions, and take into account confounding variables, namely interventions in the pleural cavity that can affect inflammatory parameters in the pleural cavity, including the installation of a pleural fluid drainage device, and recurrent pleural punctures.

ACKNOWLEDGEMENTS

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