Research Article

Haemoglobin Level and Nutritional Status Changes Among Under-Five Children Treated with Antituberculosis Therapy in Cirebon

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Abstract:

Background: Children with tuberculosis are more susceptible to have anaemia that can lead to immunosuppression. Infectious diseases and nutritional status have a mutual relation influencing each other. However, the evolution of tuberculosis-associated anaemia and undernutrition in children with short-term combination antituberculosis therapy remains poorly quantified. This study aimed at assessing the haemoglobin level and nutritional status changes among under-five tuberculosis patients in Cirebon.

Methods: A prospective cohort study was conducted from June 2016–July 2018 at Kalitanjung Medical Center. Newly diagnosed pulmonary tuberculosis patients aged under five years old initiating standard antituberculosis therapy were recruited. Patients were evaluated by performing history taking, physical examination, and body weight and haemoglobin level measurement before initiation of treatment and were re-examined at the end of treatment.

Results:. Of the 110 children included in the study, mean age was 26.6 months. 56 (50.91%) of them were anaemic, 31 (28.18%) were underweight, and 14 (12.73%) were severely underweight before initiating antituberculosis treatment. Mean hemoglobin pre-treatment was 10.75 g/dl and post-treatment was 11.55 g/dl, with 0.79 g/dl increment (95% CI 0.60404 - 0.9905054, p-value < 0.001). Mean W/A z-score pre-treatment was -1.57 and post-treatment was -0.98, with 0.59 WA/A z-score increment (95% CI 0.4789848 - 0.7046515, p-value < 0.001).

Conclusion: Anaemia and underweight were common in under-five patients with tuberculosis. After six months of therapy, undernourished and anaemic status decreased.

Keywords
Tuberculosis, anaemia, underweight, children

Introduction

Tuberculosis (TB) is an infectious disease of the respiratory system, especially in the lung parenchyma and caused by Mycobacterium tuberculosis. Tuberculosis is the ninth leading cause of death worldwide and is ranked above HIV/AIDS as a cause of death from a single infectious agent [1]. In 2016, there were approximately 1.3 million deaths associated with tuberculosis [2] and an estimated 10.4 million people fell ill from the disease, 56% of them were in five countries: India, Indonesia, China, the Philippines and Pakistan [2, 3]. TB has not only significant impact on child health and under-five morbidity and mortality in areas where it is endemic but also has multiple indirect effects that trap people in a vicious circle of poverty and vulnerability, even facilitating the vertical transmission of other infectious diseases, including HIV [6] [7]. Children with TB are more susceptible to have anaemia that can lead to immunosuppression [8] [9]. Infectious diseases and nutritional status have a mutual relation influencing each other. Pediatric patients with infectious disease and malnutrition have delayed disease recovery and higher morbidity and mortality rates than pediatric patients without malnutrition [4, 5]. The success in coping with TB is expected to become one of the factors that play a role in providing a solution for malnutrition problems arising in Indonesia. However, the evolution of TB-associated anaemia with short-term combination antituberculosis therapy, especially in children remains poorly quantified [10].

Objective

This study aimed at assessing the haemoglobin level and nutritional status changes after six months of standard tuberculosis treatment among under-five tuberculosis patients in Kalitanjung Medical Center, Cirebon, Indonesia.

Methods

The setting of the study population was in the out-patient department of Kalitanjung Medical Center from June 2016 – July 2018. While most of the *patients* were from Cirebon and the *surrounding areas, their* sociodemographic features are very diverse.

The study design used was prospective cohort study with a follow- up period of six months that was also the duration of the tuberculosis treatment, which consists of an intensive phase and maintenance phase. All eligible patients who fulfilled the inclusion criteria were enrolled in the study. Patients were evaluated by performing history taking, physical examination, body weight and haemoglobin level measurement before initiation of treatment and were re-examined at six months of antituberculosis therapy.

Diagnosis of tuberculosis were made based on Indonesian Pediatric Tuberculosis Scoring System which includes household contact, tuberculin skin test result, nutritional state, fever of unknown origin >= 2 weeks, cough >= 3 weeks, lymph node enlargement (axillary, cervical, and inguinal lymph node), joint swelling, and chest X-ray result. Patients were diagnosed with tuberculosis if the scoring is >=6.

Inclusion criteria used was: (1) age 0 – 53 months; (2) newly diagnosed as tuberculosis (TB score>=6); and (3) the parents has signed the informed consent. While the exclusion criteria used was (1) patients with other comorbidities, i.e infectious disease, diabetes mellitus, kidney problem, congenital anomaly, tumor, or other chronic disease; (2) patients taking iron supplementation; (3) patients age >5 years at the end of treatment; (4) patients continued their treatment outside the clinic; and (5) patients who had incomplete or missing data. **C**hild's anthropometric status was measured using standardised methods described by the World Health Organization. Weight was measured to the nearest 10^{th} gram on an electronic scale. The nutritional status indicator used was weight-for-age z-score (W/A z-score). This indicator was calculated and plotted to 2006

WHO Anthro calculator and WHO Child Growth Standards [7, 8, 9]. Classification of the W/A z-score variable the main outcome (dependent variable) were severely underweight (z-score < -3), underweight (z-score ≥ -3 and < -2), normoweight (z-score ≥ -2 and < +2), and overweight (z-score ≥ +2). Based on WHO anaemia definition for under-five, anaemia status pre-treatment was categorized into *no anaemia* (haemoglobin level >= 11 g/dL) and *anaemia* (haemoglobin level < 11 g/dL).

Data were analysed using STATA 15.1 (StataCorp LLC). The W/A z-score was derived using STATA zscore06. The W/A z-score increment was calculated from the difference between W/A z-score pre-treatment and W/A z-score post-treatment. Univariate analysis was done to make some descriptive statistics to show baseline and clinical characteristics of the study population, show the distribution of the data, and importantly measure the prevalence of anaemia and malnutrition pre- and post-treatment. Means of haemoglobin level and W/A z-score (weight-for-age z-score) pre- and post-treatment was measured and analysed using *pair t-test* because the data were coming from the same source of population. Stratified analysis was done using the Mann Whitney test to see how baseline anaemia (pre-treatment anaemia) associated with nutritional status changes. A p-value of < 0.05 is considered as statistically significant.

Results

Of the 110 patients included in the study, 56 (50.91%) were anemic, 31 (28.18%) were underweight, and 14 (12.73%) were severely underweight at diagnosis of tuberculosis. Mean haemoglobin level pre-treatment was 10.75 g/dl and mean haemoglobin level post-treatment was 11.55 g/dl (95% CI 0.60404 - 0.9905054, p-value < 0.001). Mean W/A z-score pre-treatment was -1.57 and mean W/A z-score post-treatment was -0.98 (95% CI 0.4789848 - 0.7046515, p-value < 0.001).

Characteristics (n=110)	**Pre-treatment**	**Post-treatment**
Age	Mean = 26.6 months	
Gender		
Boys	62 (56.36%)	
Girls	48 (43.64%)	
Anaemia status		
Anaemia	56 (50.91%)	32 (29.09%)
No anaemia	54 (49.09%)	78 (70.91%)
W/A z-score		
Severely underweight	14 (12.73%)	3 (2.73%)
Underweight	31 (28.18%)	24 (21.82%)
Normoweight	65 (59.09%)	81 (73.64%)
Overweight	0	2 (1.82%)
Tuberculin skin test		
Positive	103 (93.63%)	-
Negative	3 (2.73%)	-
Not available	4 (3.64%)	-
Chest X-ray		
Lymphadenopathy	(40, 36.37%)	-
Peribronchial infiltrates	(30, 27.27%)	-
Normal	(8, 7.27%)	-
Not available	(32, 29.09%)	-
Edema	0	0

Table 1. Clinical characteristics pre and post-treatment

In the analysis process, patients were categorized into *anaemia* or *no anaemia* based on anaemia status pre-treatment. By using a test for normality (Shapiro-Wilk test), W/A z-score in both categories were shown to be normally distributed (p-value < 0.001). Furthermore, using test for homogeneity (Levene's test) the W/A z-score variances was equal (p-value > 0.05) because the resulting p-value of Levene's test was more than the significance level (0.05). There was no difference between the variances in the population. The obtained differences in sample variances were likely to occur based on sampling from a population with equal variances.

At pre-treatment evaluation, of 56 (50.91%) children with anaemia, 9 (16.07%) of them were severely underweight, 17 (30.36%) were underweight, and 30 (53.57%) were normoweight. Of 54 (49.09%) of them were 5 (9.26%) who were severely underweight, 14 (25.93%) were underweight, 35 (64.81%) were normoweight. These statistics showed that the incidence of undernutrition was higher in children with anaemia at diagnosis than in children without anaemia.

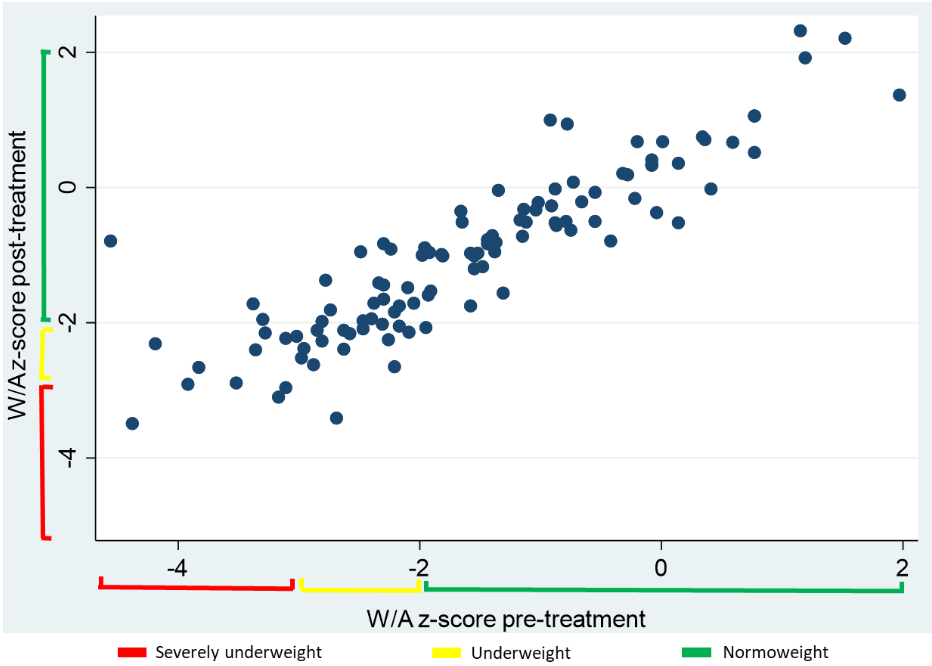

Figure 1. Scatter plot of nutritional status pre- and post-treatment

Mean of W/A z-score increment in children with anaemia was 0.66 (95% CI 0.52 - 0.79, p-value < 0.05) and in children without anaemia was 0.52 (95% CI 0.33 - 0.70, p-value < 0.05). Some children who had anaemia at baseline had recovered at the time of follow-up. Thus, stratified analysis was done based on changes in anaemia status.

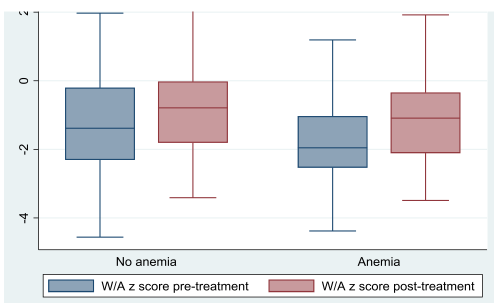

Figure 2. Weight-for-age z-score changes based on anaemia status at baseline.

There were 27 (24.5%) children with anaemia at baseline and remained anaemic at completion of antituberculosis therapy, 29 (26.4%) children with anaemia at baseline and shifted to become non-anaemic at completion of antituberculosis therapy, 5 (4.5%) children without anaemia at baseline and shifted to become anaemic, 49 (44.5%) children without anaemia at baseline and remained non-anaemic. Since the data was not normally distributed, median was used to measure central tendency.

	No anemia > No anemia (n=49)	No anemia > Anemia (n=5)	Anemia > No anemia (n=29)	Anemia> Anemia (n=27)
Median of W/A *z*-score increment	0.43	0.58	0.62	0.53

Table 2. Median of W/A *z*-score increment based on anaemia status at baseline.

The W/A z-score increment was highest in children who were anaemic at baseline then shifted to become non-anaemic at the end of treatment, and lowest in children without anaemia at baseline and remained non-anaemic.

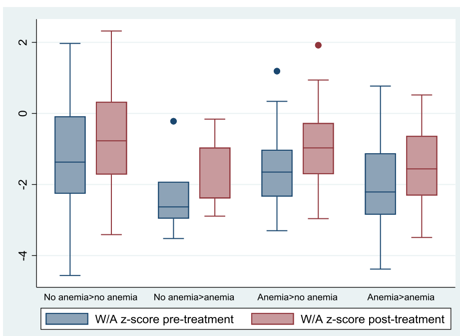

Figure 3. Weight-for-age *z*-score changes based on anaemia status evolution.

Discussion

From June 2016 until July 2018, 110 under-five children who visited Kalitanjung Medical Center met the inclusion and exclusion criteria of the study, consisting of 62 (56.36%) boys and 48 (43.64%) girls. Mean age was 26.6 months old. More than half (59.09%) of the tuberculosis patients were normoweight, and 40.9% had undernutrition. Sidabutar *et al.* found that 168 out of 279 of the TB patients (60.2%) were undernourished.

From their study, 103 subjects (61.3%) were 1–3 years old. However, the study could not discern whether the undernutrition occurred before or after the subjects suffered from tuberculosis [14].

Our study showed that the number of normoweight TB patients increased from 65 (59.09%) at baseline to 81 (73.64%) children at the end of treatment. Furthermore, the number of severely underweight children decreased from 14 (12.73%) to 3 (2.73%), while the number of underweight children decreased from 31 (28.18%) to 24 (21.82%). There was a statistically significant difference in W/A z-score increment (W/A z-score pre- and post-treatment). The mean increment of W/A z-score in all patients was 0.59 (95% CI 0.4789848 - 0.7046515, p-value < 0.001). Mean of W/A z-score increment in children with pre-treatment anaemia was 0.66 (95% CI 0.52 - 0.79, p-value < 0.05) and 0.52 (95% CI 0.33 - 0.70, p-value < 0.05) in children without pre-treatment anaemia. Ninety-nine children (90%) gained weight after six months of antituberculosis therapy, but 11 (10%) patients lost their weight.

Malnutrition and tuberculosis are both problems in most of the developing countries. Tuberculosis can lead to malnutrition and malnutrition may predispose the disease. The pathogenesis of malnutrition occurs through insufficient food intake and metabolism change [15]. Malnutrition in tuberculosis is caused by a decrease in appetite, anorexia, micronutrient malabsorption, cough, and fever, which result in insufficient food intake and metabolism alteration [14] [17]. Poor nutrition leads to protein-energy malnutrition and micronutrients deficiencies, which lead to immunodeficiency that will increase the host's susceptibility to infection and therefore increase the risk for developing tuberculosis. The nutritional status was improved during antituberculosis treatment [17]. Besides infection, several factors influence nutritional status, such as less intake, coinfection, psychological condition, sanitation, and also hygiene [14]. An individual and specific management need to be carried out to improve the nutritional status of the children. Dietary supplementation has yet to suggest significant benefits in children with tuberculosis [18].

Our study found that the mean haemoglobin pre-treatment was 10.75 g/dl and post-treatment was 11.55 g/dl, with 0.79 g/dl mean increment of haemoglobin level in all patients after completing antituberculosis therapy (95% CI 0.60404 - 0.9905054, p-value < 0.001). This result was consistent with previous study conducted by Minchella *et al.* where they found that tuberculosis chemotherapy is associated with significant reductions in anaemia of inflammation [8].

Under-five children with tuberculosis and anaemia would have delayed disease recovery [9], [19]. Anaemia is a common complication of pulmonary tuberculosis. Previous study conducted by Bashir *et al.* found that anaemia was observed in 44 (44%) of pulmonary tuberculosis patients of which 15 (34%) of cases were anaemia of chronic disease, 12 (27%) of cases were iron deficiency, 7 (16%) of cases were iron deficiency anaemia, 2 (5%) of cases were macrocytic anaemia and 8 (18%) of cases were normocytic normochromic anaemia. Anaemia of chronic disease is the most common condition associated with pulmonary TB. Iron deficiency with or without anaemia may contribute to advancing the disease [20]. Although the precise mechanism of anaemia in pulmonary tuberculosis is not known, anaemia of inflammation, as well as anaemia of iron deficiency, has been implicated [16]. In our study, children with anaemia at baseline and shifted to become non-anaemic had the highest increase in W/A z-score after six months of therapy. This finding was associated with previous study conducted by Lee *et al.* showed that initial high haemoglobin was the predictive factor for nutritional status resolution [10]. This probably because the child with anaemia had consumed more iron-containing food or had given iron supplementation unknown from the research investigator, but we could not quantify this variable as it might not entirely be recalled by the parents and recorded by the research investigator. Many medical and non-medical factors influence the study results. Non- medical factors were, among other things, family's food security, changes to the children's diet that the parents made during the course of treatment, adherence to the treatment, as well as parents' educational background and economic status, whereas medical factor was, among other things, unknown coinfection or comorbid.

For future studies, it is recommended to use weight-for-height (W/H) or body mass index-for-age (BMI/A) indicator to assess the nutritional status of the children. 'Underweight' is a composite indicator; therefore, it may be challenging to interpret. Children who have low weight-for-age (underweight) could reflect 'wasting' condition (i.e. low weight-for-height), acute weight loss, 'stunting' condition (i.e. low length/height-for-age), or both [13]. Larger samples with a control group to measure the relationship between anaemia and nutritional status changes and to investigate the urgency of dietary supplementation in tuberculosis-associated anaemia are critically needed.

In conclusion, anaemia is a common haematological abnormality in under-five patients with tuberculosis. Almost half of the subjects were undernourished and anaemic at diagnosis of disease. After six months of therapy, undernourished and anaemic status decreased. Close observation is needed for patients with tuberculosis-associated anaemia to look up for its specific etiology and decide the best management.

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