The Relationship Between Nutritional Status With Neutrophil Levels and Neutrophil Lymphocyte Ratio of Pulmonary Tuberculosis in Ario Wirawan Pulmonary Hospital Salatiga

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Abstract. Malnutrition in tuberculosis patients caused a decreased of immunity system, limited development of lymphoid tissue, decreased plasma complement levels and increased the body's susceptibility to infection and the severity of infection. Tuberculosis infection has the potential to increase the number of neutrophils and decrease lymphocytes in the blood. An increased neutrophil-lymphocyte rasio indicates systemic inflamation, increasing the severity and risk of retreatment for tuberculosis. This research was conducted to determine the relationship between nutritional status and neutrophil levels and neutrophil lymphocyte rasio in pulmonary tuberculosis patients. This study used a cross-sectional research design involving 40 pulmonary tuberculosis patients. Analysis of the relationship between and nutritional status and neutrophil levels using the Pearson Product Moment statistical test. Analysis of the relationship status and neutrophil lymphocyte rasio using the Spearman Rank statistical test. As many as 70% of respondents had severe malnutrition with an BMI average 17.24 ± 2.03 kg/m2. Most respondents (62,5%) hag high neutrophil levels and 72.5% respondents high neutrophil lymphocyte rasio (NLR). Based on Pearson Product Moment statistical analysis, it is known that there is no significan relationship between nutritional status and neutrophil levels with a pvalue 0f 0.213. The correlation coefficient shows a value of -0.201. Spearman Rank statical analysis shows that there is nosignificant relationship between nutritional status and neutrophil lymphocyte rasio (NLR) with a p value of 0.400. The correlation coefficient shows a value of -0.137. In conclusion, there is no relationship between nutritional status and neutrophil lymphocyte rasio (NLR) in this study.

Keywords: Nutritional Status, Neutrophils, Neutrophil Lymphocyte Ratio, Tuberculosis

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1 INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by Mycobacterium Tuberculosis. It is estimated that about a quarter of the global population has had TB [1]. WHO's Global Tuberculosis Report in 2023 reported that Tuberculosis is the second ranks in the cause of death due to infection after coronavirus disease (COVID-19). Malnutrition is a predisposing factor for tuberculosis. Malnutrition can lead to a decrease in the body's immunity, increased susceptibility to infection and an increase in the severity of infection. On the other hand, tuberculosis is the cause of malnutrition, which is caused by low food intake, impaired absorption of nutrients in the intestines, increased basal metabolic needs, increased catabolism processes and increased nutrient needs due to infections [2]. The Global Leadership Conversation Initiative on Malnutrition (GLIM) 2019 states that in determining the identification of malnutrition, indicators used to diagnose malnutrition are needed, namely unexpected weight loss, low BMI, decreased muscle mass, decreased food intake and inflammatory diseases [3].

Malnutrition can cause disturbances in the immune system's defense function in the digestive tract, impaired cytokine production, limited development of lymphoid tissue, decreased plasma complement levels that will affect the elimination of pathogens4. One of the immune system part is neutrophils. Muhammad Harry, 2022 said that one of the abilities of neutrophils as the front line of defense against infection is their movement and ability to infiltrate tissues [5]. In addition to neutrophils, lymphocytes also affect the body's defenses against infections. Lymphocytes can enhance the immune response by direct attack on pathogens (T cells) and through antibodies (B cells) [5]. TB infection can increase the number of neutrophils (neutrophilia) and decrease the number of lymphocytes (lymphocytopenia). An increase in the ratio between neutrophils and lymphocytes/ neutrophilto lymphocyte ratio (NLR) indicates an increase in pro-inflammatory cytokines [6]. Based on this, a study was conducted to determine the relationship between nutritional status and neutrophil levels and neutrophil lymphocyte (NLR) ratios in pulmonary tuberculosis patients in the inpatient room of Lung Hospital dr. Ario Wirawan Salatiga.

2 METHOD

This study used a cross sectional research design which was carried out in March – April 2024 in the inpatient room of the Lung Hospital dr. Ario Wirawan Salatiga. The population in this study was all pulmonary tuberculosis patients. The sample used by 40 respondents with inclusion criteria was adult patients aged 19 – 59 years, nutritional status in the malnutrition category according to the GLIM 2019 criteria: BMI < 20 kg/m2, there was a weight loss of >5% in the last 6 months or 10% after the last 6 months, the patient was examined for handgrip strength, laboratory examination of neutrophil levels and neutrophil ratio of lymphocytes (NLR). The variables in this study were nutritional status, neutrophil levels and neutrophil lymphocyte ratio (NLR). The data collection method in this study is that weight and height data are collected by measuring weight and height using a digital scale measuring device of the Elitech One Station brand with a maximum capacity of 150 kg, and a height measuring of 85 – 210

cm. Hand grip strength data using a CAMRY brand dynamometer handgrip measuring device with a measurement scale of 0.1 kg. Weight loss data was collected through interviews with questionnaire aids. Neutrophil levels and neutrophil ratio of lymphocytes used secondary data from the patient's electronic medical record. The dependent variable is neutrophil level and neutrophil ratio of lymphocytes, while the independent variable is nutritional status. Bivariate analysis of the relationship between nutritional status and neutrophil levels using the Pearson Product Moment statistical test and analysis of the relationship between nutritional status and neutrophil ratio of lymphocytes using the Rank Spearman statistical test with a pvalue of < 0.05. This research has received approval from the Health Research Ethics Commission of the Faculty of Nursing and Health Sciences with No: 192/KE/03/2024 involving tuberculosis patients.

3 RESULTS

The research was conducted in the infectious inpatient room of the Lung Hospital dr. Ario Wirawan Salatiga with a sample of 40 respondents. Data on respondent characteristics including gender, education level, and length of hospitalization are presented in table 1. Univariate analysis including data on nutritional status, weight loss, functional status (hand grip strength), neutrophil levels and neutrophil ratio of lymphocytes is presented in table 2.

Table 1. Subject Characteristics Data

Characteristics	**Frequency (n)**	**Percentage (%)**
Gender		
Men	25	62,5
Woman	15	37,5
Sum	40	100
Education Level		
SD	9	22,5
SMP	11	27,5
High School/Vocational	16	40,0
School	1	2,5
Diploma 3	3	7,5
S1/S2	40	100
Sum		
Employment Status		
Not Working	4	10,0
Farmer	7	15,0
Merchant	6	50,0
Private Employees	20	2,5
Factory Employees	1	2,5
Driver	1	2,5
Guru	1	2,5
Sum	40	100

Table 2. Anthropometric Examination and Laboratory Results

Anthropometric Examination and Laboratory Results	Frequency (n)	Percentage (%)
Nutritional status		
Moderate malnutrition	12	30
Severe malnutrition	28	70
Sum	40	100
(*Mean,* Standard Deviation)	17,24 ± 2,03 kg/m2	
Weight loss for 6 months		
<10%	12	30
>10%	28	70
Sum	40	100
(*Mean,* Standard Deviation)	14.89 ± 8.5%	
Handgrip *strength*		
Lemah	33	82,5
Normal	7	17,5
Sum	40	100
(*Mean,* Standard Deviation)	17,26 ± 7,33 kg	
Up to Neutrofil		
Low (<50%)	3	7,5
Normal (50-70%)	12	30
High (>70%)	25	62,5
Sum	40	100
(*Mean,* Standard Deviation)	72,18 ± 12,68%	
Lymphocyte Neutrophil Ratio		
Low (<0.78)	0	0
Normal (0,78 – 3,53)	11	27,5
Height (>3.53)	29	72,5
Sum	40	100
(*Mean,* Standard Deviation)	7.85 ± 12.36	

Table 3. Relationship Between Nutritional Status and Neutrophil Levels and Neutrophil

	Nutritional Status				Total		*p value*
	Moderate Malnutrition		Severe Malnutrition				
	n	%	n	%	n	%	
Up to Neutrofil							**0.213**
Low	1	2.5	2	5.0	3	7.5	(coefficient correlation - 0.201)
Normal	1	2.5	11	27.5	12	30.0	
High	10	25.0	15	37.5	25	62.5	
Lymphocyte Neutrophil Ratio							**0.400**

Low	0	0	0	0	0	0	(coefficient correlation - 0.201)
Normal	2	5.0	9	22.5	11	27.5	
High	10	25.0	19	47.5	29	70.0	

Based on the results of the data normality test, the nutritional status and neutrophil levels had a normal data distribution with a pvalue of 0.200 (pvalue > 0.05) for nutritional status data, and a pvalue of 0.067 (pvalue > 0.05) for neutrophil level data. The results of the Pearson Product Moment statistical test showed that there was no significant relationship between nutritional status and neutrophil levels in malnourished patients with a pvalue of 0.213 (pvalue > 0.05). Correlation coefficient shows a value of -0.201. Based on the results of the data normality test, the nutritional status and neutrophil ratio of lymphocytes (NLR) had an abnormal data distribution with a pvalue of 0.200 (pvalue > 0.05) for nutritional status data, and a pvalue of 0.000 (pvalue ≤ 0.05) for lymphocyte neutrophil ratio (NLR) data. Statistical test analysis uses the Rank Spearman nonparametric test. The results of the Rank Spearman statistical test showed that there was no relationship between nutritional status and the neutrophil lymphocyte ratio (NLR) in malnourished patients with a pvalue of 0.400 (pvalue > 0.05). Correlation coefficient shows a value of -0.137.

4 DISCUSSION

Based on the data on the characteristics of the respondents, it is known that the percentage of male respondents is greater than that of women, which is 62.5 %. The results of Riskesdas in 2018 showed that 50.5 % of TB patients were male. Men have 2.4 times greater risk factors than women [7]. Men have a greater risk of developing TB because men consume alcohol and tobacco more often (smoking) and behaviors that can affect tuberculosis infection to become an active disease [8]. The average length of hospitalization of pulmonary TB patients with malnutrition was 7.73 ± 2.27 days. The shortest length of stay is 4 days and the longest length of stay is 14 days. Research conducted by Tonko et al shows that the average length of treatment for TB patients in hospitals is 14 days. TB with comorbid clusters such as malnutrition, kahexia, and anemia has a long stay of 20 days, while liver disease and hepatitis have a LOS of 23 days and complications from drugs have a LOS of 20 days [9].

The average body mass index (BMI) of pulmonary TB patients with malnutrition was 17.24 ± 2.03 kg/m2. As many as 70% of respondents had nutritional status in the category of severe malnutrition. Based on the 2019 GLIM criteria, a person is categorized as severely malnourished if they have a BMI of <18.5 kg/m^2 and moderate malnutrition if they have a BMI of <20 kg/m^2. The results of the Magassouba et al study in Guinea showed that 64.7% had a BMI of less than 18.5 kg/m^2 [10]. Another study in a India hospital showed that of 834 respondents with suspected TB and active TB, 87% had undernutrition status (BMI < 18.5 kg/m^2) [11]. TB patients with a low BMI (<18.5 kg/m^2) had an increased risk of death and treatment failure. TB patients are often malnourished due to weight loss, suboptimal protein intake, muscle catabolism caused by inflammation during infection and gastrointestinal symptoms caused by high TNF levels.12 Malnutrition causes nutrient deficiency syndrome that can increase an

individual's risk of developing the disease infection, thereby increasing the likelihood of active TB, increasing the risk of treatment failure, recurrence and death [13].

Most of the malnourished pulmonary TB patients (70% of respondents) experienced a weight loss of >10kg. Research conducted by Warmelink et al., involving 192 active TB patients showed that as many as 85.3% of patients experienced weight loss before receiving TB treatment [14]. Weight loss in patients is related to the immune response and the possibility of cachexia occurring in severe cases [15]. Liu et al In his research, he also explained that chronic inflammation and changes in the endocrine system due to chronic diseases cause decreased appetite, catabolic activity and gastrointestinal disorders resulting in insufficient food intake and significant weight loss. Drastic weight loss is caused by an increase in the process of catabolism before the patient is diagnosed and the rate of basal metabolism (energy expenditure for rest) leads to an increase in energy requirements and in such conditions there is also a decrease in energy consumption due to anorex [16].

The average handgrip strength (HGS) of pulmonary TB patients with malnutrition was 17.26 ± 7.33 kg. Handgrip Strength (HGS) is related to malnutrition according to the MIS (Malnutrition and Inflamatory Score) classification and can be used as a screening tool to identify the risk of malnutrition in patients with inflammation [17]. Prolonged malnutrition processes cause the body to try to maintain body muscle mass and reduce protein use [18]. Handgrip Strength (HGS) is one of the signs of a general and progressive loss of skeletal muscle mass and strength accompanied by a decrease in physical performance [19]. HGS can serve as an indirect indicator of overall muscle grip strength [20]. Weight loss and hand grip strength in patients who started TB treatment were very low compared to after TB treatment, so good nutritional intake support is needed for recovery and improved treatment outcomes [21].

4.1 Relationship between Nutritional Status and Neutrophil Levels and Neutrophil Ratio of Lymphocytes

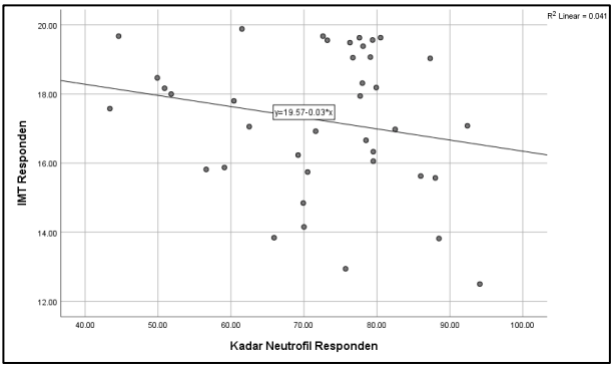

Fig. 1. Relationship between Nutritional Status (BMI) and Neutrophil Levels

The average neutrophil levels of pulmonary TB patients with malnutrition were 72.18 ± 12.68%. An increase in the number of neutrophils indicates a response to

inflammation [22]. In the early phase of infection Mycobacterium Tuberculosis, neutrophils are the most infected white blood cells with granuloma formation or lung damage and high neutrophil counts correlate with mortality, BTA-positive sputum and delayed BTA conversion [23]. Muefong and Sutherland said that neutrophils can be an early indicator of the severity of TB disease [24]. The majority of pulmonary TB respondents had a high neutrophil lymphocyte ratio value (72.5% of respondents). The neutrophil ratio of lymphocytes is associated with the severity of Pulmonary TB and increases the risk of retreatment of Pulmonary TB [25]. Research conducted by Yin et al indicates that NLR (Neutrophil Lymphocyte Ratio) ≥ 2.53 as a risk factor for TB retreatment in addition to a history of smoking, initial cavitation on thorax x-ray and age ≥ 60 years [26]. Other research conducted Miyahara et al Year 2019 suggesting that high NLR values increase the risk of tuberculosis infection. Average NLR in malnourished patients [27].

Moment statistical test showed that there was no significant relationship between nutritional status and neutrophil levels in malnourished patients with a pvalue of 0.213 (pvalue > 0.05). Correlation coefficient shows a value of -0.201. Neutrophil cells are granulocytes that are able to eliminate pathogens that enter the body by phagocytosis and enzyme formation [5]. Neutrophils increase on the first day of infection then their value will decrease. The neutrophil response will increase again after 8-15 days and persist until the end of the infection. This shows that neutrophils play an important role in the early phases of TB infection [27]. Increased neutrophils are a reaction of inflammatory processes mainly caused by bacterial infections [28].

Nutritional status is assessed through measuring body mass index using weight and height indicators. Body mass index is not the only way to classify people as obese or malnourished. Body mass index has limitations in assessing muscle mass [29]. Qurbani et al in 2020, his research revealed that weight is influenced by bones, fat, muscle and other components so that the body mass index does not fully describe the composition of the human body. Body composition consists of body fat, free fat mass, bone minerals and body fluids [30]. Based on the 2019 GLIM Consensus, one of the indicators in the assessment of malnutrition is a decrease in muscle mass. The malnutrition process continues, the body will try to maintain the body's muscle mass and reduce the use of protein by using liposylated fatty acids as an energy source [18]. Fat tissue (adipose) is composed of adipocyte fractions and vascular stromal fractions containing immune cells (macrophages, mast cells, neutrophils, T lymphocytes and B lymphocytes), preadipocytes and endothelial cells that not only act as active metabolic tissues, but also function as immunological organs and contribute to whole-body immune homeostasis [31].

This study showed that the majority of respondents (70% of respondents) experienced a weight loss of > 10% in the last 6 months (severe malnutrition). Weight loss, which is the impact of body fat loss, has the potential to increase the development of active pulmonary TB or latent TB reactivation. Adipose tissue has a role in the pathogenesis of activation and reactivation of TB infection through the mechanism of acute loss of fat cells that increases lung pathology during TB infection with increased load of M. Pulmonary tuberculosis, increased levels of pulmonary macrophages, and

enhances the anti-inflammatory environment, and as a consequence determines the activation and reactivation of TB infection [31].

4.2 Relationship between Nutritional Status and Lymphocyte Neutrophil Ratio

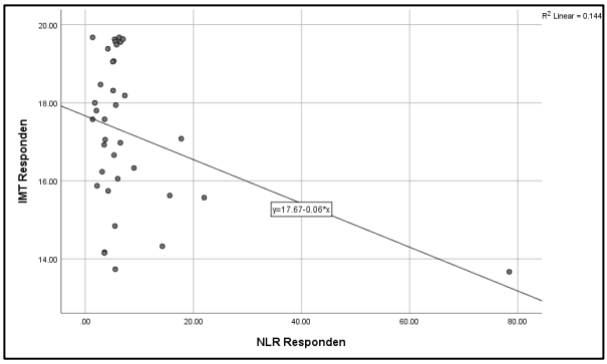

Fig. 2. Relationship between Nutritional Status and Lymphocyte Neutrophil Ratio

Statistical test analysis using nonparametric tests Rank Spearman. Statistical test results Rank Spearman showed that there was no relationship between nutritional status and the ratio of lymphocyte neutrophils (NLR) in malnourished patients to pvalue 0,400 (pvalue > 0,05). Correlation coefficient showed a value of -0.137. This is in line with the results of Anissa's research et al., 2021 which said that there was no relationship between nutritional status and the neutrophil lymphocyte ratio (NLR) in lung cancer patients at the Friendship Hospital [32]. In contrast to the research conducted by Kaya et al Year 2019 showed that NLR was higher in malnourished patients than in patients with normal nutritional status [33]. Malnutrition is related to increased susceptibility of the body to infectious disease infections by affecting pro-inflammatory cytokines and infections can also cause malnutrition due to a decrease in food intake [33].

The immune system can be affected by malnutrition conditions that impact the body's susceptibility to infection. Malnutrition can cause disturbances in the defense function of the immune system in the digestive tract, impaired cytokine production, limited development of lymphoid tissue, decreased plasma complement levels that will affect the elimination of pathogens. Lymphoid tissue functions to produce lymphocytes or white blood cells from progenitor cells such as lymphoblasts [4]. Lymphocyte cells have the ability to activate a specific adaptive immune system against antigens possessed by pathogens. In general, lymphocyte cells are composed of B and T lymphocytes [5]. Lymphocytes, especially T lymphocytes, are important immune cells against TB infection. A high number of lymphocytes is negatively correlated with the severity of TB clinically [23].

The role of lymphocytes in the adaptive immune response and the decrease in total lymphocytes can lead to a weakening of the adaptive immune response resulting in

immune dysfunction. Malnutrition is associated with a decrease in the number of lymphocytes, so patients with malnutrition are at greater risk of developing the disease [15]. The interaction between neutrophils and lymphocytes plays an important role in the innate and adaptive immune response to TB germs [23].The neutrophil ratio of lymphocytes can be used as a reflection of systemic inflammation. Clinical studies show that NLR is not only used as a marker of inflammation but can also be significantly used as a predictor of prognosis for many diseases [33]. Lymphocyte neutrophil ratios are associated with the severity of pulmonary TB and increase the risk of pulmonary TB retreatment [25].

Nutritional status assessed based on weight and height cannot describe fat tissue and fat-free mass. Body weight is divided into two functional components, namely fat mass (composed of adipose tissue) and lean mass (*free fat mass*). Adipose tissue (fat mass) has an important role in energy homeostasis and immunomodulation and can change the risk of infectious and non-communicable diseases. Reduced adipose tissue in TB patients is associated with TB severity and increased mortality [21]. Adipose tissue consists of adipocyte cells and vascular stroma fractions that contain immune cellular components such as macrophages, lymphocytes, neutrophils, eosinophils, mast cells, B cells and others that contribute to the immune response when infection occurs. Clinical research conducted by Ayyappan *et al* year 2019 suggests that although the lungs are the main site of infection *Mycobacterium Tuberculosis*, adipose tissue also serves as an important reservoir for TB bacteria [31]. The loss of fat cells is related to increased load and pathology of TB bacteria in the lungs and can affect Latent TB to active TB (clinical studies show acute fat loss reduces the number of bacteria in the fat tissue, but increases the number of bacteria in the lungs). Weight loss can be one of the indicators of a decrease in fat-free mass and fat mass [31] Clinical studies conducted Ayyappan *et al.* it also showed mice that underwent fat ablation showed active replication of M.Tuberculosis compared to mice without fat ablation. The loss of adipose tissue increases lung macrophage activity and alters inflammatory signals.

5 CONCLUSION

Most of the respondents had nutritional status in the category of severe malnutrition, neutrophil levels and neutrophil ratio of lymphocytes in the high category. In this study, it can be concluded that there is no significant relationship between nutritional status and neutrophil levels and neutrophil ratio of lymphocytes in Pulmonary Tuberculosis patients at dr. Ario Wirawan Salatiga Lung Hospital.

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