Original Article

Analysis of Monocyte to Lymphocyte Ratio and Clinical Symptoms of Clinically Confirmed Pulmonary Tuberculosis New Case Patients Before Treatment and After Intensive Phase

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Abstract

Background: Treatment evaluation of clinically confirmed pulmonary tuberculosis (TB) is limited to clinical symptoms and chest X-rays that tend to be subjective and no better than bacteriological examination. Monocytes and lymphocytes mediate the immunopathology of TB infection as a form of host defense that affects the systemic concentration of the body's defense cells. The study assesses the monocyte-to-lymphocyte ratio (MLR) to evaluate TB treatment.

Methods: Longitudinal prospective paired t-test with characteristics of clinically confirmed pulmonary TB new cases then compared to monocytes, lymphocytes, and monocyte-lymphocyte ratio (MLR) before administration of anti-tuberculosis drugs (ATD) and the end of the intensive phase.

Results: In thirty clinically confirmed pulmonary TB patients before and after the anti-tuberculosis drug (ATD) there was no difference in monocytes pre 8.3 - post 8.5 (P=0.82), there was a difference in lymphocytes pre 17.8 - post 25.6 (P<0.05) that affected the MLR ratio value pre 0.57 - post 0.39 (P<0.05).

Conclusion: This study identifies there is a significant difference in MLR before treatment and after the intensive phase of clinically confirmed pulmonary TB.

Keywords: lymphocytes, monocytes, monocyte to lymphocyte ratio, pulmonary tuberculosis

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INTRODUCTION

TB management in addition to establishing a diagnosis from bacteriological examination of sputum Acid Fast Bacilly (AFB), Gene Xpert polymerase chain reaction (PCR), gold standard culture examination certainly followed by treatment evaluation.[1] Sputum or culture conversion are expected objective examination of patients with TB.

The evaluation of clinically confirmed pulmonary tuberculosis is based on clinical improvement and the improvement of chest X-rays. However, these examinations are subjective and no better than a bacteriological examination, influenced by the inconsistency of the patient's clinical symptoms, varying reader interpretation, and the quality of chest X-rays.

TB immunopathology is the complex development of innate and adaptive immune responses optimized to eliminate TB pathogen, monocytes as the target cells of *Mycobacterium tuberculosis* (M. tb), and lymphocytes as the main effectors of immunity to TB.[1]

Active pulmonary TB patients have significantly higher values of leucocytes, lymphocytes, monocytes, and neutrophils than control populations. There are differences in MRL between active TB (pulmonary TB, extrapulmonary TB) before treatment and after treatment.[2] This study addresses the limitations of using clinical symptoms and chest X-rays to evaluate tuberculosis (TB) treatment, which are subjective compared to bacteriologic methods. It introduces the monocyte-to-lymphocyte ratio (MLR) as a novel biomarker for assessing treatment outcomes in pulmonary TB.

METHODS

This study was a prospective longitudinal cohort study conducted based on before and after

treatment. The study was conducted on 30 patients with new cases of clinically confirmed pulmonary TB and negative sputum smear results. Chest X-rays were also taken, and active TB was indicated. All study patients had no previous history of TB.

Peripheral blood was drawn to measure monocyte and lymphocyte levels, and the monocyte-lymphocyte ratio was calculated before and after anti-tuberculosis therapy (ATT) in the intensive phase. The monocyte-to-lymphocyte ratio (MLR) was determined by dividing the absolute monocyte count by the absolute lymphocyte count before and after administration of intensive phase ATT. Treatment success for TB was assessed after two months of intensive phase treatment. Success was determined based on weight gain from baseline weight and improvement in clinical symptoms (fever, cough, shortness of breath, and chest pain) and improvement in chest X-rays compared to before anti-tuberculosis (OAT) therapy.

Statistical analysis was performed using a paired t-test with SPSS software version 22.0, and statistical significance was set at $P<0.05$. Categorical data is expressed in percentages. This study received ethical approval from dr. Zainoel Abidin Hospital Banda Aceh Health Ethics Committee (019/ETIK-RSUDZA/2022).

RESULTS

New cases of clinically confirmed pulmonary TB patients were purposively sampled from dr. Zainoel Abidin Hospital and network hospitals between September 2022 and February 2023. Comorbidities of diabetes, hypertension, human immunodeficiency virus (HIV), malignancies, overlapping pulmonary and extra-pulmonary TB, and pulmonary TB with secondary infection were excluded from the study.

Of the thirty samples, 20 (66.7%) were males. Twelve patients (40%) were smokers lower than non-smokers, 18 patients (60.0%) in this study, and the entire female population, 10 patients (33.3%) did not smoke. When comparing only the male gender, 60% of all males were smokers. It is suspected that socially active adult males may be more exposed and at more significant risk than females for infection.[3,4]

Twenty-six patients (86.7%) were productive aged 18–45 years, with 4 patients (13.3%) elderly 46–65. Degenerative diseases influenced the difference in age demographics; the study exclusion criteria predominated in the elderly group. All samples in the study used fixed-dose combination drugs (FDC) according to the recommendations of the Ministry of Health of the Republic of Indonesia.

Table 1 outlines the various symptoms of clinically confirmed pulmonary TB, sorted from top to bottom. Cough showed the most symptoms, at 96.7%, while hemoptysis was only 30.0%. TB lesions on chest X-rays consist of three parts: minimal lesions, moderate lesions, and severe lesions. Moderate lesions, 66.7%, predominated in the initial diagnosis of TB. There was an improvement in all clinical symptoms and chest X-rays before and after 2 months of anti-TB therapy. There was a statistically significant increase in body weight and BMI before ATD and after the intensive phase ($P<0.001$).

Table 1. Characteristics of clinical symptoms and chest X-ray

Characteristics	Before ATD	After Intensive phase
Cough		
Yes	29 (96.7%)	0 (0.0%)
No	1 (3.3%)	30 (100%)
Malaise		
Yes	23 (76.7)	2 (6.7%)
No	7 (23.3%)	28 (93.3)
Appetite		
Decrease	18 (60.0%)	0 (0%)
Normal	12 (40.0%)	13 (43.3%)
Increase	0 (0%)	17 (56.7%)
Night Sweat		
Yes	17 (56.7%)	0 (0%)
No	13 (43.3%)	30 (100.0%)
Fever		
Yes	14 (46.7%)	0 (0%)
No	16 (53.3%)	30 (100.0%)
Hemoptysis		
Yes	9 (30.0%)	0 (0%)
No	21 (70.0%)	30 (100.0%)
Chest X-ray lession		
Minimally	2 (6.7%)	6 (20.0%)
Moderately	20 (66.7%)	23 (76.6%)
Advanced	8 (26.7%)	1 (3.3%)

Table 2. Characteristics of body weight and BMI

Characteristics	Before ATD	After Intensive pahase	*P*
Body Weight (Kg)	49.4±10.1	52.7±9.9	0.0001
Body Mass Index (BMI)	18.5±3.1	19.6±3.0	0.0001

Monocytes and lymphocytes are values that affect MLR values. There was no significant difference in monocyte biomarkers before ATT and after the intensive phase (*P*=0.82). There was a significant difference in lymphocytes (*P*<0.001) which influenced the difference in MLR (*P*<0.001). Data distribution with a Box-Plot diagram between each biomarker can be seen in Figure 1.

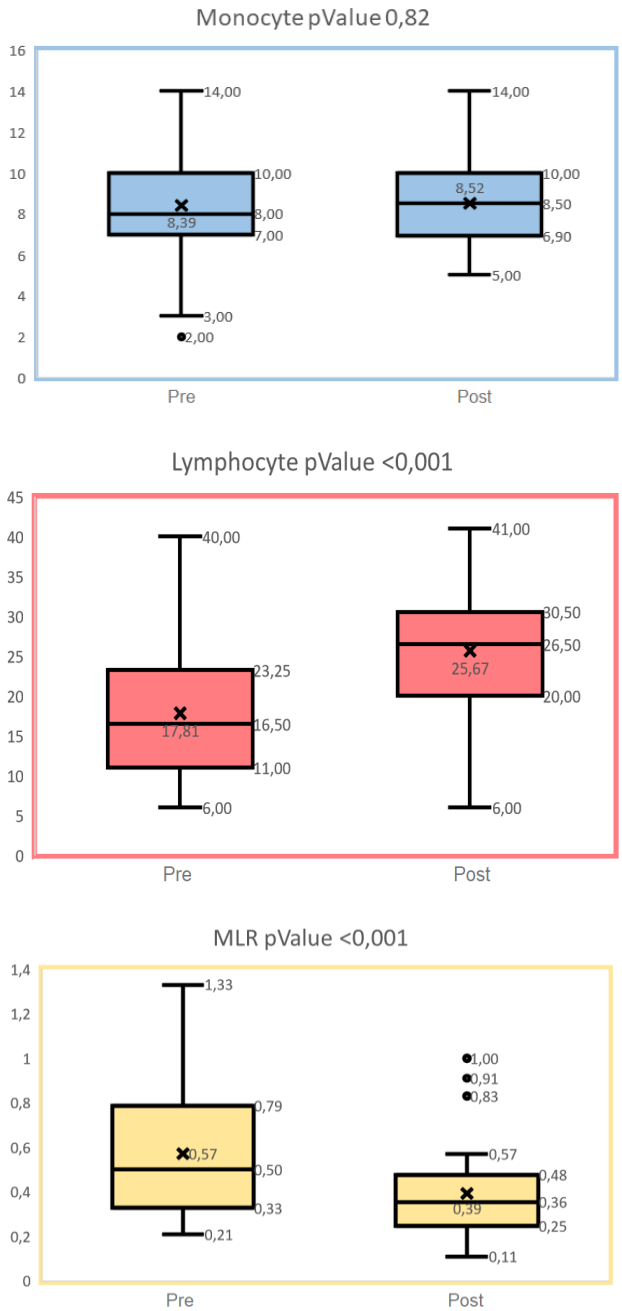

Figure 1. Box-Plot distribution of monocyte, lymphocyte, MLR of clinically confirmed pulmonary TB before ATD and after intensive phase

DISCUSSION

The gold standard for diagnosis and evaluation conversion of M.tb is to detect the presence of bacteria with culture media or AFB staining.[5,6] Other testing modalities such as GeneXpert PCR testing which specializes in M.tb. Serological examination Interferon-gamma release assay (IGRA) or tuberculin test to assess induration.[1,6] Histopathological examination of lymph node tissue, nodules, pleura fluid, bone, digestive system, skin, urinary tract, etc.[5,7] However, the available modalities have limitations in terms of treatment evaluation.

The combination of clinical symptoms such as cough, hemoptysis, fever, night sweats, body weight and appetite, malaise and chest x-ray showing infiltrates, calcifications, fibrosis, and pleural fluid depletion is used as modalities to evaluate the success of treatment but the inconsistency of patient's clinical symptoms, variety of interpretations of chest x-ray influenced by the reader or the quality of chest x-ray tend to be subjective results.

Immunity plays an important role in against infection caused by TB. Monocytes and lymphocytes can describe the state of an individual's immunity to infection. The initial interaction of M.tb occurs in the distal alveolus which is then phagocyte by innate immunity alveolar macrophage cells otherwise phagocytic cells are also target cells of M.tb which are intracellular bacteria and adaptive immunity mediated T lymphocyte is the main effector of TB immunity.[8]

The process of phagocytosis by macrophages increases the expression of various mediators or receptors that influence the circulation and differentiation of monocytes to the site of infection.[8] Macrophages also act as antigen-presenting cells (APCs) to process antigens from M.tb presenting to T lymphocytes as the main effectors of TB immunity.[9] Elaboration of cytokines from the recognition process by APCs results in proliferation of T lymphocytes into CD8+ subset for cytotoxicity in the form of apoptosis of targeted macrophage cells containing bacilli or

destroy M.tb directly, CD4+ subset for Th1/Th2 phenotype that can elaborate several cytokines to optimize macrophage and CD8+ cells in the form of autoinduction.[8,10]

M.tb can also alter the hematopoietic stem cell (HSC) subset resulting in lymphocytes being rapidly depleted by systemic infection. IFN-γ produced by immune cells results increased proportion of long-term repopulating HSC proliferation. Thus, chronic infection is not only in the peripheral but also in the HSC subsets. Therefore, the difference in the proportion of HSCs between myeloid and lymphoid may underlie the difference in the proportion of monocytes and lymphocytes in the peripheral.[11]

Reversible peripheral blood abnormalities are often associated with PTB, and these hematological changes have been used as diagnostic, prognostic, and therapeutic response markers. the results of this study are in line with the meta-analysis by Adane et al which showed that MLR has excellent diagnostic performance in detecting TB, with a sensitivity of 79.5%, specificity of 80.2%, positive likelihood ratio of 4.02, and negative likelihood ratio of 0.25. The diagnostic odds ratio reached 15.71 (95% CI=5.69-43.36), while the area under the ROC curve was 0.88 (95% CI=0.857–0.903), indicating high diagnostic accuracy. Given the limitations of sputum-based TB testing in some patients, MLR has the potential to be a simple and rapid predictive marker to distinguish TB patients from healthy individuals or those with other diseases.[12]

This study also demonstrated a substantial increase in MLR values in patients with TB compared to the control group. Previous reports have indicated alterations in the phenotype and function of circulating monocytes in TB patients compared to healthy individuals, suggesting that MLR could serve as a potential biomarker for differentiating active TB from healthy individuals. Elevated MLR in TB patients has been shown to correlate with higher monocyte counts and lower lymphocyte counts, suggesting a pivotal role for both monocytes and lymphocytes in the immune response to M.tb.[13,14]

Monocytes serve as targets for MTB growth and as antigen-presenting cells in adaptive immunity, a process that contributes to the observed increase in MLR. This increase can be explained by the early release of monocytes from the bone marrow due to immune activation. Conversely, the observed decrease in lymphocytes in peripheral blood may be attributable to migration to the site of infection, alterations in hematopoiesis, or augmented apoptosis. Furthermore, elevated MLR has been associated with monocyte gene transcription changes, which may influence their functional profile in combating M.tb.

This study also examined the role of MLR in monitoring the effectiveness of anti-TB therapy. The analysis of six studies by Adane et al showed that MLR levels decreased significantly after patients received TB. Increased MLR is known to occur in chronic inflammatory diseases, including TB, and decreases after treatment with anti-TB therapy.[2,14,15]

In contrast, the decrease in MLR in treated patients reflects the reduction in treatment-induced inflammation. This suggests that elevated MLR in TB patients is associated with inflammatory processes that are suppressed after therapy. Thus, TB patients with high MLR tend to experience a decrease after therapy, while patients with low MLR may experience an increase. This change in MLR can be used as an indicator to assess a patient's response to TB treatment.[2,14,15]

LIMITATION

The study's limitations are attributed to the relatively small sample size and the lack of follow-up after six months of ATT, which prevented a thorough analysis and limited understanding of leukocyte dynamics during ATT administration. Future research is needed to validate these findings by comparing the ratios across multiple stages of treatment.

CONCLUSION

According to our study, the MLR collected from routine complete blood counts (CBC) tests helps identify progress in the intensive phase of pulmonary tuberculosis treatment. These ratios are

inexpensive, simple, and convenient markers. However, further research is necessary to substantiate these findings.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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