ORIGINAL ARTICLE

Vitamin D, Body Mass Index, and Total Lymphocyte Count in Drug-Sensitive and Drug-Resistant Tuberculosis Patients in Banjarmasin

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ABSTRACT

Introduction: Tuberculosis (TB) remains a global health problem that causes high morbidity and mortality. Based on its classification, TB is divided into drug-sensitive (DS) and drug-resistant (DR). Several risk factors susceptible to TB are malnutrition with low body mass index (BMI), vitamin D deficiency (VDD), and low total lymphocyte count (TLC) related to low immune status. This study aimed to examine the relationship between vitamin D (VD), BMI, and TLC in the TB population in Banjarmasin.
Methods: This was an analytic observational study with a cross-sectional design. The total study sample was 42 patients, confirmed by rapid molecular testing, who had not been treated for TB in Banjarmasin from January to May 2023 and met the inclusion and exclusion criteria. Chi-Square and Fisher's exact statistical tests were used to see the relationship between VD, BMI, and TLC in DS TB and DR TB.
Results: The median age of DS TB was 38 (24-52) years old, and DR TB was 51 (37-58) years old. Most of the gender was male (24 patients/57.1%). There was a statistically significant difference between VD and BMI in DS TB and DR TB ($p = 0.048$; $p = 0.019$). There was a significant relationship between VD and TLC in DS TB and DR TB ($p = 0.048$).
Conclusion: VD and BMI significantly differed in DS TB and DR TB. There was a significant correlation between VD and TLC in TB patients.

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (M. tb). It can affect the lungs and other organs and is the second leading cause of morbidity and mortality in infectious diseases worldwide.[1–3] Based on its classification, TB is divided into two, namely drug-sensitive (DS) and drug-resistant (DR).[2] The number of TB cases in Indonesia continues to increase, with a death rate of 15,186 cases, causing delays to the current TB elimination target.[4–6] DR TB cases continue to increase, with data in 2009 in Indonesia showing 66 confirmed cases, increasing to 1,860 cases in 2015 and 8,268 cases in 2022.[4] This is a new challenge. This has an increasingly complex impact on TB elimination, which is not only sufficiently focused on treatment using anti-tuberculosis drugs (ATD) but also other forms of supportive therapy, such as nutritional therapy and controlling risk factors that cause TB. On the other hand, the coverage of TB treatment in 2021 for both DS and DR, respectively, especially in South Borneo, is still low, recorded at 27% and 11%.[4] Several studies have mentioned various factors that are increasing the risk for TB incidence, including young age, gender, human immunodeficiency infection (HIV), diabetes mellitus (DM), alcohol, smoking, malnutrition, and the presence of vitamin D deficiency (VDD).[7–9]

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M. tb will infect macrophages during infection, resulting in a cellular immune response involving T lymphocyte cells.[3,10,11] Several studies have shown that malnourished TB patients have low total lymphocyte count (TLC). Gunarsa, *et al*. (2011) found that TLC was significantly correlated with mid-upper arm circulation (MUAC) and triceps skinfold thickness.[12] Approximately 573 malnourished patients had TLC <1,200 cells/mm^3.[12] In a study conducted by Yunda, *et al*. (2020), out of 72 TB patients, 47.2% were in the underweight category (body mass index/BMI 18.73 ± 2.94 kg/m^2) with 11.1% of the sample having low TLC.[13] This is also related to the fact that there is no clear research on VDD.

The relationship between VDD in DS TB and DR TB patients with malnutrition status using BMI parameters, which is also associated with TLC in Indonesia, has never been studied. This is important because it relates to the efforts to eliminate TB both in terms of preventing the risk of infection and supporting the success of therapy. These considerations prompted this study to examine this relationship in more detail in DS and DR TB patients as a contribution to the program to accelerate TB elimination in Indonesia, especially in South Borneo.

METHODS

Collecting Samples

The sample in this study was TB patients diagnosed based on rapid molecular tests in Banjarmasin (Ulin General Hospital, Pekauman Public Health Center, and Cempaka Public Health Center) from January to May 2023, who had met the inclusion criteria, aged >18 years old, confirmed TB by rapid molecular test, not currently treated for TB, could measure height and weight, and were willing to participate in the study by signing an informed consent with exclusion criteria, pregnant females, HIV, DM, hepatitis, malignancy, taking vitamin D (VD) for 1 month, and taking steroids.

VD Serum, Leucocyte, and Lymphocyte Evaluation

Examination of VD, leukocytes, and lymphocytes in the Laboratory of Clinical Pathology at Ulin General Hospital, Pekauman Public Health Center, and Cempaka Public Health Center, Banjarmasin, used the Architect 25-OH VD 5P02 (Abbott, USA) tool and found VDD < 20ng/ml, VD insufficiency 20-29.9 ng/ml, normal 30-90 ng/ml.[14] In a study by Rostina (2008), TLC was calculated from leukocyte x lymphocytes in percentage based on the Ministry of Health of the Republic of Indonesia.[15] Yunda, *et al*. (2020) used a combination of normal TLC values ≥1,200 cells/mm^3 and low TLC values <1,200 cells/mm^3 for TB patients.[13]

Anthropometric Evaluation

Body weight and height were measured using the Seca 755 and GEA brands, which Banjarbaru Health Facility Security Loka Calibration Laboratory has calibrated. BMI was calculated by dividing body weight (expressed in kilograms) by the square of height (in meters) kg/m^2 and, based on the World Health Organization (WHO), is categorized as severely underweight (<16 kg), underweight (<18.5 kg), normal weight (18.5-22.9 kg/m^2), overweight (23-29.9 kg/m^2), and obese (≥30 kg/m^2).[16]

Data Collection and Processing

The data source used in this study was primary data collected based on the results of examining levels of VD, leukocytes, and lymphocyte serum in the percentage of TB patients before being given ATD. Each datum was then collected and analyzed.

Data Analysis

In this study, statistical computer software was utilized for the purpose of outlining data and outcomes with the aid of descriptive statistics. Univariate analysis was used to describe the value of data distribution (central tendency) with the mean and standard deviation (SD) if normally distributed. It is presented with the median and interquartile range if not normally distributed. Bivariate analysis used the Chi-Square test on data with nominal and ordinal scales. Data that could not be performed by the Chi-Square test was analyzed using Fisher's exact test.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Commission of the Research and Development Agency of Ulin General Hospital, Banjarmasin (no. 081/I-Reg Riset/RSUDU/23) and the Faculty of Medicine, Lambung Mangkurat University, Banjarmasin (no. 020/KEPK-FK ULM/EC/II/2023), and performed in accordance with the principles of the Declaration of Helsinki. Written informed consents were obtained.

RESULTS

Table 1. Characteristics of research subjects

Variable	Total (n = 42)	DS TB (n = 28)	DR TB (n = 14)
Age (years old), median (range)	43(24-55)	38 (24-52)	51 (37-58)
Gender			
- Male, n (%)	24 (57.1%)	15 (35.7%)	9 (21.4%)
- Female, n (%)	18 (42.9%)	13 (31%)	5 (11.9%)
			42 (100%)
Smoking status			
- Smoking	18 (42.85%)	11 (26.2%)	7 (16.67%)
- Not smoking	24 (57.14%)	17 (40.4%)	7 (16.67%)
			42 (100%)
History of TB			
- Yes, n (%)	15 (35.71%)	3 (7.14%)	12 (28.57%)
- No, n (%)	27 (64.28%)	25 (59.52%)	2 (4.76%)
			42 (100%)
VD (ng/ml)			
- Normal (30-90), n (%)	2 (4.8%)	2 (4.8%)	0 (0%)
- Insufficiency (20-29.9), n (%)	19 (45.2%)	9 (21.4%)	10 (23.8%)
- Deficiency (<20), n (%)	21 (50%)	17 (40.5%)	4 (9.5%)
			42 (100%)
BMI (kg/m^2)			
- Normal (18.5-22.9), n (%)	9 (21.4%)	9 (21.4%)	0 (0%)
- Underweight (<18.5), n (%)	33 (78.6%)	19 (45.2%)	14 (33.3%)
			42 (100%)
TLC (cells/mm^3)			
- Normal (≥1,200), n (%)	20 (47.6%)	11 (55%)	9 (45%)
- Low (<1,200), n (%)	22 (52.4%)	17 (77.3%)	5 (22.7%)
			42 (100%)
Mean ± SD			
- VD (ng/ml)		18 ± 6.6	21 ± 4,3
- BMI (kg/m^2)		17.18 ± 2.89	15.95 ± 1.73
- TLC (cells/mm^3)		1,347 ± 781.36	1,549 ± 797.41

Independent T-test analyzed. TB: Tuberculosis, VD: Vitamin D, BMI: Body Mass Index, TLC: Total Lymphocyte Count.

Table 2. Different analysis of VD, BMI, and TLC in DS TB and DR TB

Variable	Total (n = 42)	DS TB (n = 28)	DR TB (n = 14)	p-value
VD (ng/ml)				
- Normal (30-90)	2 (4.76%)	2 (7.14%)	0 (0%)	
- Insufficiency (20-29.9), n (%)	19 (45.2%)	9 (32.1%)	10 (71.4%)	*0.048$^\alpha$
- Deficiency (<20), n (%)	21 (50%)	17 (60.7%)	4 (28.5%)	
BMI (kg/m^2)				
- Normal (18.5-22.9)	9 (21.4%)	9 (32.1%)	0 (0%)	*0.019$^\beta$
- Underweight (<18.5)	33 (78.6%)	19 (67.8%)	14 (100%)	
TLC (cells/mm^3)				
- Normal (≥1,200)	20 (47.6%)	11 (39.2%)	9 (64.2%)	0.126$^\alpha$
- Low (<1,200)	22 (52.4%)	17 (60.7%)	5 (35.7%)	

$^\alpha$: Chi-square, $^\beta$: Fisher's exact test, significant with p-value < 0.05. TB: Tuberculosis, VD: Vitamin D, BMI: Body Mass Index, TLC: Total Lymphocyte Count.

Table 3. Analysis of the relationship between VD, BMI, and TLC in DS TB and DR TB

Variable	VD			p-value
	Normal (30-90 ng/ml)	Normal (30-90 ng/ml)	Normal (30-90 ng/ml)	
BMI (kg/m^2)				
- Normal (18.5-22.9)	1 (2.4%)	3 (7.1%)	5 (11.9%)	
- Underweight (<18.5)	1 (2.4%)	16 (38.1%)	16 (38.1%)	0.405$^\beta$
TLC (cells/mm^3)				
- Normal (≥1,200)	1 (2.4%)	13 (31%)	6 (14.3%)	
- Low (<1,200)	1 (2.4%)	6 (14.3%)	15 (35.7%)	*0.048$^\beta$

$^\beta$: Fisher's exact test, *significant with p-value < 0.05. VD: Vitamin D, BMI: Body Mass Index, TLC: Total Lymphocyte Count.

Table 4. Analysis of the relationship between VD, BMI, and TLC in DS TB and DR TB

Variable	TLC		p-value
	Normal (≥1,200 cells/mm^3	Low (<1,200 cells/mm^3)	
BMI (kg/m^2)			
Normal (18.5-22.9)	6 (30%)	3 (13.6%)	0.269$^\beta$
Underweight (<18.5)	14 (70%)	19 (86.4%)	

$^\beta$: Fisher's exact test, *significant with p-value < 0.05. BMI: Body Mass Index, TLC: Total Lymphocyte Count.

DISCUSSION

Based on Table 1, the median age of the sample was 43 (24-55) years old. This is supported by Desissa, *et al*. (2018), whose study sample of TB patients with productive age, in which the age range of the TB samples obtained was <25-87 years old and the mean age was 32.69 years old.[17] In another study by Anisah, *et al*. (2021) in a DR TB sample, the results showed that the age group >40 years old had a risk of 1.28 times for the occurrence of DR TB compared to the age group <40 years old.[18] Another study by Baya, *et al*. (2019) in DR TB patients found the average age was 39.31 ± 14.64 years old (range 18-83 years old) and only 62.6% (134 from 214 sample) were less than 40 years old.[19]

This study found that the gender was dominated by males, as many as 24 samples (57.1%). This was supported by data obtained from the Basic Health Research (RISKESDAS) in South Borneo, where males were more dominant than females infected with TB both in DS TB and DR TB due to several supporting factors.[20] Males have higher mobility than females, as well as air pollutants from outdoors, especially exposure to industry, which increases the risk of TB infection in males, and also due to lifestyle, namely smoking.[18,21,22] Male patients with DR TB who smoke in Indonesia have a higher number of cases, which is 1.5 times compared to females. In a study conducted by Anisah, *et al*. (2021), it was found that males had a 1.28 times higher risk of suffering from DR TB.[18]

In this study, there were 18 patients (42.85%) with smoking status. This is consistent with the theory that smoking plays a role in the pathogenesis of TB, which can harm the immunological response or dysfunction of the cilia in the airways, causing a reduced immune response and disrupting macrophages with or without decreased CD4.[23,24] Secondary DR TB is caused by inadequate drug doses and inadequate medication adherence.[2,9,25] Similarly, in this study, the incidence of secondary DR TB was caused by inadequate drug dosages and poor adherence to taking medication.

The mean VD in this study was DS TB 18 ± 6.65 ng/ml and DR TB 21.17 ± 4.33 ng/ml. This is supported by Saragih, *et al*. (2015), who stated the mean VD in TB compared to healthy people was 25.21 ± 7.93 ng/ml and 21.50 ± 9.37 ng/ml.[26] An almost identical study was performed by Herlina, *et al*. (2018) in Padang, comparing DR TB, which also had lower VD values compared to people who had contacts at home, 32.21 ± 11.5 ng/ml and 31.7 ± 9.11 ng/ml, respectively.[23] In another study by Saragih, *et al*. (2015) in Medan, in DR TB samples and household contacts as well as controls in healthy people, the mean VD results were 32.21 ± 11.5 ng/ml, 31.7 ± 9.11 ng/ml, and 26.86 ± 6.22 ng/ml, respectively.[26] In this study, the results showed that the VD level of DR TB was higher than DS TB. This could be due to the difference in sample size and the fact that most of the DR TB samples had more exposure to sunlight related to their work than the DS TB samples. Furthermore, in this study, 13 of the 28 DS TB samples were female, all of them wearing clothes that predominantly covered their skin, thereby causing 7-dehydrocholesterol (7-DHC) not to be exposed to ultraviolet B (UVB) radiation that did not change to VD. Thus, the VD value obtained was lower than DR TB. It might also be because the DS TB sample obtained predominantly experienced complaints of decreased appetite. Hence, the food intake obtained was less, while the DR TB sample did not have complaints of decreased appetite. Whether there was a connection between albumin, which acts as a D-binding protein (DBP), and low VD and the possibility of polymorphism of the genotype and VDR polymorphism in the TB samples still requires further research.

Based on the results of Fisher's exact test, it was found that BMI with DS and DR TB gave significant results (p = 0.019). Tedja, *et al*. (2014) found that most subjects in Jakarta were malnourished when they entered the hospital.[27] A total of 229 hospitalized pulmonary tuberculosis patients (66.4%) had a BMI <18.5 kg/m^2.[27] In anthropometric assessments using BMI based on a study by Gongora, *et al*. (2019), most of the study population showed poor nutrition.[28] Only around 30% of TB patients and contacts showed normal BMI.[28] Kadri, *et al*. (2022) in Padang showed that patients with DS and DR TB had malnutrition condition, whereas nutritional status had odds ratio (OR) of 10.92 as one of the risk factors for DR TB.[29] In addition, Soeroto, *et al*. (2020) also found that patients with DR TB and normal BMI had 1.21 times higher chance of successful treatment compared to patients

with underweight BMI.[30] Another study by Aristiana and Wartono (2018) that compared the nutritional status of DS TB and DR TB patients found that DR TB had more underweight patients (13 patients/51.7%), while DS TB had 46 patients (78%) with normal nutritional status and had significant results between nutritional status and DR TB (p = 0.005, OR 3.79), which showed that underweight nutritional status had a 3.79 times greater risk of suffering from DR TB compared to normal nutritional status.[31] Nutrition also influences the tendency recovery from TB infection. Malnutrition conditions will increase the immunity of the body and increase the susceptibility of the host to infection, as it has been established as a risk factor for DS and DR TB since several years ago.[7,29] Malnutrition in DR TB patients is associated with a higher mortality rate.[29] Low BMI (below 18.5 kg/m^2) was associated with an increased risk of death and relapse of TB.[32]

The mean BMI in this study was DS TB 17.18 ± 2.89 and DR TB 15.95 ± 1.73. It is almost the same as a study conducted by Wang, *et al*. (2019), which compared the BMI in TB samples with controls and obtained a mean TB BMI of 22.03 ± 3.41 and controls of 22.78 ± 2.98.[8] Based on Fisher's exact test, there was no significant relationship in this study between TLC in DS TB and DR TB (p-value = 0.126) with the average value of TLC in DS TB patients being 1,347 ± 781.36 while DR TB was 1,549 ± 797.41. Even though the TLC range was more or less the same, in a study conducted by Yunda, *et al*. (2020) in Pekanbaru, the median TLC for TB samples was 1,930 (620–4,230) cells/mm^3, and 11.1% of samples had low TLC.[13] This difference may be caused by the fact that the sample in the aforementioned study had received TB therapy. Therefore, the number of M. tb decreased, increasing the TLC. Additionally, the subjects in that study came from outpatient settings with minimal comorbidities.[13]

This study showed that there were significant differences in VD and BMI levels in DS TB and DR TB with respective values of $p < 0.05$ (p = 0.048 and p = 0.019) (Table 2), but there was no significant difference in TLC in DS TB and DR TB (p = 0.126). This is in line with the study of Ramkumar, *et al*., which found that VDD is related to TB and is a risk factor for developing TB, with VD levels based on the order of the largest to the smallest of 300 samples, namely VDD (55%), insufficiency (11%), and normal (34%).[33] In another study by Merker (2019), out of 828 samples of TB patients, 58.2% experienced VDD, and the VDD condition was said to be associated with an increased 180-day mortality.[34]

Different results were found in the comparison of TLC. Even though a low lymphocyte count was found, the two groups had no significant difference. This might be due to the samples examined being TB patients without comorbidities. Most of the DS TB samples taken were hospitalized and accompanied by secondary infections, which resulted in the possibility that the value of the TLC was lower, with 50% of DS TB samples being hospitalized and 100% of DR TB samples being hospitalized. Only 1 out of 14 samples had secondary infectious conditions. However, in general, the values of TLC owned by both DS TB and DR TB in this study were both low values, proving that low TLC in TB can be found.

Table 3 shows no significant relationship between VD and BMI in patients with DS and DR TB (p = 0.405). The same was found in a study by Saragih, *et al*. (2015), who found that there was no significant relationship between VD levels and BMI in pulmonary TB samples (p-value = 0.203).[26] A systematic review and meta-analysis of observational studies by Song, *et al*. (2021) combining the risk estimates from three studies regarding the relationship between the lowest VD serum concentration compared to the highest with the risk of being underweight also found an insignificant relationship (Risk Estimate: 1.12; 95% CI: 0.81, 1.56; I2 = 49.2%).[35] Differently, Ramkumar, *et al*. (2018) obtained that BMI affects VD (p-value < 0.001) in TB patients.[33] Another study by Harahap (2021) in Medan also showed that there was a significant relationship (p-value = 0.007) between VD and BMI.[14]

This study was slightly different. This might be due to differences in the smaller number of samples compared to existing studies. This study also did not include existing comorbidities such as DM, hepatitis, kidney failure, HIV, or malignancy, which can affect VD and BMI. VD metabolism in the body is also influenced by DBP, which converts 7-DHC to pre-vitamin D3 through UVB exposure. It is affected by each person's albumin level. Whether the presence of intestinal malabsorption syndrome or disease and inflammation of the gastrointestinal tract, which can also interfere with the absorption of VD in the intestine and abnormalities related to thyroid hormone in the study sample were also not included as exclusion criteria, and some of these risk factors also affect VDD and BMI. Therefore, further research is needed regarding its existing risk factors. In addition, looking at the source of VD, namely from intakes that contain high VD, even though only about 20% comes from intake, this also quite influences the results of the VD obtained. The rest comes from sun exposure. The results of this study can be accepted if the sample has sufficient sunlight exposure to produce VD. Other factors influencing VD levels are skin pigmentation, use of sunscreen, seasons, latitude, time, use of anticonvulsants, and obesity.[35]

Based on Table 3, it was found that VD with

TLC in DS TB and DR TB gave significant results (p-value = 0.028). Wang, *et al*. (2021) performed a study in patients with comorbid DM successively with VD.[36] The low, moderate, and severe results with lymphocytes were 1.55 ± 0.99, 1.75 ± 0.75, and 1.62 ± 0.58, with significant differences of p-value = 0.016. It can be seen that patients with low VD have a decrease in lymphocyte count. VDD is known to increase the risk of developing DM.[36] In another study by Lungu, *et al*. (2022) with TB samples with HIV, the CD4 counts in TB samples and contacts were 556.5 (465-702.5) and 754 (623-875), respectively, with a p-value = 0.002, with normal VD results and normal CD4 counts independently protecting against TB.[37] Yang, *et al*. (2022) found analysis of T lymphocyte subsets with VD sufficiency, insufficiency, or deficiency has an impact on increasing in $CD4^+$ and $CD8^+$ T cells during ATD treatment.[38]

Lymphocytes play a role in the immune response to M. tb infection. T lymphocytes will be activated and proliferate in the acute phase of M. tb infection. Therefore, lymphocytosis can occur early in infection and in the latent phase. However, lymphopenia can occur in the active phase (a decrease in the number of lymphocytes below 2,000/mm^3), indicating an active TB process due to a decrease in CD4 cells and cytokine secretion after mitogen stimulation. The effect of VD on Th2 cells inhibits interleukin-4 (IL-4) transcription and upregulates IL-4 in both rat and human T cells. VD will induce regulation of IL-10 and T cell development. In addition, VD also upregulates the intestinal receptor CCR9 and inhibits CXCR3 in T cells, which can potentially change the homing properties of Th cells. VD inhibits Th1 and Th17 responses, induces Treg responses, and controls proliferation and Th cells.[38] VD controls proliferation, CD8 production, and IL-2, and has the potential to develop into effector T cells that produce IFN-γ, IL-17, and granzyme B. VD also controls the expansion of iNKT cells during this process. Finally, VD also changes the production of cytokines by iNKT cells earlier, which can later form a T-cell response.[39] There has been little research on the relationship between VD and TLC in TB to date.

Table 4 shows that there was no significant relationship between BMI and TLC (p-value = 0.269). Patiung, *et al*. (2014) assessed that there was no relationship between BMI and CD4 in the TB sample, with p-value = 0.378.[40] In a study conducted by Gunarsa, *et al*. (2011), the results were significantly different between TLC and BMI between samples with BMI <18 kg/m^2 compared to BMI ≥18.5 kg/m^2 (p = 0.01).[12] Tyastarini and Saraswati (2017) found that in patients with DM, there was a significant difference between the TLC and BMI (p < 0.001).[41] Malnutrition status is closely related to the disease suffered and has many risk factors. Several factors, such as inadequate intake, changes in metabolism, loss of nutrients, and decreased absorption, greatly affect malnutrition.[41]

Gunarsa, *et al*. (2011), who conducted a study on the entire population of internal medicine patients in Jakarta, also found a significant correlation between malnutrition and TLC <1,200 cells/mm^3 and between severe malnutrition and TLC <900 cells/mm^3.[12] Tojek, *et al*. (2020) found that an increase in TLC range was associated with slight rise in body weight, BMI, biochemical parameters, and scores assessing nutritional risk.[42] Another study conducted by Iizuka, *et al*. (2023) in Japan found lymphocyte dan cholesterol as markers of nutritional status were significantly lower in underweight group and the percentages corresponding to lymphocytes <1,600/µl and cholesterol <180 mg/dl, with p-value of 0.00057 each.[43] Lymphocytes reflect the nutritional condition and level of lymphocytes have been shown to vary with degree of malnutrition.[43] Celullar immune response will occur and involve T lymphocyte cell when infection process like M. tb attack the macrophages.[3,10,11]

Altika and Wijayanti (2020) assessed the mean lymphocyte values in multidrug resistance (MDR) TB samples with controls obtained 15.75 ± 1.796 and 32.89 ± 5.728 with p = value 0.000, meaning there was a significant difference.[44] Another similar study was conducted by Diallo, *et al*. (2020), who compared the increase in BMI with the lymphocyte count in MDR TB patients and found no significant difference (p-value = 0.3289).[45] Malnutrition is associated with decreased body mass, including atrophy of the thymus gland, which ultimately causes lymphopenia. In addition, the presence of IL is also associated with a decrease in the number of lymphocytes in malnutrition.[45] So far, the mechanism of lymphocyte reduction in malnutrition cannot be clearly described, but it is thought to be related to atrophy of the thymus gland and IL.

This study is different from other studies. This might be because one of them is when TB begins to be active, the number of leukocytes is slightly elevated, and the number of lymphocytes is still below normal. When it begins to heal, the number of leukocytes returns to normal and the number of lymphocytes remains high. In addition, the study sample only focused on TB, while the study by Gunarsa, *et al*. (2011) had more than one disease and did not only focus on TB, which was able to affect the decrease in BMI and the low TLC.[12] Thus far, there is still little research on the relationship between BMI and TLC in TB.

CONCLUSION

This study showed there was a significant difference between VD and BMI levels in DS TB and DR TB. There was a significant relationship between VD and TLC in DS TB and DR TB patients, which indicates VD correlates with TLC in TB. This could be the basis for recommendations for VD supplementation and the level of TLC, which can be used as one of the nutritional parameters aside from BMI in TB patients. Further research is needed with additional examinations, such as albumin and VDR polymorphism, as one of the conditions that can affect VD and BMI in TB.

Limitations

In this study, there were several limitations, including the limited number of samples, less homogeneous distribution of data, and uncontrollable confounding factors, such as food intake, which might have a biased effect on the results of this study. Another weakness of this study is the recall bias of the sample. Memory bias can occur during anamnesis assessment of drugs consumed and food intake because it depends on the memory of research subjects, all of which can affect statistical tests and research results.

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Conflict of Interest

The authors declared there is no conflict of interest.

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Authors' Contributions

Designed the study: SR, JJ, IN, MI, HH, EK, SS. Conducted the experiment, performed the statistical analyses, participated in sample collection, and drafted the manuscript: SR. Contributed to the manuscript revision: SR, IN. All authors contributed and approved the final version of the manuscript.

REFERENCES

1. Isa M, Nurrasyidah I, Nikmah EH, *et al*. Nutritional Status of Hospitalized Tuberculosis Patients in South Kalimantan: A Cross-Sectional Study. *Mutiara Med J Kedokt dan Kesehat* 2022; 22: 129–135. [Journal]
2. Isbaniah F, Burhan E, Sinaga BYM, *et al*. *Tuberkulosis: Pedoman Diagnosis dan Penatalaksanaan di Indonesia*. 2nd ed. Jakarta: Perhimpunan Dokter Paru Indonesia (PDPI), https://bukupdpi.klikpdpi.com/wp-content/uploads/2022/08/BUKU-GUIDELINE-TB-2021.pdf (2021).
3. Sia JK, Rengarajan J. Immunology of Mycobacterium tuberculosis Infections. *Microbiol Spectr*; 7. Epub ahead of print July 2019. [PubMed]
4. Indonesia KKR. *Dashboard TB Indonesia*. Jakarta, https://tbindonesia.or.id/dashboard-tb-indonesia/ (2021).
5. Sugiarti S, Ramadhian MR, Carolia N. Vitamin D sebagai Suplemen dalam Terapi Tuberkulosis Paru. *Major Med J Lampung Univ* 2018; 7: 198–202. [Journal]
6. Reviono R. *Tuberculosis: Unfinished Battle Melawan Efek Samping pada Kasus TB Resisten Obat*. Surakarta: UNS Press, 2018.
7. Tellez-Navarrete NA, Ramon-Luing LA, Muñoz-Torrico M, *et al*. Malnutrition and Tuberculosis: The Gap between Basic Research and Clinical Trials. *J Infect Dev Ctries* 2021; 15: 310–319. [PubMed]
8. Wang Q, Ma A, Gao T, *et al*. Poor Vitamin D Status in Active Pulmonary Tuberculosis Patients and Its Correlation with Leptin and TNF-α. *J Nutr Sci Vitaminol (Tokyo)* 2019; 65: 390–398. [PubMed]
9. Wibowo A, Burhan E, Putra AC. Pola Resistansi Kuman Tuberkulosis dan Regimen Pengobatan pada Pasien Tuberkulosis Resisten Obat di Rumah Sakit Pusat Rujukan Respirasi Nasional Persahabatan Jakarta. *J Kedokt Univ Lampung* 2021; 5: 1–6. [Journal]
10. Baluku JB, Anguzu GT, Bongomin F, *et al*. Absolute Eosinophil Count Correlates with Temperature and CD4 Count Independently of HIV Infection among Tuberculosis Patients. *Trop Med Int Health* 2020; 25: 1079–1084. [PubMed]
11. Hammami F, Koubaa M, Mejdoub Y, *et al*. The Association between Vitamin D Deficiency and Extrapulmonary Tuberculosis: Case-Control Study. *Tuberculosis (Edinb)* 2021; 126: 102034. [PubMed]
12. Gunarsa RG, Simadibrata M, Syam AF, *et al*. Total Lymphocyte Count as a Nutritional Parameter in Hospitalized Patients. *Indones J Gastroenterol Hepatol Dig Endosc* 2011; 12: 89–94. [Journal]
13. Yunda D, Witjaksono F, Nurwidya F. Correlation between Protein Intake, Fat Free Mass, and Total Lymphocyte Count with Quality of Life in Pulmonary Tuberculosis Patients Undergoing Intensive Phase Treatment in Pekanbaru, Riau Province. *Mol Cell Biomed Sci* 2020; 4: 128. [Journal]
14. Harahap FH. Hubungan Faktor Risiko Tuberkulosis terhadap Kadar Vitamin D Serum pada Pasien Tuberkulosis. *JIMKI J Ilm Mhs Kedokt Indones* 2021; 9: 1–8. [Journal]

15. Rostina R, Aprianti S, Arif M. Prediksi Jumlah Sel Limfosit T CD4+ Menggunakan Nilai TLC (Total Lymphocyte Count) pada Penderita HIV/AIDS. *Indones J Clin Pathol Med Lab* 2018; 14: 64–65. [Journal]
16. Iqbal M, Puspaningtyas DE. *Penilaian Status Gizi ABCD*. Jakarta: Salemba Medika, https://penerbitsalemba.com/buku/08-0271-penilaian-status-gizi-abcd (2018).
17. Desissa F, Workineh T, Beyene T. Risk Factors for the Occurrence of Multidrug-Resistant Tuberculosis among Patients undergoing Multidrug-Resistant Tuberculosis Treatment in East Shoa, Ethiopia. *BMC Public Health* 2018; 18: 422. [PubMed]
18. Anisah A, Sumekar D, Budiarti E. Demographics and Comorbidities with Incident Drug Resistant Tuberculosis. *J Ilm Kesehat Sandi Husada*; 10. Epub ahead of print 31 December 2021. [Journal]
19. Baya B, Achenbach CJ, Kone B, *et al*. Clinical Risk Factors associated with Multidrug-Resistant Tuberculosis (MDR-TB) in Mali. *Int J Infect Dis* 2019; 81: 149–155. [PubMed]
20. Kesehatan BP dan P. *Laporan Provinsi Kalimantan Selatan Riskesdas 2018*. Jakarta, https://repository.badankebijakan.kemkes.go.id/id/eprint/3896/ (2019).
21. Lu Z, Jiang W, Zhang J, *et al*. Drug Resistance and Epidemiology Characteristics of Multidrug-Resistant Tuberculosis Patients in 17 Provinces of China. *PLoS One* 2019; 14: e0225361. [PubMed]
22. Affandi VP. Rokok dan Kejadian Konversi Sputum Pasien Tuberkulosis. *J Ilm Kesehat Sandi Husada*; 8. Epub ahead of print 30 December 2019. [Journal]
23. Herlina N, Sinaga BYM, Siagian P, *et al*. Serum Vitamin D Level and Susceptibility to Multidrug-Resistant Tuberculosis among Household Contacts. *IOP Conf Ser Earth Environ Sci* 2018; 125: 12143. [ResearchGate]
24. Silva DR, Muñoz-Torrico M, Duarte R, *et al*. Risk Factors for Tuberculosis: Diabetes, Smoking, Alcohol Use, and the Use of Other Drugs. *J Bras Pneumol* 2018; 44: 145–152. [PubMed]
25. Kementerian Kesehatan Republik Indonesia. *Pedoman Nasional Pelayanan Kedokteran Tata Laksana Tuberkulosis*. Jakarta: Kementerian Kesehatan Republik Indonesia, 2020.
26. Saragih JP, Sinaga B, Amir Z. Hubungan Kadar Vitamin D dalam Darah dengan Kejadian Tuberkulosis Paru. *J Respirologi Indones* 2015; 35: 51–56. [Journal]
27. Tedja I, Syam AF, Rumende CM. Status Nutrisi Pasien Rawat Inap Tuberkulosis Paru di Rumah Sakit Cipto Mangunkusumo, Jakarta. *Indones J CHEST Crit Emerg Med* 2014; 1: 95–98. [Journal]
28. Campos-Gongora E, López-Martínez J, Huerta-Oros J, *et al*. Nutritional Status Evaluation and Nutrient Intake in Adult Patients with Pulmonary Tuberculosis and Their Contacts. *J Infect Dev Ctries* 2019; 13: 303–310. [PubMed]
29. Kadri A, Machmud R, Putra A, *et al*. Factors Associated of Multidrug-Resistance Tuberculosis among Minangkabau Ethnicity in Indonesia. *Open Access Maced J Med Sci* 2022; 10: 1736–1739. [Journal]
30. Soeroto AY, Pratiwi C, Santoso P, *et al*. Factors Affecting Outcome of Longer Regimen Multidrug-Resistant Tuberculosis Treatment in West Java Indonesia: A Retrospective Cohort Study. *PLoS One* 2021; 16: e0246284. [PubMed]
31. Aristiana CD, Wartono M. Faktor-Faktor yang Mempengaruhi Kejadian Multi Drug Resistance Tuberkulosis (MDR-TB). *J Biomedika dan Kesehat* 2018; 1: 65–74. [Journal]
32. Kurnia AD, Masruroh N, Melizza N. Factors Related to the Low Nutritional Status among Tuberculosis Patients. *J Keperawatan Padjadjaran* 2020; 8: 42–48. [Journal]
33. Ramkumar V, Raja MK, Subramaniam SR, *et al*. A Study of Serum Vitamin D Levels in Newly Diagnosed Pulmonary Tuberculosis. *J Med Sci Clin Res* 2018; 6: 31974–31980. [Journal]
34. Merker M, Amsler A, Pereira R, *et al*. Vitamin D Deficiency is Highly Prevalent in Malnourished Inpatients and Associated with Higher Mortality: A Prospective Cohort Study. *Medicine (Baltimore)* 2019; 98: e18113. [PubMed]
35. Song C, Sun H, Wang B, *et al*. Association between Vitamin D Status and Undernutrition Indices in Children: A Systematic Review and Meta-Analysis of Observational Studies. *Frontiers in Pediatrics* 2021; 9: 665749. [PubMed]
36. Wang S-Y, Shen T-T, Xi B-L, *et al*. Vitamin D Affects the Neutrophil-to-Lymphocyte Ratio in Patients with Type 2 Diabetes Mellitus. *J Diabetes Investig* 2021; 12: 254–265. [PubMed]
37. Lungu PS, Kilembe W, Lakhi S, *et al*. A Comparison of Vitamin D and Cathelicidin (LL-37) Levels between Patients with Active TB and Their Healthy Contacts in a High HIV Prevalence Setting: A Prospective Descriptive Study. *Trans R Soc Trop Med Hyg* 2022; 116: 336–343. [PubMed]
38. Yang H, Chen H, Ma Y, *et al*. Effects of 25-Hydroxy Vitamin D on T Lymphocyte Subsets and Sputum Smear Conversion during Antituberculosis Treatment. *Int J Infect Dis* 2022; 121: 17–23. [PubMed]
39. Rocha NP, Fortes RC. Total Lymphocyte Count and Serum Albumin as Predictors of Nutritional Risk in Surgical Patients. *Arq Bras Cir Dig* 2015; 28: 193–196. [PubMed]
40. Patiung F, Wongkar MCP, Mandang V. Hubungan Status Gizi dengan CD4 pada Pasien TB Paru. *e-CliniC*; 2. Epub ahead of print 15 May 2014. [Journal]
41. Tyastarini NPAT, Saraswati MR. Hubungan Jumlah Limfosit Total dengan Status Nutrisi pada Pasien Diabetes Melitus Tipe 2 Rawat Inap di Rumah Sakit Umum Pusat Sanglah Denpasar Tahun 2014. *E-Jurnal Med Udayana*; 6, https://ojs.unud.ac.id/index.php/eum/article/view/33461 (2017).
42. Tojek K, Banaś W, Czerniak B, *et al*. Total Blood Lymphocyte Count as a Prognostic Factor among Unselected Inpatients. *Adv Med Sci* 2020; 65: 141–

148. [PubMed]
43. Iizuka K, Sato H, Kobae K, *et al*. Young Japanese Underweight Women with 'Cinderella Weight' are Prone to Malnutrition, including Vitamin Deficiencies. *Nutrients*; 15. Epub ahead of print May 2023. [PubMed]
44. Altika Si, Wijayanti IT. Analisis Status Asam Ascorbat, Nilai Limfosit dan Lama Pengebotan Pasien TB MDR di RSUD Soewondo Pati. *Coping Community Publ Nurs* 2020; 8: 289–296. [Journal]
45. Diallo A, Diallo BD, Camara LM, *et al*. Different Profiles of Body Mass Index Variation among Patients with Multidrug-Resistant Tuberculosis: A Retrospective Cohort Study. *BMC Infect Dis* 2020; 20: 315. [PubMed]