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Original Article

Correlation Between Tuberculosis Type and Comorbidities with Nutritional Recovery Rates Post-Tuberculosis Treatment in Pediatric Patients

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Abstract:

Background: Tuberculosis remains a significant cause of mortality in children. Nutritional status is one of the major risk factors for tuberculosis severity. This study investigated the factors influencing nutritional status in tuberculosis patients.

Methods: This is a retrospective, cross-sectional study conducted in the tertiary national-referral hospital in Jakarta, Indonesia. Data were obtained from electronic health records from 2012-2018. This study included patients aged 0-18 years-old who were diagnosed and treated with anti-tuberculosis drugs. Patients who did not complete the therapy for minimum 2 months were excluded.

Results: A total of 207 patients were included in this study. The type of tuberculosis was associated with the nutritional status of children after 2 months of treatment (p value = 0.014; 95% CI = 0.422 - 0.914). Children with extrapulmonary TB showed better improvement in nutritional status compared to those with pulmonary TB. Comorbidities were also associated with nutritional status (p-value = 0.020; CI95% = 1.063 - 2.382). Patient without comorbidities experience better nutritional status improvement than those with comorbidities.

Conclusion: The nutritional status of tuberculosis patients improved after the 2-months of treatment. The type of tuberculosis and the presence of comorbidities influence the outcomes of nutritional status during anti-tuberculosis treatment.

Keywords: children, comorbidities, nutritional status, tuberculosis, types

Introduction

Tuberculosis infection or TB is a disease caused by Mycobacterium tuberculosis bacteria. Tuberculosis remained the world's second leading cause of death in 2022 with 7.5 million people were newly diagnosed with TB, and 12% were children.[1] Reduction in appetite, macro and micronutrient malabsorption, as well as altered metabolism were observed and contributed to wasting in tuberculosis patients. Furthermore, protein and micronutrient deficiency in malnutrition increased vulnerability to infection and potentially exacerbate the disease progression.[2] Previous study revealed that undernutrition increased the risk of tuberculosis severity and adverse treatment outcomes such as delayed recovery, relapse, and mortality.[3] Study in Malawi also showed that patients with moderate-severe malnutrition exhibited higher mortality during the first four weeks treatment, compared to patients with normal nutritional status and mild malnutrition.[4] However, study had also shown that effective treatment of TB improved the nutritional status and subsequently the outcome of patients with TB.[5]

Several factors have been revealed to contribute in the occurrence of tuberculosis and the result of treatment in patient with tuberculosis. Tuberculosis is closely associated with both communicable diseases (CDs) such as diabetes and noncommunicable diseases (NCDs), including HIV/AIDS.[6] Other comorbidities, such as malignancy, heart disease, inflammatory bowel disease, and sickle cell disease have also been observed to increase patients' susceptibility to TB by compromising the immune system.[7] Presence of comorbid conditions were also seen to impact the outcome of TB. Comorbidities such as HIV and diabetes were reported to independently affect the result of TB treatment.[8] Previous studies have also shown that co-infection with HIV caused lower daily intake, nutrient deficiencies, malnutrition, wasting, and severe disease in patient with TB[6, 9]

Another factor that might contribute to tuberculosis and the treatment result is the type of tuberculosis. Studies show that extrapulmonary TB presents a higher mortality rate due to severe forms like miliary or disseminated TB and the higher HIV prevalence.[10]Additionally, study by Kumar et al. revealed that patient with extrapulmonary tuberculosis is associated with successful treatment of tuberculosis.[11] However, study on the success rate of tuberculosis treatment between types of tuberculosis and the relation with nutritional status is still scarce. Considering the potential relationship between nutritional status and factors influencing the success of tuberculosis therapy, this study aimed to examine the relationship between the level of improvement in nutritional status post-treatment with factors affecting the success of tuberculosis therapy in children, particularly on the type of tuberculosis and comorbid conditions.

Methods

This is a retrospective, cross-sectional study conducted in the tertiary national-referral teaching hospital in Jakarta, Indonesia. This study was approved by The Ethics Committee, with the approval number: 0489/UN2.F1.D1/KBK/PDP.01/2018. All data were collected from electronic medical health record. Patient aged 0-18 years old, who were diagnosed and treated with anti-tuberculosis drugs in 2012-2018, were included in this study. Meanwhile, patient with incomplete record of body weight and height, and patient who did not complete the anti-tuberculosis therapy for minimum 2 months were excluded.

Operational definitions of this study were as followed. Pulmonary tuberculosis was defined tuberculosis infection affecting the lung parenchyma, excluding the pleural and lymph nodes of the lung hilum. Extrapulmonary tuberculosis was characterized by tuberculosis infection in organs other than the lungs, including pleura, meninges, pericardium, lymph nodes, bones, joints, skin, intestines, kidneys, and urinary tract. Comorbid conditions were diseases that accompanied the diagnosis of tuberculosis and limited to diseases that impaired the immune system (including HIV/AIDS), autoimmune diseases, heart, lung, liver, and kidney diseases, malignancies, and other conditions that could potentially compromise the patient's nutritional status. Furthermore, this study used weight-per-length for children aged < 2 years old and weight-per-height for children aged > 2 years old, as the indicator for growth and development. The indicators were plotted using WHO chart for children aged up to 5 years old and CDC curve chart for children above 5 years of age. Nutritional status was interpreted by calculating and plotting the percentage of ideal body weight (%IBW) according to the relevant WHO or CDC charts based on the patients' age. The percentage of ideal body weight was calculated using the formula: percentage actual body weight divided by percentage of ideal body weight. An improvement in nutritional status was defined as an increase of 5% or more, while a decrease or smaller increase was categorized as no improvement.

Statistical analysis were conducted using SPSS ver. 24. Chi square test was used to conduct the bivariate analysis, with $p < 0.05$ considered as significant.

Results

A total of 207 pediatric patients were included in this study. Participants were subsequently categorized into 2 different groups based on the type of tuberculosis and the presence of comorbidities. Based on the type of tuberculosis, 109 patients were diagnosed with pulmonary tuberculosis, while 98 were classified as having extrapulmonary tuberculosis. Among the extrapulmonary cases, lymphadenitis tuberculosis was the most common, followed by tuberculosis related to the central

nervous system (e.g., meningitis and meningoencephalitis) and skeletal tuberculosis (e.g., coxitis and spondylitis). Furthermore, 96 out of the 207 patients were found to have comorbidities alongside their tuberculosis diagnosis, with HIV, malignancies, and congenital heart disease being the most prevalent. The demographic characteristics of the study population are presented in **Table 1**.

The nutritional status of the all participants are illustrated in **Table 2** and **Table 3**. Overall, there is a declining trend in the number of patients with malnourished and undernourished nutritional status after 2 months of treatment. Similar trends were also observed regardless of tuberculosis type or the presence of comorbidities, as there was a consistent reduction in the number of malnourished and undernourished patients accompanied with an increase in the number of patients with normal nutritional status after two months of treatment in all groups. Based on the percentage of ideal body weight before and after 2 months of intensive antituberculosis therapy, the average increase in nutritional status after 2 months of treatment was 1.54% in the pulmonary TB group and 4.02% in the extrapulmonary TB group. Patients with extrapulmonary tuberculosis exhibited a 2.5-fold greater increase of %IBW compared to patients with pulmonary TB. Furthermore, the average increase in nutritional status after therapy in groups with or without comorbidities were 1.64% and 3.85%, respectively. Patients without any comorbidities showed a 2.3-fold greater improvement in nutritional status compared to patients with comorbidities.

Table 4 exhibited the association between type of tuberculosis and presence of comorbidities with nutritional status after treatment. The analysis showed a significant difference in the proportion of patient with improved nutritional status between the two groups, with the p-value of 0.014 and 0.020, respectively.

Discussion

The proportion of gender between tuberculosis patient in this study were nearly equal, with 55.1% of the patient were male and 44.9% were female. This aligns with previous studies, which revealed that the prevalence of pediatric tuberculosis was not significantly different between genders. Furthermore, our study reported higher prevalence of pediatric tuberculosis in children above 5 years old. This contrasts with earlier studies that reported a higher prevalence of TB in children under 5 years of age. However, a recent systematic review by Siddalingaiah et al. indicated that tuberculosis is more commonly reported in patients over 5 years of age.[12] This discrepancy could be attributed to the difficulty in obtaining sputum samples from young children, which may impede the diagnostic process in this age group. Moreover, young children often present with non-specific clinical and radiological findings, further complicating the diagnosis in this population.

Table 1. Characteristics of the Participants

Characteristics	Frequency (n (%))
Age (years)*	6.0 (0.3-18.0)
< 5 years old	83 (40.1)
≥ 5 years old	124 (59.9)
Gender	
Male	114 (55.1)
Female	93 (44.9)
Tuberculosis	
Pulmonary	109 (52.7)
Extrapulmonary	98 (47.3)
Extrapulmonary Tuberculosis	
Lymphadenitis	27 (27.6)
Central Nervous System	19 (19.4)
Skeletal	18 (18.7)
Miliary	13 (13.3)
Pleural	9 (9.2)
Abdominal	7 (7.1)
Ocular	6 (6.1)
Cutaneous	4 (4.1)
Pericarditis	4 (4.1)
Laryngeal	1 (1.0)
Orchitis	1 (1.0)
Comorbidities	
Yes	111 (53.6)
No	96 (46.4)
Types of Comorbidities	
HIV	21 (21.9)
Malignancy	13 (13,5)
Heart disease	13 (13,5)
GERD	11 (11,5)
Thalassemia	10 (10,4)
Epilepsy	9 (9,4)
Autoimmune disease	7 (7,3)
Kidney disease	6 (6,3)
Mental retardation	4 (4,2)
Developmental delay	4 (4,2)
Cerebral Palsy	4 (4,2)
Congenital Digestive Tract	3 (3,1)
Malformation	3 (3,1)
Anemia	2 (2,1)
Type 1 Diabetes Mellitus	1 (1,0)
Empyema	1 (1,0)
Bell's Palsy	

Table 2. Nutritional Status Among Pediatric TB Patients Before and After Therapy

Nutritional Status	Total Participant	
	Before Therapy (%)	After Therapy (%)
Malnutrition	22 (10.6)	16 (7.7)
Underweight	72 (34.8)	57 (27.5)
Normal	96 (46.4)	111 (53.6)
Overweight	9 (4.3)	13 (4.8)
Obese	8 (3.9)	10 (4.8)

Table 3. Nutritional Status Among Pediatric TB Patients Before and After Therapy Based on Types of TB and Presence of Comorbidities

Nutritional Status	Types of Tuberculosis				Presence of Comorbidities			
	Pulmonary		Extrapulmonary		Yes		No	
	Before (%)	After (%)	Before (%)	After (%)	Before (%)	After (%)	Before (%)	After (%)
Malnutrition	19 (17.4)	15 (13.8)	3 (3.31)	1 (1.0)	9 (8.1)	6 (5.4)	13 (13.5)	10 (10.4)
Underweight	37 (33.9)	28 (25.7)	35 (35,7)	29 (29.6)	43 (38.7)	30 (27.0)	33 (34.4)	27 (28.1)
Normal	56 (42.4)	58 (63.2)	50 (51.0)	53 (54.1)	50 (45.0)	61 (55.0)	43 (44.8)	51 (53.1)
Overweight	6 (5.5)	5 (4.6)	3 (3.1)	8 (8.2)	3 (2.7)	8 (7.2)	5 (5.2)	5 (5.2)
Obese	1 (0.9)	3 (2.8)	7 (7.1)	7 (7.1)	6 (5.4)	6 (5.4)	2 (2.1)	3 (3.1)

Table 4. Association between Type of Tuberculosis and Presence of Comorbidities with Improvement in Nutritional Status

Parameters	Nutritional Status		RR (95% CI)	p
	Improved	Not Improved		
Type of Tuberculosis			0.621 (0.422 - 0.914)	0.014
Pulmonary	29 (26.6)	80 (73.4)		
Extrapulmonary	42 (42.9)	56 (57.1)		
Presence of Comorbidities				0.020
Yes	46 (41.4)	65 (58.6)	1.591 (1.063 - 2.382)	
No	25 (26.0)	71 (74.0)		

Malnutrition and tuberculosis form a vicious cycle. Malnutrition weaken the immune system and increase the risk of tuberculosis progression, while the inflammatory response in tuberculosis further worsen the nutritional status.[13] Tuberculosis patient often experience anabolic block caused by pro-inflammatory cytokines, which disrupts the use of amino acid for protein synthesis leading to malnutrition.[14, 15] However, studies have shown that the administration of anti-tuberculosis treatment in the first two months improved the nutritional status and can be regarded as a valuable indicator of treatment success, as this phase coincides with the most significant reduction of bacillary load. A study conducted in Vietnam reported that then majority of the weight gain occurs within the first 2 months of treatment.[16] Similarly, our study revealed an improvement of nutritional status in pediatric TB patients after 2 months of intensive treatment. The improvement were also seen across all groups, regardless of the tuberculosis types and existence of comorbidities.

This study found a significant association between nutritional status and both the tuberculosis type and presence of comorbidities. For the type of tuberculosis, extrapulmonary tuberculosis were 0.6 times more likely to experience nutritional status improvement compared to the pulmonary tuberculosis group (RR = 0.621, 95% CI: 0.422 – 0.914), p = 0.014. This finding is consistent with %IBW calculations, which demonstrated a higher increase of nutritional status in the extrapulmonary tuberculosis group compared to the pulmonary tuberculosis group after two months of treatment. This result aligns with the study by Laghari et al., which reported a higher treatment success rate in patients with extrapulmonary tuberculosis compared to those with pulmonary tuberculosis.[17]

Greater improvement in nutritional status among extrapulmonary TB patients in this study may be attributed to the high proportion of extrapulmonary TB cases located in the lymph nodes. In children, many cases of lymph node tuberculosis were the extension of primary TB infections from the apex of the lung or abdomen, with smaller bacterial population.[18, 19] Primary infection of TB differs from secondary infection which commonly found in adults, as secondary TB occurs due to the endogenous reactivation from pre-existing lesion.[19] Thus, in this case, secondary resistance events triggering tuberculosis reactivation in pediatric TB patients is less likely. It is also important to note that the higher success rate in the extrapulmonary tuberculosis group could be influenced by the smaller proportion of subjects in this group (23.1%) compared to the pulmonary tuberculosis group (76.9%). In contrast, the lower improvement in nutritional status among pulmonary TB patients were thought to be due to the persistent cough. Study by Devrim et al. reported a significantly higher incidence of cough symptoms in the pulmonary TB group compared to the extrapulmonary TB group (81.5% versus 36.0%; $p<0.05$).[20] This

persistent cough can interfere with food intake, making it one of the obstacles to improving nutritional status.

For the presence of comorbidities, children with tuberculosis without comorbidities have a 1,6 times greater chance of experiencing improvement of nutritional status during treatment compared to the group of children with tuberculosis and comorbidities (RR = 1,591; 95% CI = 1,063 – 2,382, p = 0.020). Additionally, the most common comorbidities among the participants were HIV (21.9%), malignancies (13.5%), and congenital heart disease (13.5%). The lower improvement observed in patients with comorbidities is postulated to result from the independent effects of each condition on the patients' nutritional status and recovery. Additionally, the presence of these concurrent conditions likely elevates the body's overall energy requirements, thereby compromising the nutritional status of these patients further.[8]

The World Health Organization has reported that HIV prevalence among children with TB ranges between 10-60%.[21] Co-infection of TB with HIV has been reported to cause serious nutritional problems, such as poor eating habits, nutrient deficiencies, malnutrition, and weight loss.[9] Moreover, patients with HIV co-infection were at higher risk to develop disseminated *Mycobacterium tuberculosis* infection, which potentially further exacerbate the existing condition.[18] Study by Ali et al. revealed a significant correlation between stage 4 HIV and CD4 counts <40% with anti-tuberculosis drug induced hepatotoxicity.[22] This condition predominantly occurs during the intensive phase of treatment, making the effective administration of anti-tuberculosis drugs more challenging.[22, 23] Hence, the coexistence of HIV and tuberculosis may disrupt the treatment and recovery process, leading to the poorer improvements in the nutritional status of these patient.

The second leading comorbidities in this study is malignancy, with the majority being hematological malignancies, primarily acute lymphoblastic leukemia and lymphoma. Patient with hematological malignancies experience immune deficiency, which increases their susceptibility to infection and hinders the recovery of TB patients.[24, 25] This immune deficiency potentially caused by the pathogenesis of the disease or the side effect of the treatment such as chemotherapy or stem cell transplantation. Additionally, chemotherapy may trigger side effects such as nausea and vomiting, leading to decreased food intake and affecting the nutritional status.[26]

The third main comorbidities found in this study was heart disease. Among 13 children with heart disease as comorbidity, 10 were diagnosed acyanotic heart disease. In acyanotic heart disease, increased pulmonary blood flow enhances perfusion in the upper lung regions, creating a more aerobic environment that favors the growth of tuberculosis bacteria.[27] Furthermore, the weight of children with acyanotic heart

disease was initially lower compared to those with cyanotic heart disease due to several contributing factors. First, acyanotic heart disease is often accompanied by pulmonary hypertension, which, along with the increased metabolic demands seen in heart disease, especially in cases of heart failure, leads to higher caloric needs and reduced intake.[28, 29] Second, reduced caloric intake due to diminished appetite, malabsorption, eating difficulties caused by dyspnea, lack of energy to eat, and nausea further contribute to poor nutritional status.[28-31]

This study is the first to examine the relationship between nutritional status, tuberculosis type, and the presence of comorbidities in Indonesian children with tuberculosis. However, several limitations should be acknowledged. The research was conducted using a retrospective observational study design, which relied on anthropometric data extracted from medical records rather than direct measurements by the researchers. Consequently, measurement bias may have occurred. Despite this, efforts were made to ensure the anthropometric data used were obtained from the same pediatric pulmonology clinic for both the initial assessment and the follow-up after two months of treatment. Furthermore, due to the lack of height data in many records, the number of subjects meeting the inclusion criteria was limited. As a result, the subjects were selected using non-probability consecutive sampling rather than random sampling.

Conclusion

In conclusion, patients with tuberculosis showed notable improvements in nutritional status after two months of treatment, with a decrease in malnutrition and an increase in good nutritional status. Furthermore, extrapulmonary TB and the absence of comorbidities are associated with greater improvement in nutritional status post-tuberculosis treatment for 2 months. These results highlights the importance of integrating nutritional management with anti-tuberculosis treatment, particularly during the initial two months of therapy, and addressing comorbidities comprehensively.

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Conflict of Interest

None declared.

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