p–ISSN: 2723 - 6609 e-ISSN: 2745-5254
Vol. 6, No. 3 March 2025 http://jist.publikasiindonesia.id/

Effect of Omega-3 Addition on Sputum Conversion, Body Mass Index, Interleukin-6, and Lymphocyte Monocyte Ratio in the Treatment of Pulmonary Tuberculosis

Ferryansyah[1], Mohamad Isa[2], Juhairina[3], Haryati[4], Ali Assagaf[5], Erna Kusumawardhani[6]
Universitas Lambung Mangkurat, Indonesia
Email: ferrypulmo2021@gmail.com, mohamad.isa@ulm.ac.id, juhairina@ulm.ac.id, haryati@ulm.ac.id, ali.assagaf@ulm.ac.id, ernakusumawardhani@ulm.ac.id

*Correspondence

ABSTRACT

Keywords: Omega-3, pulmonary tuberculosis, sputum conversion, body mass index, interleukin-6, lymphocyte monocyte ratio

This research aims to investigate the impact of omega-3 supplementation on sputum conversion, body mass index (BMI), interleukin-6 (IL-6) levels, and lymphocyte-monocyte ratio (LMR) in patients with pulmonary tuberculosis (TB). Tuberculosis is a significant health problem in Indonesia, with high incidence and mortality rates. Omega-3 fatty acids are known to have anti-inflammatory effects and may enhance the immune response, potentially supporting tuberculosis (TB) therapy. The research methods included bacteriological examination of the sputum, measurement of BMI, IL-6 levels, and MLR in patients who received additional Omega-3 compared to the control group. The results are expected to provide an overview of the effectiveness of Omega-3 as a supportive therapy in treating TB, as well as its contribution to improving patients' nutritional status and immune response. This research is expected to serve as a reference for developing more effective and affordable tuberculosis therapies.

Introduction

Tuberculosis (TB) is a disease caused by Mycobacterium tuberculosis (MTB), which can infect the lungs and other organs (Wuan et al., 2022). Tuberculosis is still a health problem in Indonesia that causes very complex health, social, economic, and cultural problems. According to the Global TB Report 2022, Indonesia has the second-highest number of tuberculosis cases in the world after India. TB cases in Indonesia are estimated at 969,000 cases. This figure represents a 17% increase from 2020, with 824,000 cases. The incidence of tuberculosis cases in Indonesia is 354 per 100,000 population (Bagcchi, 2023; Organization, 2022) Data on pulmonary TB cases in 2022 from the South Kalimantan Provincial Health Office amounted to 7,556 cases with acid-resistant bacilli (BTA) positive 3861 (51%), with cases in Banjarmasin City occupying the highest position, 1,768 cases of tuberculosis out of 719,577 residents of Banjarmasin city with 819 positive cases of BTA (46%). The high number of tuberculosis cases in Indonesia necessitates the government's commitment to combating tuberculosis by issuing Presidential Decree Number 67 of 2021 concerning Tuberculosis Control (Simarmata, 2023).

Tuberculosis can cause a chronic response. This process causes lung tissue necrosis and cavitation, facilitating the transmission of TB. (Ravimohan et al., 2018). Anti-inflammatory treatment has been proposed as an adjunct therapy in TB patients to control excessive inflammation in TB to improve TB treatment outcomes and break the TB transmission chain. One of the proposed anti-inflammatory drugs is Omega-3. Consumption of Omega-3 polyunsaturated fatty acids (PUFAs) alters the composition of phospholipid fatty acids (FAs) in cell membranes, which play a role in immune and inflammatory responses. This process is primarily mediated by the conversion of long-chain PUFAs (LCPUFAs), namely eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (Nienaber, Ozturk, et al., 2021). Omega-3s EPA and DHA serve as substrates for producing pro-resolving lipid mediators (LMs), protectants, maresins, and resolvins that aid in inflammation resolution and decrease the production of anti-inflammatory cytokines. (Nienaber, Hayford, et al., 2021). The incorporation of EPA and DHA into cell membranes also promotes cell phagocytosis and bacterial apoptosis. (Hayford et al., 2021). The addition of Omega-3s is more effective than a diet in terms of weight gain and pneumonia resolution. Therefore, Omega-3s can be considered as an adjunctive supplement for treating tuberculosis. (COGHILL et al., 2018; Nienaber, Ozturk, et al., 2021).

A study in Uganda found that Omega-3 supplementation reduced interleukin-6 (IL-6) levels in Individuals with Human immunodeficiency virus (HIV) infection. (COGHILL et al., 2018). Another study reported an association between high IL-6 levels and the positive rate of acid-resistant bacilli in sputum (BTA) and the BTA sputum conversion time in treating pulmonary TB. (Wahyudi, 2022). A study at Friendship Hospital showed that patients with BTA-positive pulmonary TB who had a body mass index (BMI) of <18.5 kg/m2 had a cumulative probability of failure and better conversion compared to patients with a BMI >18.5 kg/m2 (Tama et al., 2016).

During the inflammatory process, several pro-inflammatory cytokines, including IL-6, are involved in the MTB infection process and play a crucial role in both the acute and chronic phases of the response. (Goletti et al., 2018). IL-6 dysregulation contributes significantly to the pathogenesis of chronic inflammatory diseases, and changes in cytokine levels may reflect disease status and serve as a potential prognostic test for tuberculosis (Zimmer et al., 2022). IL-6 has been identified as a biomarker and should be further investigated as part of monitoring Tuberculosis therapy (Zimmer et al., 2022).

The status of the immune system plays a vital role in tuberculosis infection. Monocyte cells have been considered MTB target cells, and lymphocytes are the primary effector cells of TB immunity (Wang et al., 2019). As key immune cells, levels of monocytes and lymphocytes can reflect a person's immunity to infection. The peripheral blood count is the most commonly performed test in clinical practice. However, as a simple biomarker, the monocyte-to-lymphocyte ratio (MLR) is rarely used in clinical care (Wang et al., 2019).

Based on previous studies, Omega-3 has anti-inflammatory and anti-bacterial effects, suggesting it may have potential as an additional therapy to enhance the success of tuberculosis treatment and break the chain of tuberculosis transmission. In addition, Omega-3 supplements are readily available at affordable prices but are still rarely used as a complementary therapy in TB treatment. The things mentioned above build the researcher's interest in conducting this research.

This study aimed to determine the effect of Omega-3 as an adjunct therapy in treating pulmonary tuberculosis on sputum conversion, body mass index, IL-6 levels, and MLR value and performing bacteriological examination of the sputum of the control and treatment groups before and after the addition of Omega-3 at week 0, week 4, and week 8 of pulmonary TB treatment and measuring the BMI of the control and treatment groups before and after adding Omega-3 at weeks 0, 4, and 8 of pulmonary TB treatment and measuring IL-6 values in the control and treatment groups before and after the addition of Omega-3 at weeks 0, 4, and 8 of pulmonary TB treatment and measuring the MLR values of the control and treatment groups before and after adding Omega-3 at weeks 0, 4, and 8 of pulmonary TB treatment. To analyze the effect of Omega-3 addition on sputum conversion in the control and treatment groups at weeks 0, 4, and 8 of pulmonary TB treatment. To analyze the impact of Omega-3 addition on IL-6 levels in both the control group and the treatment group at weeks 0 and 4 of pulmonary TB treatment. To analyze the effects of Omega-3 addition on the MLR value of the control and treatment groups at weeks 0, 4, and 8 of pulmonary TB treatment. To analyze the effect of Omega-3 addition on the BMI of the control group and the treatment group at week 0, week 4, and week 8 of pulmonary TB treatment (Chebrolu et al., 2020).

The results of this study are expected to be scientific literacy regarding the benefits of adding Omega-3 to pulmonary TB therapy. The results of this study are expected to serve as a basis for recommendations to healthcare providers on the provision of additional Omega-3 to treat pulmonary TB patients in healthcare services. It can provide information and education to the community; the addition of Omega-3 can be used as a companion therapy for OAT to increase the success of treatment and break the chain of transmission of pulmonary TB. Provide references or materials to support the development of further research examining the role of interleukin-6 and the lymphocyte-monocyte ratio as prognostic indicators in the treatment of pulmonary tuberculosis.

Method

In this study, the research design used was an experiment, focusing on the effects of Omega-3 supplementation as an adjunct therapy in the treatment of pulmonary tuberculosis (TB). This experimental study aims to investigate the impact of Omega-3 supplementation on sputum conversion, body mass index (BMI), interleukin-6 (IL-6) levels, and maximum lymphocyte response (MLR) value in the treatment of pulmonary tuberculosis (TB). The study's purpose was achieved through interventions in both the treatment and control groups. The research was conducted at Ulin Banjarmasin Hospital and Pekauman Banjarmasin Health Center. The research period began in September 2023 and concluded in August 2024, or when the target sample size was reached.

The approach employed was quantitative, involving two groups: the treatment group, which received Omega-3 supplementation, and the control group, which did not receive supplementation. Data were collected through various health measurements, including sputum conversion, body mass index (BMI), interleukin-6 (IL-6) levels, and lymphocyte-monocyte ratio (LMR), at multiple time points during TB treatment. This enables the assessment of the therapy's impact over time.

The data source for this study is primary data collected directly from participants, with a sample of 32 tuberculosis patients. Data analysis techniques involve descriptive and inferential statistics. Descriptive statistics are used to summarize the characteristics of the sample. In contrast, inferential tests, such as the Mann-Whitney test and the t-test, are used to analyze the effect of Omega-3s on variables of interest. Data collection techniques include clinical measurements and laboratory tests, such as bacteriological sputum examinations, BMI assessments, and blood tests to determine IL-6 and MLR levels. These data points were compared between the control and treatment groups at different time intervals.

Results and Discussion

1. Characteristics of the research subject

Shows the data on the characteristics of the research subjects. The study included 32 samples, comprising 16 respondents in the control group who did not receive Omega-3 and 16 respondents in the treatment group who received Omega-3. In this study, it was found that the majority of the sample consisted of men (62.5%), with the highest age range being over 55 years old (40.6%). This distribution was similar to that of the control group (7 people, 44%) and the treatment group (6 people, 37%). The most common occupation was that of a housewife (31.2%), with a more even distribution in the control group than in the treatment group (7 individuals vs. three individuals). The most common risk factors for TB were smoking (43.7%) and TB contact (31.2%). The number of smokers in the control group was higher than in the treatment group (9 people vs. five people).

This study also found that 100% of patients had cough symptoms, followed by decreased appetite (75%) and shortness of breath (65.6%), with an even distribution in both groups. The most common history of the disease was diabetes mellitus (15.6%), followed by hypertension (6.2%). For side effects, most participants did not report any (87.5%), and only a tiny percentage experienced nausea (9.37%).

Table 1. Characteristic Data

Sample Characteristics	Total (n=32)	Control (n=16)	Treatment (n=16)
Gender			
Man	20 (62.5%)	9 (56%)	11 (69%)
Woman	12 (37.5%)	7 (44%)	5 (31%)
Age			
18-24 years old (%)	4 (12.5%)	1 (6%)	3 (19%)
25-34 years old (%)	5 (15.6%)	0 (0%)	5 (31%)
35-44 years (%)	5 (15.6%)	3 (19%)	2 (13%)
45-54 years (%)	5 (15.6%)	5 (31%)	0 (0%)
>55 years (%)	13 (40.6%)	7 (44%)	6 (37%)
Work			
Not working (%)	7 (21.8%)	1 (6%)	6 (38%)
Traders (%)	6 (18.7%)	3 (19%)	3 (19%)
Housewives (%)	10 (31.2%)	7 (44%)	3 (19%)
Parking attendants (%)	2 (6.25%)	1 (6%)	1 6%)
Helmsman (%)	1 (3.12%)	1 (6%)	0 (0%)
Private employees (%)	1 (3.12%)	1 6%)	0 (0%)
Labor (%)	1 (3.12%)	0 (0%)	1 (6%)
Farmers (%)	3 (9.37%)	2 (13%)	1 (6%)
Students (%)	1 (3.12%)	0 (0%)	1 (6%)
Risk factors			
Smoking (%)	14 (43.7%)	9 (56%)	5 (31%)
Contact TB (%)	10 (31.2%)	5 (31%)	5 (31%)
Symptom			
Cough (%)	32 (100%)	16 (100%)	16 (100%)
Cough up blood (%)	4 (12.5%)	2 (13%)	2 (13%)
Sesak napas (%)	21 (65.6%)	11(69%)	10 (62%)
Night sweats (%)	19 (59.3%)	11(69%)	8 (50%)
Decreased appetite (%)	24 (75%)	13 (81%)	11 (69%)
Weight loss	28 (87.5%)	13 (81%)	15 (94%)
None	4 (12.5%)	3 (19%)	1 (6%)
0 – 5 kg (%)	16 (50%)	9 (56%)	7 (44%)
5 - 10 kg (%)	10 (31.2%)	3 (19%)	7 (44%)
10 - 20 kg (%)	2 (6.25%)	1 (6%)	1 (6%)
>20 kg (%)	0 (0%)	0 (0%)	0 (0%)
History of previous diseases			
Diabetes Mellitus (%)	5 (15.6%)	2 (13%)	3 (19%)
Hypertension (%)	2 (6.25%)	2 (13%)	0 (0%)
Fish allergy (%)	0 (0%)	0 (0%)	0 (0%)
None (%)	25 (78.1%)	12 (75%)	13 (81%)
Side effects			
Nausea (%)	3 (9.37%)	2 (13%)	1 (6%)
Vomiting (%)	0 (0%)	0 (0%)	0 (0%)
Itching (%)	1 (3.12%)	1 (6%)	0 (0%)
Spontaneous bleeding (%)	0 (0%)	0 (0%)	0 (0%)
None (%)	28 (87.5%)	13 (81%)	15 (94%)

Conversion characteristics, IL-6, MLR and BMI

Table 2. Conversions at week 4 and week 8

Variable	Sputum BTA	Total (n=32)		Control (n=16)		Treatment (n=16)	
		n	%	n	%	n	%
Sputum M4	Neg	30	93.75	14	87.50	16	100.0
	Pos	2	6.25	2	12.50	0	0.0
Sputum M8	Neg	31	96.88	15	93.75	16	100.0
	Pos	1	3.12	1	6.25	0	0.0

Source: Data processed

Table 2 presents the characteristics of sputum conversion at weeks 4 and 8. In the fourth week of examination in the control group, 14 samples (87.50%) experienced sputum conversion to negative, and two samples (12.50%) remained positive. In contrast, all samples in the treatment group experienced negative sputum conversion (100%). In the eighth week of examination in the control group, 15 samples (93.75%) exhibited harmful conversions, and 1 sample (6.25%) remained positive. In the treatment group, all samples experienced harmful sputum conversions (100%).

Table 3. Characteristics of IL-6, MLR, and BMI values

Variable	Total	Control	Treatment
IL-6 (median) (pg/mL)			
Week 0	15.99	11.7	17.8
Week 4	7.93	6.21	8.66
Week 8	5.13	6.36	4.39
MLR (median)			
Week 0	0.64	0.61	0.64
Week 4	0.43	0.40	0.46
Week 8	0.45	0.53	0.37
IMT (median) (kg/m2)			
Week 0	18.23	18.49	17.97
Week 4	18.67	18.82	18.52
Week 8	19.01	19.01	19.02

Source: Data processed

Table 3 and Figure 1 showed that the IL-6 level in the control group was 11.7 at week 0, then decreased to 6.21 at week 4 and to 6.36 at week 8. Meanwhile, in the treatment group, the IL-6 level value was 17.8 at week 0, then decreased to 8.66 at week 4 and 4.39 at week 8.

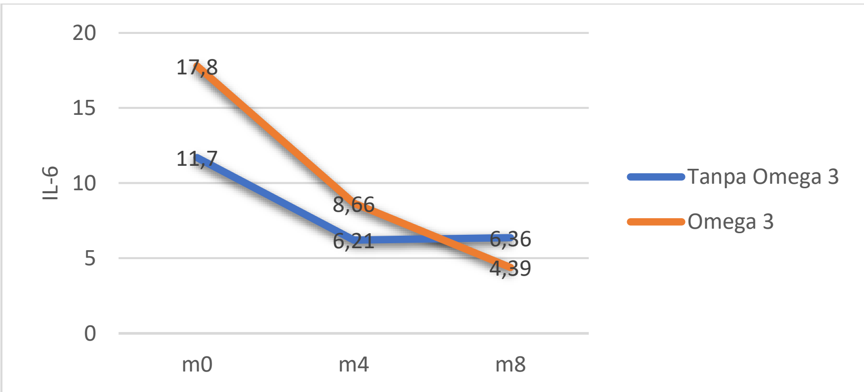

Figure 1. IL-6 Rate Graph

Table 3 and Figure 2 show an MLR value of 0.61 in the control group at week 0, which decreased to 0.40 at week 4 and to 0.53 at week 8. Meanwhile, in the treatment group, an MLR value of 0.64 was obtained in week 0, which decreased to 0.46 in week 4 and to 0.37 in week 8.

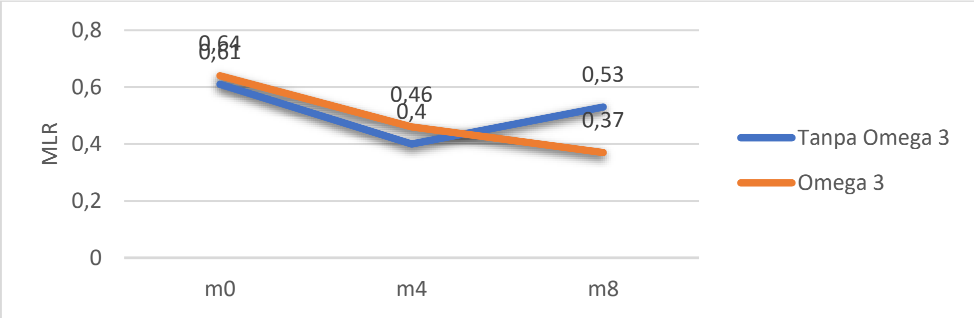

Figure 2. MLR Value Graph

In the BMI variable, the initial examination of the control group was 18.49, then increased to 18.82 in the fourth week and to 19.01 in the eighth week. Meanwhile, in the treatment group, the initial examination was obtained at 17.97, then increased to 18.52 in the fourth week and to 19.02 in the eighth week.

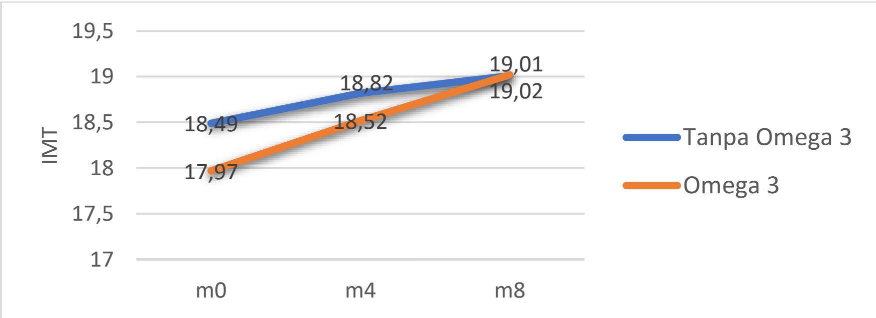

Figure 3. BMI Chart

2. Normality test

Test normality using the Shapiro-Wilk method. If the p-value is more significant than 0.05, the data are usually normally distributed.

Table 4. Normality test results

Variable	Shapiro-Wilk			Information
	Statistics	N	Mr.	
IL6 M4	0.621	32	0.000	Not Normally Distributed
IL6 M8	0.795	32	0.000	Not Normally Distributed
MLR M4	0.903	32	0.007	Not Normally Distributed
MLR M8	0.926	32	0.031	Not Normally Distributed
IMT M4	0.941	32	0.081	Normally distributed
IMT M8	0.945	32	0.103	Normally distributed

Source: Data processed

The results of the normality test yielded a significance value of less than 0.05 for the variable Interleukin-6 (IL-6) and the lymphocyte-monocyte ratio (MLR). Hence, the data was not normally distributed. Therefore, this variable was analyzed using the Mann-Whitney test. Meanwhile, the normality test results for the BMI variable yielded a significance value of >0.05, indicating that the BMI data were normally distributed. Therefore, the BMI variable was analyzed using the Independent T-test.

3. Effect of Omega-3 addiction therapy on sputum conversion

Table 5. Fischer's Exact test of the sputum conversion variable

Variable	Control		Treatment		*p*
	n	**%**	**n**	**%**	
BTA sputum week 4					
Negative	14	87.5	16	100	0.484
Positive	2	12.5	0	0.0	
BTA sputum week 8					
Negative	15	93.75	16	100	1.000
Positive	1	6.25	0	0.0	

Source: Data processed

Table 5 shows that, statistically, using the Fisher Exact test, there was no significant effect of Omega-3 addition on sputum conversion in pulmonary TB patients at week 4 (p = 0.484) and week 8 (p = 1.000).

4. Effect of Omega-3 adjuvant therapy on IL-6

Table 6. Mann-Whitney test for IL-6 levels

Variable	Control	Treatment	*p*
Delta IL-6 m0-m4	17.06	15.94	0.734
Delta IL-6 m4-m8	20.63	12.38	**0.013**

Source: Data processed

Table 6, using the Mann-Whitney test, statistically shows that adding Omega-3 had no significant effect on the decrease in IL-6 from week 0 to week 4 (p = 0.734). However, there was a substantial effect on monitoring during the 4th to 8th week of pulmonary TB treatment (p = 0.013).

5. Effect of Omega-3 adjuvant therapy on MLR

Table 7. Mann-Whitney test of the monocyte ratio variable

Variable	Control	Treatment	*p*
Delta MLR m0-m4	16.34	16.66	0.925
Delta MLR m4-m8	11.84	21.26	**0.005**

Source: Data processed

Table 7 presents the statistical results obtained using the Mann-Whitney test, indicating that adding Omega-3 had no significant effect on the decrease in MLR from the 0th to the fourth week of monitoring (p = 0.925). However, it significantly affected the monitoring of the 4th to eighth week of pulmonary TB treatment (p 0.005).

6. Effect of Omega-3 adjuvant therapy on BMI

Table 8. Independent T-test of the BMI variable

Variable	Control	Treatment	*p*
Delta IMT m0-m4	32.69	54.69	**0.047**
Delta IMT m4-m8	19.31	49.94	0.452

Source: Data processed

Table 8 presents the statistical results, obtained using the Independent T-test, showing that the addition of Omega-3 significantly affected the increase in BMI from the 0th to the fourth week of monitoring (p = 0.047), but did not affect the growth in BMI from the fourth to the eighth week (p = 0.452).

Discussion

Characteristics of the research sample

A total of 32 patients participated in this study, which was divided into two groups: 16 individuals in the control group, who did not receive Omega-3 supplementation, and 16 individuals in the treatment group, who received Omega-3 supplementation. The most common gender is male, which is 62.5%. This characteristic data aligns with the data from TB patients reported by the WHO in the 2023 Global TB Report. Specifically, in 2022, it was found that 55% of TB patients were men, 33% were women, and 12% were children.70 The research of Thuraidah et al., (2017) South Kalimantan also showed the same pattern, where 61.3% of TB patients were men. Suggest that social contact patterns are likely to contribute to the gender gap in TB burden in adults, with more disease burden in men. At the same time, the excess TB burden in men also has profound implications for MTB transmission in all genders and age groups. (Handayani, 2024; Thuraidah et al., 2017). Addressing TB overload in men is essential for improving men's health and for reducing TB incidence and death. (Chen et al., 2024; Ledesma et al., 2022).

The characteristic data based on age in this study showed that as many as 40.6% of the participants were over 55. According to Konde et al., a relationship exists between age and risk factors for pulmonary tuberculosis.73 The causes of tuberculosis infection in the elderly are primarily due to the presence of chronic comorbid diseases, decreased organ function, and decreased endurance or immunity to infection.74,75

In this study, the risk factors for pulmonary TB were in the form of a history of smoking and a history of previous TB exposure. The risk factors for smoking in this study were 43.7%, and TB contact was 31% in the control sample, while in the treatment sample, 31% were found to be smoking, and 31% had a TB contact history. Katiandago et al., in their study, stated that smoking is associated with a risk of pulmonary TB and a 2-fold risk compared to non-smokers.76 Immune responses can be weakened by smoking habits, alcohol abuse, and other diseases, such as diabetes mellitus, which can be the reason for delayed sputum conversion as well. Smoking habits and static alcohol abuse are associated with the persistence of pulmonary TB infectivity.77 Asemahagn et al., in a study, suggested that the smoking habits of TB patients were reported to be statistically significant with the length of BTA conversion. Thus, the chance of experiencing a long BTA conversion was twice as high in pulmonary TB patients who smoked any amount and frequency compared to pulmonary TB patients who did not smoke.78 Other previous studies on TB and smoking also reported supportive results; it is associated with the effects of smoking on lung defense mechanisms, lowering T cell immunity, and poor food intake, making people immunocompromised, which makes them more susceptible to developing pulmonary TB.79

In this study, the contact history of TB was 31.2%. The history of contact with TB in one family with another family member is significant because the Mycobacterium Tuberculosis germ, as the etiology of pulmonary TB, has a tiny size, is aerobic, can survive in dry sputum, and is very contagious through inhalation excretion either through breathing, coughing, sneezing or talking (droplet infection). If there are family members who suffer from active pulmonary TB, then all other family members will be vulnerable to the incidence of pulmonary TB, especially close family members. A history of contact with family members who are in the same household and have been in contact for more than or equal to 3 months is at high risk for pulmonary TB.80

For the most characteristic symptom, cough, all samples in this study experienced coughing, followed by symptoms of weight loss in 81% of cases, decreased appetite in 75%, shortness of breath in 65.6%, night sweats in 59.3%, and coughing up blood (hemoptysis) in 12.5%. Clinical symptoms of pulmonary TB develop slowly and are often non-specifically at the beginning of the disease. They can include a prolonged cough accompanied by mucus, pleuritic chest pain, hemoptysis, dyspnea, progressive weakness or fatigue, weight loss, loss of appetite (which can lead to anorexia), chills or fever, night sweats, and malaise. Sharma et al. also mention in their writing that common symptoms of tuberculosis include weight loss, night sweats, decreased appetite, and shortness of breath.82

For previous disease history data, this study reported diabetes mellitus (DM) at 15.6% and hypertension at 6.25%. The increasing prevalence of diabetes worldwide is mainly occurring in TB-endemic countries and has led to a re-emergence of the importance of the link between these two diseases. Currently, type 2 diabetes is one of the most common comorbidities and risk factors in TB patients, along with malnutrition and HIV/AIDS. Metabolic changes typical of diabetes (e.g., chronic hyperglycemia, metabolic inflammation, oxidative stress) are likely contributing to immune dysfunction in response to MTB.83 Diabetes mellitus is a significant risk factor for the development of active and latent tuberculosis. The immune mechanisms that contribute to the increased susceptibility of diabetic patients to TB are caused by defects in bacterial recognition, phagocytosis activity, and cellular activation, resulting in impaired production of chemokines and cytokines. The initiation of adaptive immunity is delayed in hyperglycemic hosts due to impaired recruitment and antigen-presenting cell (APC) function, resulting in reduced frequencies of Th1, Th2, and Th17 cells, as well as decreased cytokine secretion, which plays a significant role in macrophage activation and the inflammatory response to tuberculosis 83,84

More than half of adults with LTBI in the United States have hypertension. Importantly, we observed an association between LTBI and hypertension among those without cardiovascular disease risk factors (CVDs).85 Seegert et al., in their paper, found a much higher prevalence of hypertension among TB patients compared to the control group. Cross-sectional studies reported that the prevalence of hypertension in TB patients ranged from 0.7% to 38.3%.86 TB infection has been associated with increased systemic inflammation and immune activation, including the increased expression of tumor necrosis factor-alpha (TNF-α), interferon, and interleukin-6 (IL-6). These chemokines and dysfunctional immune responses play an essential role in the pathogenesis of hypertension and the development of active TB. .85

Effect of Omega-3 addition on sputum conversion

Omega-3 fatty acids, specifically eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), possess properties that can mitigate inflammation and enhance bactericidal activity, thereby reducing bacterial counts and increasing the phagocytosis ability of immune cells. Therefore it can be assumed that administering additional Omega-3 can aid in sputum conversion in tuberculosis patients.

In this study, when viewed from the sputum conversion data in the treatment group that received the addition of Omega-3, the sputum conversion rate was 100% in the fourth week, whereas in the control group, it was only 87.5%. However, statistically, there was no significant difference. Revi et al. stated in their paper that the conversion of BTA sputum to negative at the end of intensive phase treatment is influenced by several internal factors, including education and income level, gender, compliance, nutritional status, smoking status, and comorbidities. External factors, such as environmental conditions, BTA positivity rate, medication supervisors (PMOs), and drug availability in health facilities, can also affect BTA sputum conversion during anti-tuberculosis treatment.88 In addition, Wardani et al., in their research, also mentioned that several things can cause delays in sputum conversion, namely medication compliance, education, initial laboratory examinations, comorbidities, nutrition, and unhealthy lifestyles (Anshar et al., 2023).

In this study, data related to the severity of TB, such as thoracic photos and BTA positivity levels, were not recorded. According to Murthy et al., the study stated that the radiological severity reflects the overall severity of the disease in pulmonary TB with a positive smear. The proportion of the lung field affected by the disease at the time of pulmonary TB diagnosis was associated with a more significant grade of BTA smear. The presence of cavitation and the percentage of lung field affected on thoracic photographs predicted a 2-month positive smear on treatment.90 This information suggests that the thoracic photo data and the BTA positivity rate, not recorded in this study, may be related to the statistical results indicating that the addition of Omega-3 has no significant effect on sputum conversion, which is likely due to the varying severity of TB in the study sample.

Another factor that can mitigate the significant effect of Omega-3 addition on sputum conversion is comorbidity with Diabetes Mellitus (DM). According to the data from this study, the treatment group has a sample with a higher prevalence of DM comorbidities. In addition to being a risk factor for an increased incidence of active TB, the presence of DM simultaneously worsens treatment outcomes even in treated patients. In the pre-insulin era, the most common cause of death in DM other than diabetic coma was coinfection with TB. The incidence of DM can increase the risk of treatment failure, death, and recurrence. (Suárez et al., 2019).

In this study, the entire sample had a BMI below normal; this condition can be disruptive, so adding Omega-3 does not significantly affect the sputum conversion. Malnutrition was also significantly associated with treatment failure, including death and a longer time to sputum culture conversion. Severe incidence of pulmonary TB can lead to the formation of bilateral cavitation in the pulmonary parenchyma, which can be associated with a higher mycobacterial load and increase the likelihood of a longer time to negative sputum conversion. Therefore, nutritional counseling and supplementation during TB treatment are associated with improved immune function and bacterial clearance that can increase early sputum conversion. (Pezzella, 2019).

Effect of Omega-3 Addition on Decrease in IL-6 Levels

In this study, the results showed that Omega-3 can significantly decrease IL-6 levels during the 4th to eighth week of pulmonary TB treatment. IL-6 cytokines can be either pro-inflammatory or anti-inflammatory, and are produced in response to tuberculosis infection. The mechanism by which omega-3 fatty acids reduce cytokines involves the mediators of eicosanoids, specifically prostaglandins E1 and E2. The anti-inflammatory effects of EPA and DHA include the competitive inhibition of arachidonic acid, a metabolite that promotes inflammation and may inhibit leukocyte migration activity by altering cytoskeletal components. Resolvin and protectin are lipid mediators derived from EPA and DHA through the action of lipoxygenase. Increasing attention has led to a deeper understanding of Omega-3 Polyunsaturated fatty acids (PUFAs) as ligands for peroxisome proliferator-activated receptors (PPARs), which regulate genes involved in lipid metabolism and anti-inflammatory responses, making Omega-3 PUFAs PPAR agonists. Inhibition of nuclear factor kappa-B (NF-κB) expression, a transcription factor crucial for the synthesis of inflammatory cytokines and adhesion molecules, has been associated with the consumption of omega-3 polyunsaturated fatty acids (PUFAs).

An increase in cytokines can occur in tuberculosis and is a common phenomenon in TB patients. Increased levels of inflammatory cytokines are dramatically elevated in severe TB, and these elevated inflammatory cytokines are associated with lung inflammation and further lung damage. (Marakalala et al., 2016). Thus, the administration of Omega-3s is likely to reduce the risk of further lung damage in pulmonary TB in the future.

Omega-3 fatty acids, specifically EPA and DHA, exhibit antibacterial properties and play a role in mitigating inflammation associated with tuberculosis.96 Omega-3s can significantly lower levels of IL-6 cytokines, improve immunoregulation and anti-inflammatory conditions, and support Omega-3 fatty acids as potential therapeutic agents for diseases related to immunodeficiency.Omega-3 fatty acids can also serve as an energy source for immune cells, playing a key role in the formation of the immune response.99,100

IL-6 expression is higher in patients newly diagnosed with tuberculosis. Therefore, IL-6 can be used as a suitable marker to differentiate between active and latent TB status and monitor treatment efficacy in tuberculosis. (Téllez-Navarrete et al., 2021).

Effect of Omega-3 Addition on MLR

The results of this study showed that the addition of Omega-3 could have a statistically significant effect on the decrease in MLR value from week 4 to week 8 of pulmonary TB treatment.

Monocytes are leukocytes that can be differentiated into macrophages and dendritic cells. They have three main functions in the immune system: phagocytosis, antigen presentation, and cytokine production. After leaving the bone marrow, monocytes circulate in the bloodstream for about 1-3 days, then travel to tissues throughout the body, where they differentiate into macrophages and dendritic cells. Monocytes are a crucial component of the immune defense system, playing a vital role in the innate immune response. (Chávez-Galán et al., 2017). The heterogeneous nature of monocytes, along with their ability to differentiate into monocyte-derived macrophages or monocyte-derived dendritic cells, enables them to bridge innate and adaptive immune responses.

Lymphocytes are found in blood and lymph. Colorless fluids in lymphatic vessels connect lymph nodes to the bloodstream. T cells, B cells, and natural killer (NK) cells are different types of lymphocytes, each playing a crucial role in the immune system's functioning and influencing its response to foreign substances, such as microorganism attacks. Deviations in the number of lymphocytes from the reference value may indicate an abnormal condition. (Zhao et al., 2024).

The ratio of monocytes to lymphocytes is considered a crucial criterion for assessing a person's immune efficiency during an infectious condition, and a peripheral blood test can easily measure it. In MTB infections, an increase in the ratio of monocytes to lymphocytes indicates the severity of active TB. The monocyte-to-lymphocyte ratio can also indicate the effectiveness of treatment in tuberculosis.103 Meital et al. stated that Omega-3s can help lower monocyte count and increase lymphocyte activity, potentially changing this ratio to be more balanced and supporting the healing process. The effects of Omega-3 work by (a) competition with arachidonic acid (AA) in the biosynthesis of pro-inflammatory mediator molecules, (b) suppression of pro-inflammatory nuclear factor kappa-B (NF-κB) through modulation of toll-like receptor 4 (TLR4) signaling and activation of Peroxisome proliferator-activated receptor gamma (PPAR γ), (c) and metabolism to pro-resolution lipid mediators (resolvin, protectin, maresin) (Calvo et al., 2017; da Silva Batista et al., 2024).

In general, the results of this study suggest that MLR can be used as a simple diagnostic tool to aid in establishing the diagnosis of TB and as a means to monitor the TB treatment process. MLR is an essential biomarker for identifying TB and tracking the effectiveness of anti-TB therapy (Adane et al., 2022; Fritschi et al., 2023; Leo et al., 2024). Choudhary et al. also mentioned that MLR can be a useful diagnostic tool for diagnosing tuberculosis when microbiological confirmation is inaccessible. (Choudhary et al., 2019).

Theresia, (2016) In their study, revealed that although the ratio of monocytes to lymphocytes is associated with the risk of TB disease, the ratio of monocytes to lymphocytes is a non-specific marker of inflammation in several populations, including pregnant women infected with HIV, people starting antiretroviral therapy, infants vaccinated with BCG, and adolescents latently infected with TB. From this data, it can be concluded that in pregnant women, people with latent HIV and TB are not advised to use the MLR test as an additional test to help diagnose tuberculosis and become an indicator of the severity of tuberculosis disease.

In this study, a decrease in MLR values was observed in conjunction with a reduction in IL-6 levels in patients with tuberculosis. This opens up opportunities for MLR to be a more accessible and cost-effective method for monitoring treatment.

Effect of Omega-3 addition on BMI increase

The study's results statistically showed a significant effect of adding Omega-3 on the increase in BMI of pulmonary TB patients from week 0 to week 4. Research conducted by Moradi et al. indicates that omega-3 supplementation may increase the sensation of hunger, potentially leading to higher carbohydrate intake. Additionally, Omega-3s can also increase cravings for sugary foods. (Loddenkemper et al., 2016).

Damsbo et al. also showed that Omega-3 fatty acids can increase appetite. These findings have the potential to be beneficial for patients with impaired nutritional status. The central nervous system, with high levels of Omega-3, can modulate its function. Some studies suggest that Omega-3 intake may affect the transmission of monoaminergic neurotransmitters involved in appetite regulation. (Gasmi et al., 2022). The sensation of hunger is related to long-term energy balance and can be influenced by Omega-3 fatty acids. Omega-3 supplementation for three weeks increases the sensation of hunger and the desire to eat, while reducing feelings of fullness. Genetic factors, such as those affecting PPARγ, can influence the sensation of hunger and lead to increased appetite.

Increasing BMI in tuberculosis patients can reduce the mortality rate of tuberculosis. Whitehouse (2018) posited that being overweight was not significantly associated with the risk of death, but being underweight was significantly associated with a higher risk of TB-specific and non-TB-specific deaths during treatment. These findings suggest that, to reduce TB-specific and non-TB-specific deaths, comprehensive treatment should be given to underweight patients during TB treatment (Parbhoo et al., 2020). The addition of Omega-3 to this study can significantly increase the BMI of patients with pulmonary TB, suggesting that the inclusion of Omega-3 in the treatment of pulmonary TB may indirectly reduce the mortality rate of tuberculosis.

Implication:

Factors that affect employee performance: In addition to Omega-3, other factors, such as medication adherence, nutritional status, socioeconomic factors, and the presence of comorbid diseases, can also impact performance. Further discussion of the role of these factors in sputum conversion, IL-6, MLR, and BMI in TB patients could deepen our understanding of the results.

Conclusion

Based on the analysis of the effect of Omega-3 addition on sputum conversion, IL-6 levels, MLR, and BMI values in the treatment of pulmonary TB, the following conclusions can be drawn: There is an effect of Omega-3 addition on sputum conversion at week 0 to week 4 monitoring (100% vs. 87.5%), and monitoring week 4 to week 8 (100% vs. 93.8%) of pulmonary TB treatment, but the statistical test is not significant. The addition of Omega-3 significantly affected the decrease in IL-6 levels from the fourth to the eighth week of monitoring pulmonary TB treatment (p = 0.012). The addition of Omega-3 significantly affected the decline in MLR from the 4th to the eighth week of monitoring pulmonary TB treatment (p = 0.004). Adding Omega-3 affected the increase in BMI from week 0 to week 4 of pulmonary TB treatment (p 0.047).

References

Adane, T., Melku, M., Ayalew, G., Bewket, G., Aynalem, M., & Getawa, S. (2022). Accuracy of the monocyte-to-lymphocyte ratio for tuberculosis diagnosis and its role in monitoring anti-tuberculosis treatment: A systematic review and meta-analysis. *Medicine*, *101*(44), e31539.

Anshar, D., Fadhilla, G., & Wulansari, W. (2023). Correlation between Family Support and Health Professional Education on Tuberculosis Patient Compliance at Public Health Centers, Tasikmalaya. *Jurnal Sains Farmasi & Klinis*, *10*(3), 314–319.

Bagcchi, S. 2023. WHO's global tuberculosis report 2022. *The Lancet Microbe, vol. 4, no. 1*, e20.

Calvo, M. J., Martínez, M. S., Torres, W., Chávez-Castillo, M., Luzardo, E., Villasmil, N., Salazar, J., Velasco, M., & Bermúdez, V. (2017). Omega-3 polyunsaturated fatty acids and cardiovascular health: A molecular view into structure and function. *Vessel Plus*, *1*, 116–128.

Chávez-Galán, L., Ramon-Luing, L., Carranza, C., Garcia, I., & Sada-Ovalle, I. (2017). Lipoarabinomannan decreases galectin-9 expression and the tumor necrosis factor pathway in macrophages, favoring the intracellular growth of Mycobacterium tuberculosis—Frontiers *in Immunology*, *8*, 1659.

Chebrolu, P., Laux, T., Chowdhury, S., Seth, B., Ranade, P., Goswami, J., & Chatterjee, S. 2020. The risk of refeeding syndrome among severely malnourished tuberculosis patients in Chhattisgarh, India. *Indian Journal of Tuberculosis*, *67*(2), 152–158.

Chen, Y., Chen, W., Cheng, Z., Chen, Y., Li, M., Ma, L., Zhou, N., Qian, J., Zhu, Y., &

Liu, C. (2024). Global burden of HIV-negative multidrug-and extensively drug-resistant tuberculosis based on the Global Burden of Disease Study 2021. *Science in One Health*, *3*, 100072.

Choudhary, R. K., Wall, K. M., Njuguna, I., Pavlinac, P. B., LaCourse, S. M., Otieno, V., Gatimu, J., Stern, J., Maleche-Obimbo, E., & Wamalwa, D. (2019). Monocyte-to-lymphocyte ratio is associated with tuberculosis disease and declines with anti-TB treatment in HIV-infected children. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, *80*(2), 174–181.

COGHILL, A. E., SCHENK, J. M., MAHKOUL, Z., OREM, J., PHIPPS, W., & CASPER, C. (2018). Omega-3 decreases interleukin-6 levels in HIV and HHV-8 co-infected patients: results from a randomized supplementation trial in Uganda. *AIDS (London, England)*, *32*(4), 505.

da Silva Batista, E., Nakandakari, S. C. B. R., Ramos da Silva, A. S., Pauli, J. R., Pereira de Moura, L., Ropelle, E. R., Camargo, E. A., & Cintra, D. E. (2024). Omega-3 Pleiad: A Multipoint Anti-Inflammatory Strategy. *Critical Reviews in Food Science and Nutrition*, *64*(14), 4817–4832.

Fritschi, N., Vaezipour, N., Buettcher, M., Portevin, D., Naranbhai, V., & Ritz, N. (2023). Ratios from complete blood count as markers for TB diagnosis, treatment, prognosis: a systematic review. *The International Journal of Tuberculosis and Lung Disease*, *27*(11), 822–832.

Gasmi, A., Nasreen, A., Menzel, A., Gasmi Benahmed, A., Pivina, L., Noor, S., Peana, M., Chirumbolo, S., & Bjørklund, G. (2022). Neurotransmitter Regulation and Food Intake: The Role of Dietary Sources in Neurotransmission. *Molecules*, *28*(1), 210.

Goletti, D., Arlehamn, C. S. L., Scriba, T. J., Anthony, R., Cirillo, D. M., Alonzi, T., Denkinger, C. M., & Cobelens, F. (2018). Can we predict tuberculosis cure? What tools are available? *European Respiratory Journal*, *vol. 52, no. 5*.

Handayani, L. (2024). Studi Epidemiologi Tuberkulosis Paru (TB) di Indonesia: Temuan Survey Kesehatan Indonesia (SKI) 2023. *Jurnal Kendari Kesehatan Masyarakat*, *4*(1), 59–67.

Hayford, F. E. A., Ozturk, M., Dolman, R. C., Blaauw, R., Nienaber, A., Loots, D. T., Brombacher, F., Smuts, C. M., Parihar, S. P., & Malan, L. (2021). Longer-term Omega-3 LCPUFA is a more effective adjunct therapy for tuberculosis than ibuprofen in a C3HeB/FeJ tuberculosis mouse model—Frontiers *in Immunology*, *12*, 659943.

Ledesma, J. R., Ma, J., Vongpradith, A., Maddison, E. R., Novotney, A., Biehl, M. H., LeGrand, K. E., Ross, J. M., Jahagirdar, D., & Bryazka, D. (2022). Global, regional, and national sex differences in the worldwide burden of tuberculosis by HIV status, 1990–2019: results from the Global Burden of Disease Study 2019. *The Lancet Infectious Diseases*, *22*(2), 222–241.

Leo, S., Narasimhan, M., Rathinam, S., & Banerjee, A. (2024). Biomarkers in diagnosing and therapeutic monitoring of tuberculosis: a review. *Annals of Medicine*, *56*(1), 2386030.

Loddenkemper, R., Lipman, M., & Zumla, A. 2016. Clinical aspects of adult tuberculosis. *Cold Spring Harbor Perspectives in Medicine*, *6*(1), a017848.

Marakalala, M. J., Raju, R. M., Sharma, K., Zhang, Y. J., Eugenin, E. A., Prideaux, B., Daudelin, I. B., Chen, P.-Y., Booty, M. G., & Kim, J. H. 2016. Inflammatory signaling in human tuberculosis granulomas is spatially organized. *Nature Medicine*, *22*(5), 531–538.

Nienaber, A., Hayford, F. E. A., Variava, E., Martinson, N., & Malan, L. (2021). The manipulation of the lipid mediator metabolism as adjunct host-directed therapy in tuberculosis—Frontiers *in Immunology*, *12*, 623941.

Nienaber, A., Ozturk, M., Dolman, R. C., Zandberg, L., Hayford, F. E. A., Brombacher, F., Blaauw, R., Smuts, C. M., Parihar, S. P., & Malan, L. (2021). Beneficial Effects of Long-Chain n-3 Polyunsaturated Fatty Acid Supplementation on Tuberculosis in Mice. *Prostaglandins, Leukotrienes and Essential Fatty Acids*, *170*, 102304.

Organization, W. H. (2022). *WHO Global Task Force on TB Impact Measurement: Report of a Subgroup Meeting on Methods Used by WHO to Estimate TB Disease Burden, 11-12 May 2022, Geneva, Switzerland*. World Health Organization.

Parbhoo, T., Sampson, S. L., & Mouton, J. M. (2020). Recent developments in the application of flow cytometry to advance our understanding of Mycobacterium tuberculosis physiology and pathogenesis. *Cytometry Part A*, *97*(7), 683–693.

Pezzella, A. T. (2019). History of pulmonary tuberculosis. *Thoracic Surgery Clinics*, *29*(1), 1–17.

Ravimohan, S., Kornfeld, H., Weissman, D., & Bisson, G. P. (2018). Tuberculosis and Lung Damage: From Epidemiology to Pathophysiology. *European Respiratory Review*, *27*(147).

Simarmata, R. N. (2023). *Implementasi Kebijakan Peraturan Presiden Nomor 67 Tahun 2021 dalam Penanggulangan Tuberkulosis Paru di RSUD Dr. Pirngadi Kota Medan Sumatera Utara*. Universitas Medan Area.

Suárez, I., Fünger, S. M., Kröger, S., Rademacher, J., Fätkenheuer, G., & Rybniker, J. (2019). The diagnosis and treatment of tuberculosis. *Deutsches Aerzteblatt International*, *116*(43).

Tama, T. D., Adisasmita, A. C., & Burhan, E. (2016). Indeks massa tubuh dan waktu terjadinya konversi sputum pada pasien tuberkulosis paru BTA positif di RSUP Persahabatan tahun 2012. *Jurnal Epidemiologi Kesehatan Indonesia*, *1*(1), 1–8.

Téllez-Navarrete, N. A., Ramón-Luing, L. A., Muñoz-Torrico, M., Osuna-Padilla, I. A., & Chávez-Galán, L. (2021). Malnutrition and tuberculosis: the gap between basic research and clinical trials. *The Journal of Infection in Developing Countries*, *15*(03), 310–319.

THERESIA, T. T. (2016). *PENGARUH JUMLAH CD4 AWAL TERHADAP KESINTASAN 10 TAHUN PASIEN HIV/AIDS*.

Thuraidah, A., Astuti, R. A. W., & Rakhmina, D. (2017). Anemia dan Lama Konsumsi Obat Anti Tuberculosis. *Medical Laboratory Technology Journal*, *3*(2), 42–46.

Wahyudi, D. (2022). *Hubungan Kadar Interleukin 6 Terhadap Konversi Sputum Pada Pengobatan Tuberkulosis Paru= Relation Of Interleukin 6 Levels With Sputum Conversion In The Pulmonary Tuberculosis Treatment*. Universitas Hasanuddin.

Wang, W., Wang, L., Liu, Y., Yang, F., Zhu, L., & Zhang, X. (2019). Value of the monocyte-to-lymphocyte ratio for monitoring tuberculosis therapy. *Canadian Journal of Infectious Diseases and Medical Microbiology*, *2019*, 1, 3270393.

Whitehouse, E. R. 2018. *Cardiovascular risk among patients with drug-resistant tuberculosis and HIV in South Africa*. The Johns Hopkins University.

Wuan, A. O., Sari, N. K. Y., Rogaleli, Y., & Olin, W. (2022). Screening kadar C-Reaktivin Protein pada penderita TB dengan terapi obat anti-tuberculosis di Kabupaten Kupang. *KREATIF: Jurnal Pengabdian Masyarakat Nusantara*, *2*(3), 129–135.

Zhao, J., Peng, W., Wu, S., & Wang, W. (2024). Evaluation of disease activity in systemic lupus erythematosus using the standard deviation of lymphocyte volume combined with red blood cell count and lymphocyte percentage. *Scientific Reports*, *14*(1), 22470.

Zimmer, A. J., Lainati, F., Aguilera-Vasquez, N., Chedid, C., McGrath, S., Benedetti, A., MacLean, E., Ruhwald, M., Denkinger, C. M., & Kohli, M. 2022. Biomarkers Correlating with Active Pulmonary Tuberculosis Treatment Response: A Systematic Review and Meta-Analysis. *Journal of Clinical Microbiology*, *60*(2), e01859- 21.