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Vitamine D Deficiency Leukocyte Ratio: Unraveling the impact on Multidrug Resistant Tuberculosis Patients

Fardiah Tilawati Sitanggang, James Perdinan Simanjuntak, Siti Sakdiah
[1]Medical Laboratory Technology Department, Health Polytechnic of Jambi, Indonesia

Corresponding author: Fardiah Tilawati Sitanggang (e-mail: fardiahtilawati@poltekkejambi.ac.id).
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ABSTRACT Tuberculosis (TB) remains an important health problem in Indonesia,the problems more complex with phenomenon of multi-drug resistance Tuberculosis (MDR) which cause worse prognosis, long treatment,high risk of transmission to other and side effect of treatment. Vitamin D plays a role in non specific and specific immune responses in *Mycobacterium tuberculosis (M.tb) infection*. Vitamin D have a role in hematopoiesis and affects the early development of monocytes and granulocytes. *M.tb* infection causes changer in the ratio of neutrophil cells, lymphocytes and monocytes. Changes in the ratio reflect an increase or decrease of effective immune response. Using a case control design, this study will evaluate the correlation between vitamin D, leukocyte ratio and MDR-TB patients among MDR-TB patient cases and TB patient controls. Independent variable in this study were vitamin D levels, leukocyte ratios consisting of NLR, MLR, NMLR, and clinical status of respondents were the dependent variable. The result of this study found that vitamin D levels of TB patients all showed values that were within range of in the insufficiency and deficiency categories. From this result, the NLR and NMLR parameters were able to show that immune status problems were mainly found in the MDR-TB patients. The discovery of the fact that the NLR and NMLR parameters and Vitamin D have potential as biological markers of immune conditions in a TB patient with multidrug –TB patients should be observed with other marker parameters that have been proven in previous studies.

INDEX TERMS MDR-TB, Vitamin D, Leukocyte ratio.

I. INTRODUCTION

Tuberculosis (TB) causes 1.6 million deaths TB cases in the world are 10.4 million and 45% of cases occur in Southeast Asia. In 2018, there are 511.893 TB cases in Indonesia [1]. The problem of TB is currently becoming more complex with the emergence of the phenomenon of Mycobacterium tuberculosis which is multi-drug Tuberculosis that causes worse prognosis, longer treatment, high cost, high risk of transmission to others and many side effects of treatment [1]. The World Health Organization (WHO) estimates that there are 23,000 cases of MDR/RR TB in Indonesia. The rate of finding cases of MDR-TB is increasing every year but is not matched by the number of treatments for MDR- TB patients. In 2017, the treatment rate for MDR- TB patients was 59% but decreased in 2018 to 51% and the loss to follow-up (LFU) rate was 30%. The high number of LFU MDR-TB is a separate problem [2]. The incidence of MDR-TB in Jambi City in 2018 and 2019 was 68 and 20 cases and from 2020 to August were 10 cases [3], [4], [5]. The incidence and infection of TB in the body are influenced by the status of a person's immune response. The immune response aims to eliminate the cause of infection. Many factors affect the immune response, one of which is nutrition. Nutrients have an immunomodulatory effect in controlling infectious and inflammatory processes. Malnutrition causes changes in the balance of the immune response, which significantly increases an individual's susceptibility to infection or progression of infection to disease [6]. Vitamin D plays a role in nonspecific and specific immune responses in Mycobacterium tuberculosis infection. Vitamin D will induce a series of antimicrobial responses such as autophagy induction, increase phagolysosomal fusion from macrophages, induce nitrogen and oxygen reactivation, and increase cathelicidin release and activation and immune modulation. The result of activation and induction is the killing and suppression of the multiplication of Mycobacterium tuberculosis [7]. Study about the role of vitamin D in TB patients with MDR-TB has not been done much. Research conducted by Huang et, al [7] showed that

vitamin D levels were lower in MDR-TB patients compared to TB patients and healthy people and lower in MDR-TB patients who had not received treatment than those who had received treatment. His research showed an increase in vitamin D levels began to occur in the fourth and sixth months. Elsafi et al. (2020) showed that serum vitamin D levels of TB patients were significantly lower than those in environmental contacts and much lower in MDR TB patients than non-MDR TB patients. The results of the study also showed severe vitamin D deficiency in TB patients. Different results were shown in other studies, were in his study showed vitamin D levels in MDR TB were slightly higher than in household contacts and healthy people, and his study concluded that there was no significant relationship between vitamin D deficiency and the incidence of MDR-TB [8]. In addition to the immune response, vitamin D also plays a role in cell hematopoiesis. The role of vitamin D in hematopoiesis is to influence the early development of monocytes and granulocytes. In the process of hematopoiesis, the bioactive form of vitamin D (1,25 (OH)2D3) will suppress the formation of colony-forming units of granulocyte macrophages (CFU-GM) and in turn induce colony-forming units of macrophages, so that the development of granulocyte cells is suppressed and directs cell development to monocytes and macrophages[9], [10]. Mycobacterium tuberculosis infection causes changes in the ratio of neutrophil cells, lymphocytes and monocytes. Changes in these ratios reflect an increase in the effective immune response and changes in these ratios have been shown to correlate with inhibition of the growth of Mycobacterium tuberculosis [7] [11]. Several studies have been conducted to associate changes in this ratio with the risk of tuberculosis incidence, disease progression and risk of treatment failure. Research showed a significant difference in the value of the neutrophil to lymphocyte ratio (NLR) in patients with confirmed bacteriological pulmonary TB and DRUG-resistant TB. Where the NLR value < 2.91 is more suggestive of DRUG-resistant TB [12]. The other study showed different results where TB patients with NLR values of 2.53 had a greater chance of undergoing repeat treatment than NLR < 2.53 (OR = 1.99) so that in their research concluded that the NLR values before treatment can be used to determine the probability of treatment failure [13] Another study by Wang et al. (2015) showed that the ratio of monocytes to lymphocytes <9% or> 25% was a predictor of active TB. After treatment, the monocyte-to-lymphocyte ratio is almost normal. The research of Wang showed that the ratio of monocytes to lymphocytes in TB patients before treatment was higher than in healthy controls. After treatment, the ratio of TB patients decreased drastically but was still high compared to healthy controls[14].

II. RESEARCH METHODS

This study is an analytic observational study with a case-control design. The case-control design was used to see how vitamin D and Leukocyte ratio correlated between MDR-TB patients as cases and TB patients as controls. Several health centers in Jambi City are referrals for examination of TB patients with Multi drug-TB using the GeneXpert MTB/RIFert method, namely Pakuan Baru, Paal X, and Simpang Kawat Health Centers in Jambi City as sampling sites. Meanwhile, the laboratory examination at the Immunology Laboratory, Clinical Chemistry Laboratory, Bacteriology Laboratory and Hematology Laboratory, Department of Medical Laboratory Technology, Ministry of Health Polytechnic Jambi, was carried out from January 2021 to October 2021. This study received ethical approval from the research ethics committee of the Health Polytechnic of Jambi with No. LB.02.06/2/022/2021 dated January 16, 2021.

The population in this study were Multi-drug TB patients who did a GeneXpert MTB/RIF sputum examination at the Pakuan Baru Health Center Laboratory, Paal X, Simpang Kawat Jambi City, during the data collection period. The control population was TB patients who performed the GeneXpert MTB/RIF sputum examination.

The sampling technique was a total population of 37 people where the cases were TB patients with MDR TB resistance who were examined with the inclusion criteria including TB patients and MDR-TB patients based on sputum samples with GeneXpert MTB/RIF and sign informed consent, and not in the exclusion criteria include pregnant and lactating women, individuals with a history of HIV, Hepatitis B, Hepatitis C, kidney disease, known from medical records or based on a doctor's diagnosis, taking supplements vitamin D, receiving immunodulator or systemic corticosteroid therapy within two weeks. After obtaining research, by filling out questionnaires, interviews and medical record from several health , respondents who include the inclusion criteria and do not include the exclusion criteria, the respondent will sign an informed consent and fill out the questionnaire, followed by taking 6 ml of sputum and venous blood, which will then be sent to the laboratory for examination of 25 hydroxyvitamin levels using the ELISA method in the Immunology laboratory, blood smear to examine the ratio of neutrophil to lymphocytes and the ratio of monocytes to lymphocyte. Data from the examination and questionnaires were processed and analyzed using univariate and bivariate methods with SPSS. Bivariate analysis used the square test to analyze the relationship between vitamin D and leukocyte ratio between multidrug TB patients and TB patients.

III. RESULT

This study was conducted in the period from January to August 2021 in three Puskesmas in Jambi City, where the total number of these studies was 37 people. Based on the data collected in all interviews conducted in this study, a description of the patient's characteristics related to personal status, treatment status, and characteristics of other activities of patients related to improving their health and endurance was obtained. The characteristic data obtained from the interviews have been analyzed and shown in the TABLE 1

TABLE 1
Characteristic of TB patients

Age	Mean (SD)	40.8 (15.9) years
	IQR	5 – 70 years
Sex	Male	51.6%
	Female	48.4%
Education level	No school	3.2%
	SD	16.1%
	SMP	12.9%
	SMA	64.5%
	PT employee	3.2%
Job	Worker	16.1%
	Jobless	83.9%
TB suffering periods	Mean (SD)	3.9 (3.3) months
	IQR	0 – 17 months
DRUG consumption	Mean (SD)	3.5 (2.7) months
	IQR	0 – 12 months
The regularity of DRUG consumption	Regular	78.4%
	Irregular	5.4%
	Didn't start yet	16.2%
Grievance because of DRUG	There isn't	37.8%
	There is	45.9%
	Didn't start yet	16.2%
Another drugs consumption (routine)	No	48.6%
	Yes	51.4%
Sumplement consumption	No	54.1%
	Yes	45.9%
Sunbathe activity	No	48.6%
	Yes	51.4%

In addition to the above, patient characteristics related to the patient's treatment status were also obtained through direct interviews and have also been further confirmed by the TB Puskesmas program officers or laboratory officers, who were then grouped into three groups, the first group is the observation group for non-drug resistant cases (Non-drugresistant TB) are TB patients who have undergone treatment or have taken Obat anti Tuberculosis (DRUG) obtained as many as 26 patients; the second group as the observation group of resistant cases (Multidrug TB) were TB patients who had undergone repeated treatment and were declared as Multidrug patients, there were 5 patients, and the third group as the control group (new TB) are pulmonary TB patients who have just been detected and have not undergone treatment or have not taken DRUG, obtained as many as 6 patients as shown in FIGURE 1. In addition, the immune characteristics of all patients observed in this study were determined based on the values of laboratory test parameters, vitamin D levels and the value of the ratio of white blood cells that play an active role in the immune system (NLR, MLR and NMLR).

The immune status of TB patients was assessed based on the results of the examination of several parameters that had been previously determined by the research team. Parameters of vitamin D levels, parameters of the ratio of several types of white blood cells. including neutrophil cells, lymphocytes and monocytes consisting of NLR (*neutrophil/lymphocyte ratio*), MLR (*monocyte/lymphocyte ratio*), and NMLR (*neutrophil-monocyte/lymphocyte ratio*). The results of the examination of these four parameters are shown in the FIGURE 2-5.

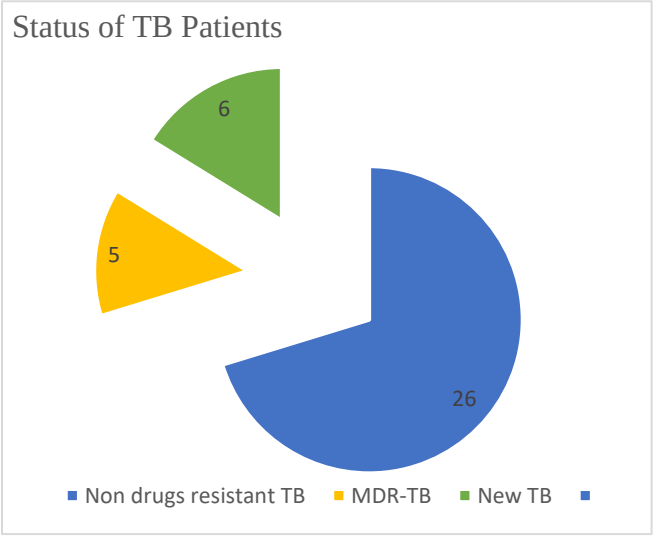

FIGURE 1. Status of TB patient

TABLE 2
Characteristic of of laboratory test resutl

Characteristic	VitD	NLR	MLR	NMLR
Range	5 – 30	0.34 – 6.75	0.03 – 0.6	0.55 – 7.08
Mean	22.8	2.05	0.24	1.93
Median	23	1.97	0.22	1.78
IQR	21 – 26	1.52 – 2.3	0.12 – 0.35	1.02 – 2.40
one-way ANOVA (p)	0.777	0.002*	0.356	0.000*
Abnormal:	100%	8.1%	40.5%	67.6%
- New TB	100%	3.8%	30.8%	73.1%
- Non drugs resistant TB	100%	40%	80%	100%
- MDR-TB	100%	0%	50%	16.7%
Fisher's exact test	1	0.055	0.126	0.007*

IQR = Interquartil range; *) = significant statistical test;

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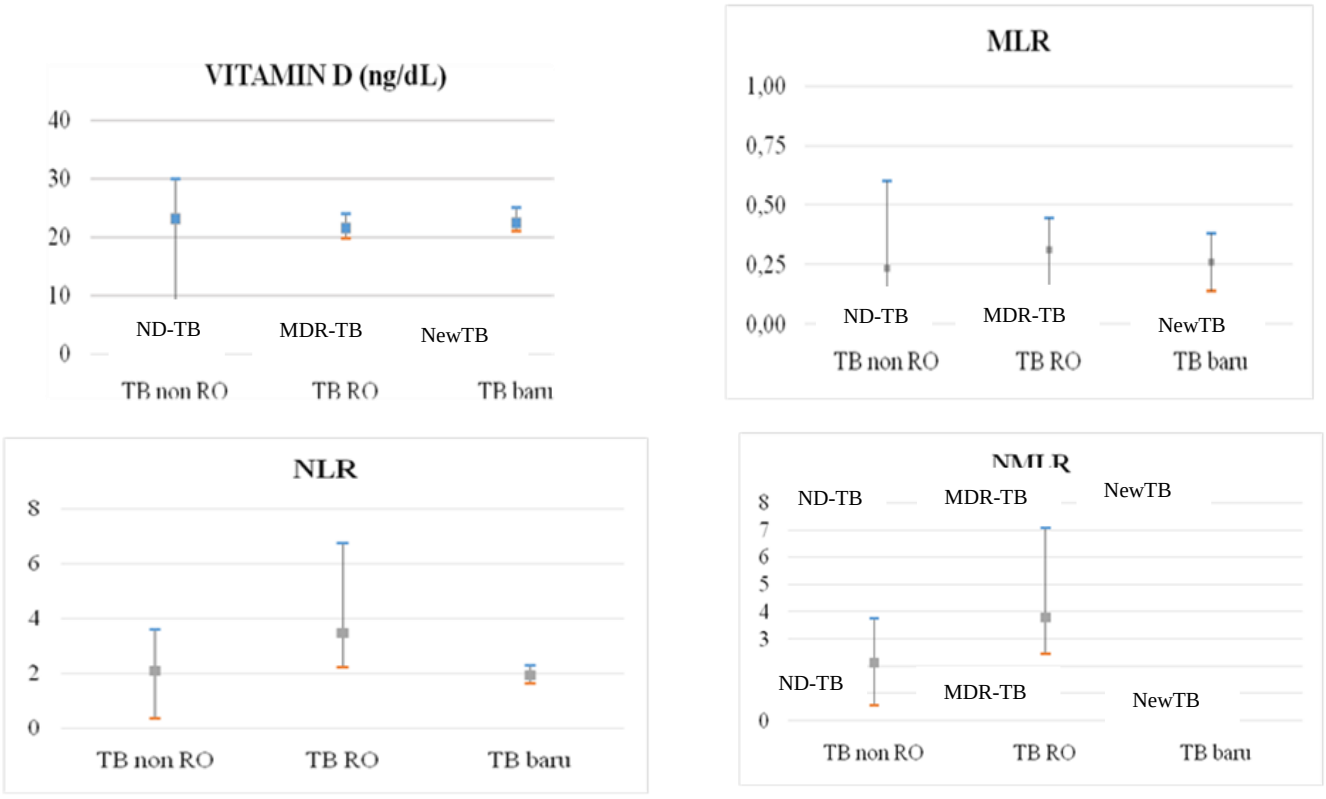

FIGURE 2. Vitamin D, NLR, MLR, NMLR Of TB patients based on their treatment

Description: ND-TB: Non drugs resistant TB, MDR-TB: Multi drugs TB, New TB: New T

A. VITAMINE D

Based on the FIGURE 2, it can be seen that all the results of the examination of vitamin D levels in 37 TB patients, most of them (89.2%) were in the range of insufficiency values (vitamin D deficiency). Three patients with vitamin D deficiency were found in the non-drug resistant TB group (11.5%) and one was found in the MDR- TB group (20%). In the group of TB patients who were newly detected and had not undergone treatment, there were no cases of deficiency. Based on the results of statistical analysis conducted with the one-way ANOVA test, p-value> 0.05 was obtained, so it can be concluded that there is no difference in the results of this parameter examination between the three groups observed with an overall average value of 22.8 ng/mL.

B. NLR

The results of the calculation of the NLR value showed an increasing trend in the group of pulmonary TB patients with multidrug-TB. Cases of increased ratio were only found in 1 person (3.8%) from the non drug TB patient group and 2 (40%) from the multi drug TB group with a cut off value of 2.91. There were no cases of increased NLR values in the new TB group. Fisher's exact test concluded that there was no significant difference in the frequency of case finding of increased NLR between each group ($p = 0.054$). Statistical analysis using one-way ANOVA test obtained p-value <0.05, so it can be concluded that the results of the parameter examination between the three groups observed were significantly different. The analysis using Tukey's HSD test (honestly signicant difference) even shows that the difference is very significant if done by comparing the multi-drug TB group which is the main target of case-control observation in this study against the other two comparison groups ($p < 0.01$). There was no difference between the two comparison groups ($p > 0.05$).

This fact shows that the NLR value can be used as a parameter that has the potential as a marker to distinguish a patient's status related to drug treatment, where the immune condition indicated by an increase in NLR tends to indicate a problem in the treatment that the patient is undergoing. However, in the non drug resistant and new TB groups, no significant difference was found, so this NLR value did not differentiate the immune conditions of the patients in the two groups.

C. MLR

FIGURE 2 it is found that from the analysis using the cut off value (0.25/25%) it is known that the frequency of increased MLR values is most commonly found in multi-drugs TB patients with a percentage of 80%. However, the frequency was not much different after an analysis using the Fisher's exact test statistic ($p = 0.126$) with an average value of 0.238. Further analysis with one-way ANOVA obtained p-value > 0.05 which means that there is no difference in MLR results in the three groups so that the MLR value cannot be used as a parameter that distinguishes various immune conditions in TB patients.

D. NMLR

NMLR is the ratio between the neutrophil count, macrophage and lymphocyte count. The macrophage count was obtained from the sum of the neutrophil count and the monocyte count. The overall average value of the calculated NMLR is 1.93 which is above the cut off value (1.2). FIGURE 2-5 shows the tendency for NMLR values to be much higher in the multi - drugs TB patient group compared to other groups. The results of Fisher's exact test analysis showed that the condition of immunity in TB patients based on the NMLR value differed significantly between each group. This difference is supported by the results of the analysis of the one-way ANOVA test which observed the ratio value of each group which concluded that there were differences in the value of the NMLR calculation results in the three groups. This difference is supported by the results of the analysis of the one-way ANOVA test which observed the ratio value of each group which concluded that there were differences in the value of the NMLR calculation results in the three groups

This fact shows that NMLR has the potential as a marker to differentiate patient status related to DRUG treatment, where the immune condition indicated by increased NMLR tends to be more and more found in patients with treatment problems. The results of the Tukey's HSD test between multi-drug TB and other groups were significantly different, although a significant difference in Tukey's HSD test results was also not found between the non drug resistant TB and new TB groups, making it more potential as a marker of the development of immune conditions that lead to treatment problems in TB patients.

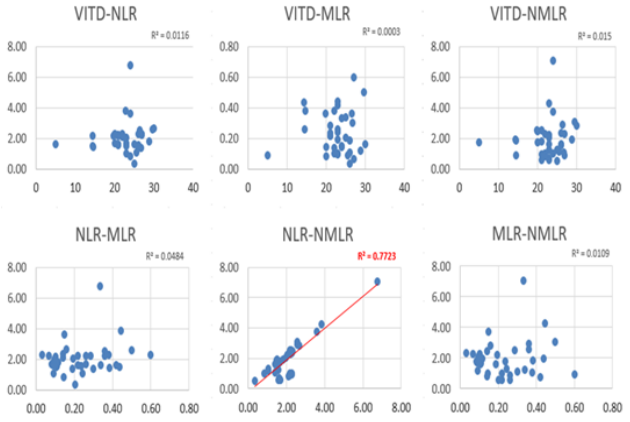

FIGURE 3. Correlation Between Examination Parameters Immune Status Performed.

From the FIGURE 3, it can be seen that only the NLR and NMLR parameters show a correlation. This is in accordance with the FIGURE 3 generated from the two parameters in the previous discussion which states that the two ratio parameters are able to show significant differences in patients with drug treatment problems, namely patients who are included in the multi-drugs TB group in this study. The correlation shown by these two parameters confirms that utilizing the ratio of NLR

and NMLR for monitoring TB patients is highly recommended.

IV. DISCUSSION

The results showed that the average vitamin D levels in the three experimental groups were almost the same. The statistical test results with the one-way ANOVA test concluded that there was no significant difference between the three groups observed in the average vitamin D levels. In this study, most TB patients (89.2%) had vitamin D levels in the range of values indicating the condition of vitamin deficiency (insufficiency). As many as 10.8% were in deficiency values (< 20 ng/mL), and none of the vitamin D levels were in the normal range. The results of this study are the same as research conducted by (Herlina, 2018) where the results showed that there was no significant difference in vitamin levels in the three groups observed, the TB group, resistant TB, and healthy people[8]. The average vitamin D level in his study was in the insufficiency range. The results of this study are different from the study conducted, where the study showed that the average vitamin D level i by Huang et al. (2016) MDR-TB patients was lower than TB patients and healthy people [7]. The results concluded that there was a relationship between low levels of vitamin D and the incidence of MDR-TB. This difference causes the many factors that affect vitamin D levels in the blood. In forming vitamin D, the vitamin D measured in this study is the form of 25OHD that circulates freely. Before reaching circulation, this form of 25OHD is derived from the conversion of 7-dehydrocholesterol to vitamin D3 in human skin and from dietary intake of vitamin D3, followed by hydroxylation of vitamin D3 in the liver to 25OHD as the main form of vitamin D in circulation.[15] [16] [17].

Huang (2016) proved that sun exposure was associated with vitamin D levels in MDR TB patients. In this study, it was shown that most TB patients (51.4%) did sunbathing activities, when viewed from the research data showed sunbathing activities were carried out in the range of 08.00 to 10.00 WIB, and this activity was carried out for an average of 20 minutes[7]. FIGURE 6 shows that sunbathing activities carried out of the conversion of 7-dehydrocholesterol to vitamin D3 are less than optimal. The results of research conducted by Elsafi (2020) showed that the optimal time to get the intensity of the sun's UVB rays is 1 hour before and after noon. If the exposure is carried out in the optimal period, it takes 7.5 minutes, while the exposure at 09.00 am takes 25 minutes, and if the exposure is carried out at an earlier time, it takes longer[15]. Research data show that no TB patients took vitamin D supplements, while other dietary intakes were not studied. Then another factor that is quite important is the hydroxylation process in the liver. The hydroxylation process is influenced by the CYP27A1 (25-OHase) enzyme. The presence of disturbances in this enzyme will also affect vitamin D levels in the blood. Another factor that affects vitamin D levels is the condition of the rate of vitamin D synthesis in the skin, such as increased skin pigmentation, increasing age, and the use of sunscreen. Then the impaired absorption of food in the intestines can also affect the intake of vitamin D levels. In this study, the above factors were not calculated in each sample group, so the possibility of bias could occur [18][19] [20]

The study's results on NLR, MLR, and NMLR showed significant differences in the values of NLR and NMLR in the observed groups and no significant differences in MLR values in the observed groups. The results of the study prove that the values of NLR and NMLR can be used as marker parameters to distinguish patient status related to DRUG treatment. This is indicated by the value of Tukey's HSD test results between TB RO and other groups, which are very significant differences.

The results of this study are the same as those of Elisabeth S. et al. (2018), which showed a significant difference between the NLR values in patients with TB and multi-drug TB patients. The results of studies on MLR and NMLR values between TB patients and multi-drug TB patients have not been found at this time [21]. Currently, the research has only observed MLR values in TB patients and healthy people before and after receiving therapy and NMLR values in patients in the TB and non-TB groups. The results of the research by Wang et al. (2019) showed that TB patients before treatment had a higher MLR value than the healthy group. The study of Wicaksono (2018) and Wang et al. (2019) showed that there was a significant difference in the MLR value in TB patients before and after treatment, where the MLR after treatment was lower than before treatment. Wang et al. (2019) also concluded that MLR values could be used for diagnosis and treatment monitoring [14], [22]. The results of this study found that there was no significant difference in the MLR value between the three groups observed. Still, when viewed from the average MLR value, it showed that the MLR value in RO TB patients was higher than in the other two groups, although the difference was not significant. The results of the study by Jeon et al. (2019) showed that the NMLR value of TB patients was significantly higher than that of healthy people [23].

TB patients have chronic inflammation that alters the hematological profile. Neutrophils, monocytes, and lymphocytes play an important role in the innate and adaptive immune responses against Mycobacterium tuberculosis infection. Neutrophil cells play a role in the innate immune response, and monocytes are important components of the innate immune response, acting as a liaison for the adaptive immune system through antigen presentation to lymphocytes. Meanwhile, lymphocytes are part of the cellular adaptive immune system, which is an effective defense against pulmonary TB. Compared to healthy people, patients with TB tend to have an increase in the number of neutrophils and monocytes and a decrease in the number of lymphocytes [24] [25]. Changes in the value of neutrophils, monocytes, and lymphocytes are strongly associated with inflammatory conditions. Many studies show that NLR, MLR, and NMLR values can be used as biomarkers for diseases other than ESR and CRP [22] [26]. From this study, respondent or TB patiens can know the status progression status of the disease, and

progress of medical treatment, and impact to resolve or decrease the problem of high case of MDR TB.

Elisabeth S. et al. (2018) argued that the physiologic immune response of circulating leukocytes to various inflammatory conditions is characterized by an increase in neutrophil count and a decrease in lymphocyte count and that NLR is considered to have a more vital ability to predict bacteremia than neutrophils or lymphocytes alone. Neutrophils are the most frequently influential phagocytic cells and contribute significantly to controlling TB infection in the blood [12]. Initially, neutrophils were thought to have no role in TB infection because they have a short life span and do not respond to intracellular pathogens such as TB, but recent studies have shown that neutrophils play a role from the first day of TB infection to granuloma formation. The neutrophil response will last until the end of the infection[27]. Studies have reported an inverse correlation between the development of pulmonary TB and the number of neutrophils in the peripheral blood of patients with active pulmonary TB. The lack of neutrophil counts in vitro causes the immune system to fail to limit the growth of Mycobacterium tuberculosis [28]. The results of Jeon et al. (2019) concluded that NLR was a predictive marker for various infectious diseases, and Elisabeth S. et al. (2018) study concluded that NLR values < 2.91 are more suggestive of Multidrug-TB. Mycobacterium tuberculosis infection will activate monocyte cells or macrophages in innate and adaptive immune responses. Monocytes are the target cells of Mycobacterium tuberculosis and lymphocytes are the main effector cells of TB immunity. As key immune cells, the number of monocytes and lymphocytes reflects the state of individual immunity against Mycobacterium tuberculosis infection [12], [23] [29].

TB is associated with increased production and release of monocytes in the bone marrow, so that there will be an increase in the number of monocytes and MLR values [22]. Naranbhai et al. (2015) stated that an increase in MLR is a consequence of an interferon-mediated inflammatory process that causes an anti-mycobacterial process in infection and MLR can be used as a diagnostic marker for TB in TB patients [6]. MLR is associated with inhibition of the growth of Mycobacterium tuberculosis in vitro[30] [31]. The balance of immune response in patients is better described by the neutrophil plus monocyte/lymphocyte ratio or NMLR. [23]. NMLR is used to predict disease progression in patients. NMLR studies in TB patients have not been widely carried out. In the study of Jeon et al. (2019), NMLR was the first marker developed in TB patients. The results showed that the NMLR value could be used as a stronger predictive factor than the NLR in differentiating tuberculosis (TB) from non-TB infectious lung disease, and the study showed that an NMLR value of more than 3.95 was suspected or considered for the diagnosis of infectious TB [23] [32].

V. CONCLUSION

Most of the TB patients observed had problems with their immune response status, especially patients with multidrug TB patients. Immune status related to vitamin D levels of pulmonary TB patients all showed values within the range of interpretation which was included in the category of insufficiency and deficiency. The NLR and NMLR parameters that were carried out showed that immune status problems were mainly found in the TB group with Multidrug-TB. The research found that the NLR and MLR, Vitamin D can be potential biomarker to know the progress of medical treatment of MDR TB patients. It is necessary to do further research using a larger number of samples of pulmonary TB patients considering the number of patients observed in this study is still small, so it can lead to the assumption that the Figure obtained in this study does not represent the general condition of pulmonary TB patients. The discovery of the fact that the NLR and NMLR parameters have potential as biological markers of immune conditions in a TB patient with multidrug –TB patients should be observed with other marker parameters that have been proven in previous studies. This is considering that the results found in this study cannot be related to the results of the examination of vitamin D levels, which all show similarities, namely abnormally low, which is included in the category of insufficiency and deficiency.

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BIOGRAPHY

Fardiah Tilawati Sitanggang was born in jambi city, Indonesia in 1988. she received master degree in biomedical science from the university of sriwijaya in 2019. from 2009-2013 she was a medical laboratory technology at governor clinic jambi. in 2014 until 2017 she was a lecturer assistant at academy of health analyst. since 2019 she has been a lecturer at poltekkes kemenkes jambi . her research interest include immunology, microbiology hematology diagnostics, and biomedic.

James Perdinan Simanjuntak was born in Jambi City , Indonesia in 1974. He received Master degree in Environment science from the University of Jambi in 2019. From 2002 until 2004 he was a assistant lecturer at Academy of health analyst. Since 2006 he has been a lecturer at Poltekkes Kemenkes Jambi as Clinical chemistry lecturer. His research interest includes clinical chemistry, microbiology, Hematology diagnostics, and biomedic.

Siti Sakdiah was born in Jambi City, Indonesia in 1975. She received Master degree in Biomedical science from the University of sriwijaya in 2019. From 2001 until 2003 she was a assistant lecturer at Academy of health analyst. Since 2005 she has been a lecturer at Poltekkes Kemenkes Jambi as Clinical chemistry lecturer Her research interest includes Immunology, Hematology diagnostics, microbiology and biomedic.