VOL. 41, No. 3, Juli 2021

p-ISSN 0853-7704
e-ISSN 2620-3162

JURNAL RESPIROLOGI INDONESIA

Majalah Resmi Perhimpunan Dokter Paru Indonesia
Official Journal of The Indonesian Society of Respirology

Akreditasi RISTEKDIKTI
Surat Keputusan Menteri Riset dan Teknologi Nomor: 200/M/KPT/2020 Tanggal 23 Desember 2020, Peringkat 2
Website: http://www.jurnalrespirologi.org

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Official Journal of The Indonesian Society of Respirology

SST : Surat Keputusan Menteri Penerangan RI
No.715/SK/DitjenPPG/SST/1980 Tanggal 9 Mei 1980

Alamat Redaksi
PDPI Jl. Cipinang Bunder, No. 19, Cipinang Pulo Gadung
Jakarta Timur 13240 Telp: 02122474845
Email : editor@jurnalrespirologi.org
Website : http://www.jurnalrespirologi.org

Diterbitkan Oleh
Perhimpunan Dokter Paru Indonesia (PDPI)
Terbit setiap 3 bulan (Januari, April, Juli & Oktober)

Jurnal Respirologi Indonesia
Akreditasi Peringkat 2
Sesuai Keputusan Menteri Riset dan Teknologi/Kepala Badan
Riset dan Inovasi Nasional Republik Indonesia
Nomor: 200/M/KPT/2020 Tanggal 23 Desember 2020

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DAFTAR ISI

Artikel Penelitian

Tinjauan Pustaka

Pleural Fluid Leukocyte Level Test For Establishing Tuberculous Pleural Effusion in Patients with Exudative Pleural Effusion

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Abstract

Background: *Tuberculous pleural effusion is an accumulation of fluid in the pleural cavity produced by Mycobacterium tuberculosis (MTB). The gold standard of TB pleural effusion diagnosis is to obtain TB bacilli in pleural fluid or pleural tissue. However, this is often constrained due to the low identification level of these bacilli and the slow growth of MTB cultures. This study aimed to assess the pleural fluid leukocyte level in establishing a diagnosis of pleural effusion caused by TB.*

Methods: *This was a diagnostic study conducted on 111 patients with pleural effusion, caused by TB, malignancy or non-TB infections that were assigned by supporting examinations obtained from medical records, which then assessed for pleural fluid leukocytes. Statistical analysis was performed using Kruskal Wallis Test and Receiver Operating Characteristic (ROC) curve to attain the cut-off point of pleural fluid leukocyte level.*

Results: *Pleural fluid leukocyte levels in TB cases were significantly different when compared to pleural effusion caused by malignancy and non-TB infections (P<0.001). Pleural fluid leukocyte level ≥1100 cell/mm^3 was a cut-off diagnostic test for tuberculous pleural effusion with a sensitivity of 77% and specificity of 60.3%.*

Conclusion: *Pleural fluid leukocyte level ≥1100 cell/mm^3 could assist in diagnosing tuberculous pleural effusion.* ***(J Respirol Indones 2021; 41(3): 156–60)***

Keywords: *leukocyte level, pleural effusion, tuberculosis*

Uji Kadar Leukosit Cairan Pleura dalam Menegakkan Efusi Pleura Tuberkulosis Pada Pasien Efusi Pleura Eksudatif

Abstrak

Latar Belakang: *Efusi pleura tuberkulosis (TB) adalah akumulasi cairan dalam rongga pleura yang disebabkan oleh Mycobacterium tuberculosis (MTB). Baku emas diagnosis efusi pleura TB adalah ditemukannya basil MTB di cairan pleura atau jaringan pleura, namun hal ini sering terkendala karena rendahnya tingkat identifikasi basil tersebut serta pertumbuhan biakan MTB yang lambat. Penelitian ini bertujuan untuk menilai kadar leukosit cairan pleura dalam menegakkan diagnosis efusi pleura yang disebabkan oleh MTB.*

Metode: *Penelitian ini merupakan uji diagnostik yang dilakukan pada 111 orang pasien efusi pleura TB, keganasan atau infeksi non-TB yang ditegakkan berdasarkan pemeriksaan penunjang yang diperoleh dari rekam medis, lalu dilakukan penilaian leukosit cairan pleura dari masing-masing kasus. Analisis statistik dilakukan dengan uji Kruskal Wallis dan kurva ROC (Receiver Operating Characteristic) untuk mencari titik potong kadar leukoist cairan pleura.*

Hasil: *Kadar leukosit cairan pleura pada kasus TB berbeda bermakna jika dibandingkan dengan efusi pleura yang disebabkan oleh keganasan dan infeksi non-TB (P <0,001). Kadar leukosit cairan pleura ≥1100 sel/mm^3 merupakan titik potong uji diagnostik efusi pleura TB dengan nilai sensitivitas 77 % dan spesifisitas 60,3 %.*

Kesimpulan: *Kadar leukosit cairan pleura ≥1100 sel/mm^3 dapat membantu diagnosis efusi pleura TB.* ***(J Respirol Indones 2021; 41(3): 156–60)***

Kata kunci: *kadar leukosit, efusi pleura, tuberkulosis*

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INTRODUCTION

The high incidence of pleural effusion is led by the time delay of patients having an examination for their health complaint. Dirty environment brought in the risk factors for pleural effusion, namely the inadequate sanitation, dense population, low socio-economic conditions, as well as lack of health facilities and infrastructures and also the poor knowledge about health.[1]

Pleural effusions account for 2.7% of other respiratory tract infections.[2] Pleural effusions occur due to inflammatory or non-inflammatory processes. Non-inflammatory pleural effusions could develop due to decreased oncotic pressure or elevated hydrostatic pressure.[1] Diagnosis of pleural effusion must be confirmed through careful history taking and physical examinations, definite diagnosis through thoracocentesis/pleural puncture, pleural biopsy, and pleural fluid analysis.[3] Clinicians now spend a lot of effort looking for new parameters that could assist in diagnosing the etiology of pleural effusion.

One parameter that has been developed to determine the underlying cause of pleural effusion was pleural fluid leukocyte level. To date, pleural fluid leukocyte level has been widely used to diagnose empyema, which is generally induced by a spreading parapneumonic effusion. However, in recent years, various studies began to demonstrate the ability of this parameter to increase the probability of tuberculous pleural effusion. Therefore, this study aimed to determine the role of pleural fluid leukocyte level in diagnosing tuberculous pleural effusion.

METHOD

This was an analytical study with a diagnostic test design. The sampling was done using consecutive sampling. The results expected from this study were the level of sensitivity, specificity, positive predictive value, negative predictive value, and status of accuracy and cut-off value. This study was conducted for four months, starting from April to August 2019, at the Department of Pulmonology and Respiration Medicine, Faculty of Medicine Universitas Sumatera Utara/H. Adam Malik Hospital.

Study subjects were Tuberculosis (TB) patients who met the inclusion criteria, namely pleural effusion patients with known underlying etiology and were more than or equal to 18 years old. The exclusion criteria were pleural effusion patients who had coagulation disorders and pleural effusion patients with sepsis.

The expected sensitivity for protein content was 85%. If the deviation (d) was acceptable for a sensitivity of 15% and a confidence interval of 95% (α=0.05; z=1.96), then for the sensitivity test, a minimum sample was required. The minimum sample size needed in this study was 111 subjects with pleural effusions.

The data collected were processed using statistical software. To obtain the cut-off point of the pleural fluid protein content, ROC (Receiver Operating Characteristic) curve was used. This study was approved by the Health Research Ethics Commission of Faculty of Medicine Universitas Sumatera Utara, Medan.

RESULT

Table 1 showed that all study subjects were patients treated in the Pulmonary Ward of H. Adam Malik Hospital Medan.

Table 1. Characteristics of study subjects

Characteristics		n	%
Gender	Male	63	56.8
	Female	48	43.2
Age (years old)	<40	16	14.4
	40 - 49	28	25.2
	50 - 59	31	27.9
	60 - 69	26	23.4
	≥70	10	9.0
Level of Education	Elementary School	46	41.4
	Junior High School	37	33.3
	Senior High School	28	25.2
Occupation	Retired	4	3.6
	Farmer	28	25.2
	Government employees	12	10.8
	Driver	20	18.0
	Housewife	33	29.7
	Entrepreneur	8	7.2
	Unemployed	6	5.4
Diagnosis	Tuberculosis (TB)	48	43.2
	Pneumonia	35	31.5
	Malignancy	28	25.2
Total		111	100.0

A pleural fluid examination procedure was carried out to confirm exudative pleural effusion based on the results of the pleural fluid analysis. Of the 111 study subjects, 56.8% were male, and 43.2% were female. Most of the subjects were in the age range of 50–59 years (27.9%) and 40–49 years (25.2%).

The majority of the subjects had a primary education level of elementary school background (41.4%). Based on occupation mostly were, housewife (29.7%) and farmers (25.2%).

All the subjects underwent a series of examinations to determine the underlying etiology, including sputum cytology, sputum molecular rapid test (MRT), culture for aerobic and anaerobic bacteria of the sputum and pleural fluid, and pleural fluid analysis.

Patients who had bacterial growth in the sputum and pleural fluid with no signs of TB infection were declared to have pneumonia/pleuropneumonia as the etiology. Patients with malignant features from sputum cytology, pleural fluid cytology, or histopathology from bronchoscopy samples were stated to have malignancy as the etiology. Subjects with the presence of MTB detected either through direct smear or MRT of the sputum, or exhibiting a response from anti-TB drugs administration, were declared to have TB as the underlying etiology. Of the 111 study subjects, it was found that 43.2% had TB, 31.5% had pneumonia, and the remaining 25.2% had malignancy as their etiology of exudative pleural effusion.

Table 2 describes the results of pleural fluid analysis between patients diagnosed with TB and those with diseases other than TB. From table 2 it is shown that there was a significant difference in the number of WBC between TB and non-TB subjects (*P*=0.001), where the number of WBC on TB patients was higher (1546 cells/mm^3) than non-TB patients (635 cells/mm^3).

The ROC curve is a curve adequate to measure the capability of a diagnostic test in predicting disease. The basic concept of the ROC curve is that the wider the area under the curve (AUC), the better the diagnostic test is to diagnose.

Figure 1 describes the ROC curve where the pleural fluid WBC count is represented by a yellow line. The figure indicates that the line formed by the pleural fluid WBC does not intersect with the diagonal line, which means this parameter is suitable to be used as a diagnostic test.

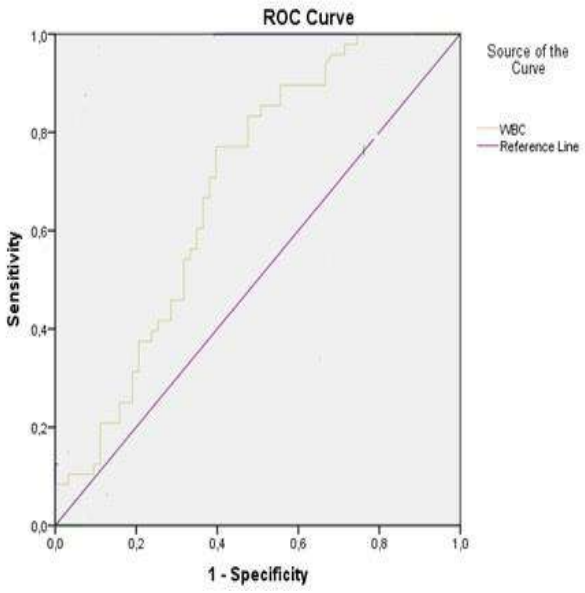

Figure 1. The ROC curve for pleural fluid protein, glucose and WBC levels

Since WBC level is intended as a screening tool to distinguish between TB pleural effusion and other cases, a ROC curve coordinate analysis was performed by looking for the value with the best sensitivity compared to the specificity. Hence, it was found that the best cut-off value for WBC was 1100 cells/mm^3 (number of pleural fluid leukocytes).

Table 2. Comparison of pleural fluid analysis results

		TB (n=48)		Non–TB (n=63)		*P* value
		median	min - max	median	min - max	
WBC	(cells/mm^3)	1546	172–33139	635	14–9474	0.001*
MN	(%)	84.3	50.8–97.7	84.3	0.3–99.5	0.34
PMN	(%)	17	2.3–55	15.7	0.0–112	0.97

Note: *) significant with *Mann-Whitney test*; WBC=white blood cells; MN=mononuclear cells; PMN=polymorphonuclear cells

Based on the previous explanation, there was one parameter that was good enough to be biomarkers of TB pleural effusion, namely the pleural fluid leukocyte level. Therefore, a diagnostic test was performed to see the sensitivity and specificity of pleural fluid WBC, as shown in Table 3 below.

Table 3. Diagnostic test of pleural fluid WBC count

WBC count	TB	Non-TB	Total
≥ 1100 mg/dl	37	25	62
< 1100 mg/dl	11	38	49
Total	48	63	111

Sensitivity	= (37/48) ×100% = 77%
Specificity	= (38/63) ×100% = 60.3%
Positive predictive value (PPV)	= (37/62) ×100% = 59.6%
Negative predictive value (NPV)	= (38/49) ×100% = 77.5%

DISCUSSION

Tuberculous pleural effusion is a manifestation of paucibacillary mycobacterial infection in the pleural space, which results from early parenchymal lesions and produces an immunologic response that increases the pleural fluid formation and reduces pleural discharge.

Initially, there is a rapid neutrophilic inflammatory response within the symptomatic pleura. This process is followed by a protracted lymphocyte-induced immune reaction accompanied by the formation of pleural granulomas and the release of adenosine deaminase (ADA). It is, therefore, plausible that the likelihood of positive pleural fluid culture decreases over time since the effusion becomes lymphocyte-dominated, while the number of TB germs that survive is minimal.[4]

Tuberculous pleural effusion is predominantly thought to develop as a result of a delayed hypersensitivity reaction. An experiment in which a substance containing tuberculin protein was injected into the pleural cavity of mice resulted in a pleural effusion that was very rich in protein within 24 hours of injection, which was completely suppressed by serum antilymphocytes. Based on this model and the fact that the investigators were unable to culture MTB from pleural fluid, the pathogenesis was thought to be due to delayed hypersensitivity. This is the most important pathogenesis, followed by the possibility of direct infection of the pleural space.[4]

The pathogenesis of tubular effusion due to TB is not much different from the pathogenesis of TB in the lung parenchyma. The pathogenetic hypothesis of pleural tuberculosis suggests that immunity such as strong type 1 T-helper cells (Th1-interferon dominant) is essential for the containment of MTB, while this protective effect is countered by the cytokines released by type 2 T-helper cells, particularly interleukins (IL-4). Activated CD3+ and CD4+ Th1 cells, through the release of interferon-gamma (IFN-γ) and other Th1 cytokines, activate macrophages to kill MTB, whereas Th2 cytokines can suppress this effect.[4]

Polymorphonuclear leukocytes are the first cells to respond, can persist predominantly for the first 24 hours, and are then followed by macrophages, peaking at 96 hours, and then by lymphocytes. It appears that the inclusion of polymorphonuclear leukocytes is a specific response to pleural injury either through itself or interactions with macrophages, playing a role in the host defense mechanism against tubercular bacilli.[4]

The predominance of Th1 immune reactions in TB pleural effusion is confirmed by high levels of IFN-γ, and other inflammatory cytokines (e.g., IL-12), while the proportion of T-helper cells in pleural fluid is also increased compared to serum, thus creating a localized pleural space. The frequency of T-cells producing IL-4, representing Th2 immunity, is significantly lower in pleural fluid compared to peripheral blood.[4]

The macroscopic appearance of pleural fluid is yellowish in more than 80% of cases. Microscopically, the identification of MTB in pleural fluid is found in less than 10% of cases. There is an exception in patients with empyema due to TB with HIV, where the result may be higher (>20%). Pleural fluid culture can be performed on both solid and liquid media as frequently used, the BACTEC MGIT semi-automatic system (Becton Dickinson-Franklin Lakes, NJ, USA), or by manual culture methods which allow for simultaneous drug resistance testing such as the

microscopic-observation drug susceptibility (MODS) assay.[4]

When using solid culture media, the sensitivity was reported to be low at about 12% to 30%. However, liquid culture media displayed better sensitivity, which was up to 70%. A further benefit of using liquid media was the significantly shorter culture time required to produce yields, being two weeks, whereas solid media was six weeks.[4]

A study from von Groote-Bidlingmaier et al compared positive culture results from large-volume (100 ml) pleural fluid with low-volume (5 ml) liquid culture media in patients with a high probability of TB. The results obtained were not significantly higher for larger volumes, namely 53.5% and 50%, respectively (P=0.75).[5]

In the same study, subjects with HIV positive had more frequent positive results of MTB pleural fluid cultures than those with HIV negative. The combination of pleural fluid culture and sputum culture in establishing TB pleural effusion was very reasonable for initial examination, with a combined diagnostic result of nearly 80%.[5]

In a recent study, the reported diagnostic results were 63% for pleural fluid culture, 48% for sputum culture and 79% for combined pleural fluid and sputum culture using liquid culture media.[4]

CONCLUSION

From our study, it can be concluded that there was a significant difference in pleural fluid leukocyte levels due to TB and non-TB (P <0.05). We could use pleural fluid leukocyte level ≥1100 as a cut-off diagnostic test for tuberculous pleural effusion with sensitivity and specificity of 77% and 60.3%, respectively, while the positive and negative predictive values were 59.6% and 77.5%.

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