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

Soraya Riefani1, Juhairina Juhairina2, Mohamad Isa1, Erna Kusumawardhani1, Haryati Haryati1, Shaogi Syam3, Ira Nurrasyidah1*
1Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Lambung Mangkurat University/Ulin General Hospital, Banjarmasin, Indonesia.
2Department of Clinical Nutrition, Faculty of Medicine, Lambung Mangkurat University/Ulin General Hospital, Banjarmasin, Indonesia.
3Department of Respiratory Medicine, University College London, London, United Kingdom.

ARTICLE INFO

Article history:
Received 7 August 2023
Received in revised form 13 December 2023
Accepted 16 January 2024
Available online 30 January 2024

Keywords:
Body mass index,
Vitamin D,
Total lymphocyte count,
Tuberculosis.

Cite this as:

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 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.1-6 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).7-8

*Corresponding author: ira.nurrasyidah@ulm.ac.id

Jurnal Respirasi (Journal of Respiriology), p-ISSN: 2407-0831; e-ISSN: 2621-8372.
Accredited No. 200/M/KPT/2020; Available at https://e-journal.unair.ac.id/JR. DOI: 10.20473/jr.v10-I.1.2024.14-22

This work is licensed under a Creative Commons Attribution-Share Alike 4.0 International License.
M. tb will infect macrophages during infection, resulting in a cellular immune response involving T lymphocyte cells.\textsuperscript{3,10,11} Several studies have shown that malnourished TB patients have low total lymphocyte count (TLC). Gunarsa, \textit{et al}. (2011) found that TLC was significantly correlated with mid-upper arm circulation (MUAC) and triceps skinfold thickness.\textsuperscript{12} Approximately 573 malnourished patients had TLC <1,200 cells/mm\textsuperscript{3}.\textsuperscript{12} In a study conducted by Yunda, \textit{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\textsuperscript{2}) with 11.1\% of the sample having low TLC.\textsuperscript{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.

\section*{METHODS}

\subsection*{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.

\subsection*{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.\textsuperscript{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.\textsuperscript{15} Yunda, \textit{et al}. (2020) used a combination of normal TLC values ≥1,200 cells/mm\textsuperscript{3} and low TLC values <1,200 cells/mm\textsuperscript{3} for TB patients.\textsuperscript{13}

\subsection*{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\textsuperscript{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\textsuperscript{2}), overweight (23-29.9 kg/m\textsuperscript{2}), and obese (≥30 kg/m\textsuperscript{2}).\textsuperscript{16}

\subsection*{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.

\subsection*{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.

\subsection*{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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 42)</th>
<th>DS TB (n = 28)</th>
<th>DR TB (n = 14)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years old), median (range)</td>
<td>43 (24-55)</td>
<td>38 (24-52)</td>
<td>51 (37-58)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Male, n (%)</td>
<td>24 (57.1%)</td>
<td>15 (35.7%)</td>
<td>9 (21.4%)</td>
<td></td>
</tr>
<tr>
<td>- Female, n (%)</td>
<td>18 (42.9%)</td>
<td>13 (31%)</td>
<td>5 (11.9%)</td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Smoking</td>
<td>18 (42.85%)</td>
<td>11 (26.2%)</td>
<td>7 (16.67%)</td>
<td></td>
</tr>
<tr>
<td>- Not smoking</td>
<td>24 (57.14%)</td>
<td>17 (40.4%)</td>
<td>7 (16.67%)</td>
<td></td>
</tr>
<tr>
<td>History of TB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Yes, n (%)</td>
<td>15 (35.71%)</td>
<td>3 (7.14%)</td>
<td>12 (28.57%)</td>
<td></td>
</tr>
<tr>
<td>- No, n (%)</td>
<td>27 (64.28%)</td>
<td>25 (59.52%)</td>
<td>2 (4.76%)</td>
<td></td>
</tr>
<tr>
<td>VD (ng/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Normal (30-90), n (%)</td>
<td>2 (4.8%)</td>
<td>2 (4.8%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>- Insufficiency (20-29.9), n (%)</td>
<td>19 (45.2%)</td>
<td>9 (21.4%)</td>
<td>10 (23.8%)</td>
<td></td>
</tr>
<tr>
<td>- Deficiency (&lt;20), n (%)</td>
<td>21 (50%)</td>
<td>17 (40.5%)</td>
<td>4 (9.5%)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Normal (18.5-22.9), n (%)</td>
<td>9 (21.4%)</td>
<td>9 (21.4%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>- Underweight (&lt;18.5), n (%)</td>
<td>33 (78.6%)</td>
<td>19 (45.2%)</td>
<td>14 (33.3%)</td>
<td></td>
</tr>
<tr>
<td>TLC (cells/mm³)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Normal (≥1,200), n (%)</td>
<td>20 (47.6%)</td>
<td>11 (55%)</td>
<td>9 (45%)</td>
<td></td>
</tr>
<tr>
<td>- Low (&lt;1,200), n (%)</td>
<td>22 (52.4%)</td>
<td>17 (77.3%)</td>
<td>5 (22.7%)</td>
<td></td>
</tr>
</tbody>
</table>

Mean ± SD

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 42)</th>
<th>DS TB (n = 28)</th>
<th>DR TB (n = 14)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VD (ng/ml)</td>
<td>18 ± 6.6</td>
<td>21 ± 4.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>17.18 ± 2.89</td>
<td>15.95 ± 1.73</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TLC (cells/mm³)</td>
<td>1,347 ± 781.36</td>
<td>1,549 ± 797.41</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 42)</th>
<th>DS TB (n = 28)</th>
<th>DR TB (n = 14)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VD (ng/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Normal (30-90)</td>
<td>2 (4.76%)</td>
<td>2 (7.14%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>- Insufficiency (20-29.9)</td>
<td>19 (45.2%)</td>
<td>9 (32.1%)</td>
<td>10 (71.4%)</td>
<td>*0.048α</td>
</tr>
<tr>
<td>- Deficiency (&lt;20), n (%)</td>
<td>21 (50%)</td>
<td>17 (60.7%)</td>
<td>4 (28.5%)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Normal (18.5-22.9)</td>
<td>9 (21.4%)</td>
<td>9 (32.1%)</td>
<td>0 (0%)</td>
<td>*0.019β</td>
</tr>
<tr>
<td>- Underweight (&lt;18.5)</td>
<td>33 (78.6%)</td>
<td>19 (67.8%)</td>
<td>14 (100%)</td>
<td></td>
</tr>
<tr>
<td>TLC (cells/mm³)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Normal (≥1,200)</td>
<td>20 (47.6%)</td>
<td>11 (39.2%)</td>
<td>9 (64.2%)</td>
<td>0.126α</td>
</tr>
<tr>
<td>- Low (&lt;1,200), n (%)</td>
<td>22 (52.4%)</td>
<td>17 (60.7%)</td>
<td>5 (35.7%)</td>
<td></td>
</tr>
</tbody>
</table>

α: Chi-square, β: 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

<table>
<thead>
<tr>
<th>Variable</th>
<th>VD</th>
<th>BMI (kg/m²)</th>
<th>TLC (cells/mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal (30-90 ng/ml)</td>
<td>Normal (30-90 ng/ml)</td>
<td>Normal (30-90 ng/ml)</td>
</tr>
<tr>
<td>VD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Normal (30-90)</td>
<td>1 (2.4%)</td>
<td>3 (7.1%)</td>
<td>5 (11.9%)</td>
</tr>
<tr>
<td>- Insufficiency (20-29.9)</td>
<td>1 (2.4%)</td>
<td>16 (38.1%)</td>
<td>16 (38.1%)</td>
</tr>
<tr>
<td>- Deficiency (&lt;20), n (%)</td>
<td>1 (2.4%)</td>
<td>16 (38.1%)</td>
<td>16 (38.1%)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>Normal (18.5-22.9)</td>
<td>1 (2.4%)</td>
<td>3 (7.1%)</td>
</tr>
<tr>
<td>- Normal (18.5-22.9)</td>
<td>1 (2.4%)</td>
<td>13 (31%)</td>
<td>6 (14.3%)</td>
</tr>
<tr>
<td>- Underweight (&lt;18.5)</td>
<td>1 (2.4%)</td>
<td>6 (14.3%)</td>
<td>15 (35.7%)</td>
</tr>
<tr>
<td>TLC (cells/mm³)</td>
<td>- Normal (≥1,200)</td>
<td>1 (2.4%)</td>
<td>3 (7.1%)</td>
</tr>
<tr>
<td>- Low (&lt;1,200), n (%)</td>
<td>1 (2.4%)</td>
<td>6 (14.3%)</td>
<td>15 (35.7%)</td>
</tr>
</tbody>
</table>

β: Fisher’s exact test, *significant with p-value < 0.05. VD: Vitamin D, BMI: Body Mass Index, TLC: Total Lymphocyte Count.
Based on Table 1, the median age of the sample was 43 (24-55) years old. This is supported by Desissia, 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. 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. 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.

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. 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. 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.

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. Secondary DR TB is caused by inadequate drug doses and inadequate medication adherence. 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. An almost identical study was performed by Herlinu, 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. 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. 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. A total of 229 hospitalized pulmonary tuberculosis patients (66.4%) had a BMI <18.5 kg/m². In anthropometric assessments using BMI based on a study by Gongora, et al. (2019), most of the study population showed poor nutrition. Only around 30% of TB patients and contacts showed normal BMI. 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. 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.\textsuperscript{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 (\textit{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.\textsuperscript{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.\textsuperscript{7,29} Malnutrition in DR TB patients is associated with a higher mortality rate.\textsuperscript{29} Low BMI (below 18.5 kg/m\textsuperscript{2}) was associated with an increased risk of death and relapse of TB.\textsuperscript{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, \textit{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.\textsuperscript{8} Based on Fisher's exact test, there was no significant relationship in this study between TLC in DS TB and DR TB (\textit{p} = 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, \textit{et al.} (2020) in Pekanbaru, the median TLC for TB samples was 1,930 (620–4,230) cells/mm\textsuperscript{3}, and 11.1% of samples had low TLC.\textsuperscript{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. \textit{tb} decreased, increasing the TLC. Additionally, the subjects in that study came from outpatient settings with minimal comorbidities.\textsuperscript{13}

This study showed that there were significant differences in VD and BMI levels in DS TB and DR TB with respective values of \textit{p} < 0.05 (\textit{p} = 0.048 and \textit{p} = 0.019) (Table 2), but there was no significant difference in TLC in DS TB and DR TB (\textit{p} = 0.126). This is in line with the study of Ramkumar, \textit{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%).\textsuperscript{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.\textsuperscript{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.

\textbf{Table 3} shows no significant relationship between VD and BMI in patients with DS and DR TB (\textit{p} = 0.405). The same was found in a study by Saragih, \textit{et al.} (2015), who found that there was no significant relationship between VD levels and BMI in pulmonary TB samples (\textit{p-value} = 0.203).\textsuperscript{26} A systematic review and meta-analysis of observational studies by Song, \textit{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; I\textsuperscript{2} = 49.2%).\textsuperscript{30} Differently, Ramkumar, \textit{et al.} (2018) obtained that BMI affects VD (\textit{p-value} < 0.001) in TB patients.\textsuperscript{35} Another study by Harahap (2021) in Medan also showed that there was a significant relationship (\textit{p-value} = 0.007) between VD and BMI.\textsuperscript{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.\textsuperscript{35}

Based on Table 3, it was found that VD with
Lymphocytes play a role in the immune response to M. tuberculosis infection. T lymphocytes will be activated and proliferate in the acute phase of M. tuberculosis 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/mm³), indicating an active Tuberculosis (TB) infection. VDD is known to increase the risk of lymphopenia. VDD inhibits Th1 and Th17 responses, induces Treg responses, and controls proliferation and Th cells. VDD also upregulates the intestinal receptor CCR9 and inhibits CXCR3 in T cells, which can potentially change the homing properties of Th cells. VDD inhibits Th1 and Th17 responses, induces Treg responses, and controls proliferation and Th cells. VDD 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. VDD also controls the expansion of iNKT cells during this process. Finally, VDD also changes the production of cytokines by iNKT cells earlier, which can later form a T-cell response.

There has been some research on the relationship between BMI and TLC in TB. 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. In a study conducted by Gunarsa, et al. (2011), the results were significantly different between TLC and BMI between samples with BMI <18 kg/m² compared to BMI ≥18.5 kg/m² (p = 0.01). Tyastarini and Saraswati (2017) found that in patients with DM, there was a significant difference between the TLC and BMI (p < 0.001). 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.

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/mm³ and between severe malnutrition and TLC <900 cells/mm³. 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. Another study conducted by Iizuka, et al. (2023) in Japan found lymphocyte counts and 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. Lymphocytes reflect the nutritional condition and level of lymphocytes have been shown to vary with degree of malnutrition. Celullar immune response will occur and involve T lymphocyte cell when infection process like M. tuberculosis attack the macrophages.

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. 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.

Acknowledgments
The authors would like to thank Ulin General Hospital, Pekauman Public Health Center, Cempaka Public Health Center, and the Laboratory of Clinical Pathology at Ulin General Hospital, Banjarmasin, and all the study objects.

Conflict of Interest
The authors declared there is no conflict of interest.

Funding
The study was funded by individuals and civil service agencies in South Borneo.

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


