

## Risk factors for miliary tuberculosis in children

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### Abstract

**Background** Miliary tuberculosis (TB) is a fatal form of tuberculosis with severe clinical symptoms and complications. The mortality rate from this disease remains high, therefore, it is important to identify the risk factors for miliary TB for early detection and treatment.

**Objective** To identify risk factors for miliary tuberculosis in children.

**Methods** A case-control study of children aged 0-14 years with miliary TB was conducted in Dr. Soetomo Hospital from 2010 to 2015. Data were taken from medical records. Case subjects were children with miliary TB, and control subjects were children with pulmonary TB. Patients with incomplete medical records were excluded. Case subjects were identified from the total patient population; control subjects were included by purposive sampling, with case:control ratio of 1:1. Potential risk factors were age, nutritional status, BCG immunization status, and history of contact with TB patients. Statistical analyses were done with Chi-square and logistic regression tests. P values < 0.05 were considered to be statistically significant.

**Results** A total of 72 children were analyzed, with 36 case and 36 control subjects. Nutritional status had a significant association with miliary TB in children (OR 3.182; 95%CI 1.206 to 8.398; P=0.018) in both bivariate and multivariate analyses. The probability of a child with moderate or severe undernutrition developing miliary TB was 76.09%. Other factors were not significantly associated with miliary TB.

**Conclusion** Nutritional status is significantly associated with miliary TB in children, and moderate or severe undernutrition increases the risk for developing miliary TB. [Paediatr Indones. 2017;57:63-6. doi: <http://dx.doi.org/10.14238/pi57.2.2017.63-6>].

**Keywords:** miliary tuberculosis; children; risk factors

Miliary tuberculosis (TB) is caused by hematogenous and lymphatogenous dissemination of *Mycobacterium tuberculosis* bacteria in the body, infecting multiple organs. It accounts for 3–7% of all TB cases.<sup>1</sup> Although there have been few reports on the prevalence of miliary TB in Indonesian children, the Indonesian Ministry of Health reported 1,168 cases of pediatric pulmonary acid-fast bacilli (AFB) positive TB in 2014.<sup>2</sup> The mortality rate from miliary TB is usually around 25%, but may reach 100% if left untreated.<sup>3</sup>

Complications from the disease include respiratory distress syndrome, renal failure, pericarditis, shock, disseminated intravascular coagulation, and acute respiratory failure.<sup>3,4</sup> Miliary TB in children has been closely linked to the pathogenesis of TB meningitis (TBM), the most fatal form of TB. The proportion of children with miliary TB who suffer TBM is larger than that of adults with miliary TB.<sup>4,5</sup>

Some proposed risk factors for developing miliary TB in children have been younger age, malnutrition, lack of BCG immunization, and history of contact with tuberculosis patients.<sup>4,6-8</sup> Since pediatric TB and the severe complications of miliary TB are a health

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problem in Indonesia, we aimed to identify risk factors for miliary TB in children, in order to facilitate early prevention and intervention.

## Methods

We conducted a hospital-based, case-control, retrospective study using secondary data from medical records of pediatric patients admitted to the Division of Respiriology, Department of Child Health, Airlangga University Medical School, Dr. Soetomo Hospital, Surabaya from 2010 to 2015. This study was approved by the Medical Ethics Committee of Dr. Soetomo Hospital, Surabaya, East Java, Indonesia.

Subjects were divided into case and control groups. Children under 14 years of age and diagnosed with miliary TB were selected as case subjects. Children under 14 years of age and diagnosed with pulmonary TB using Indonesian Pediatric Tuberculosis Scoring System<sup>1</sup> with a diagnostic score  $\geq 6$  were selected as control subjects. The scoring system was used only for the control subjects. Children with incomplete medical records were excluded. Cases were taken from the total population of those with miliary TB, while controls were included by purposive sampling, with a case: control ratio of 1:1.

Potential risk factors analyzed were age, nutritional status, BCG immunization status, and history of contact with TB patients. Age was categorized as  $\leq 2$  years or  $> 2$  years. Nutritional status was determined using the weight/height WHO curves for subjects under 5 years or the CDC curves for those over 5 years,<sup>1</sup> according to subject's sex. All data were taken from the medical

records. We performed bivariate Chi-square and multivariate logistic regression analyses using SPSS version 20 software. Results with P values  $< 0.05$  were considered to be statistically significant, with 95% confidence intervals.

## Results

Out of 1,184 TB patients admitted during the study period, 46 had miliary TB. Ten patients were excluded, leaving 36 subjects in the case group. Thirty-six pulmonary TB patients were included as the control group. The characteristics of the subjects are presented in **Table 1**.

**Table 1.** Characteristics of subjects

Characteristics	N=72
Age, n(%)	
< 2 years	25 (34.7)
$\geq 2$ years	47 (65.3)
Nutritional status, n(%)	
Moderate or severe undernutrition	40 (55.6)
Normal	32 (44.4)
BCG immunization status, n(%)	
No	12 (16.7)
Yes	60 (83.3)
History of contact with TB patients, n(%)	
Yes	53 (73.6)
No	19 (26.4)

Bivariate analysis of the possible risk factors showed that only nutritional status was significantly associated with miliary TB in children (OR 3.182; 95%CI 1.206 to 8.398; P=0.018). Age, BCG

**Table 2.** Bivariate analysis of miliary tuberculosis risk factors in children

Variables	Case (n=36)	Control (n=36)	OR	95%CI	P value
Age, n					
< 2 years	16	9	2.400	0.882 to 6.528	0.083
$\geq 2$ years	20	27			
Nutritional status, n					
Moderate or severe undernutrition	25	15	3.182	1.206 to 8.398	0.018
Normal	11	21			
BCG immunization status, n					
No	9	3	3.667	0.902 to 14.901	0.058
Yes	27	33			
History of contact with TB patients, n					
Yes	25	28	0.649	0.225 to 1.871	0.422
No	11	8			

immunization status, and history of contact with associated with miliary TB in children (OR 3.182; 95%CI 1.206 to 8.398; P=0.018). Age, BCG immunization status, and history of contact with TB patients were not significantly associated with miliary TB (Table 2).

Multivariate analysis revealed similar results, with nutritional status as the only significant risk factor of miliary TB in children (Table 3). The probability of a child with moderate or severe undernutrition developing miliary TB was found to be 76.09%.

from active TB disease and TB infection.

We found no statistically significant associations between age, BCG immunization status, or history of contact with TB patients and the incidence of miliary TB in children. However, we suggest that younger age and negative BCG immunization status may also increase the risk of miliary TB, as reported by previous studies.<sup>6,7</sup>

The difference between our findings and those of previous studies may be due to several reasons. First, age in our study may have been affected by the

**Table 3.** Multivariate analysis of miliary risk factors in children

Variables	Coefficient (B)	OR	95%CI	P value
Age	0.702	2.017	0.653 to 6.235	0.223
Nutritional status	1.165	3.204	1.166 to 8.805	0.024
BCG immunization status	0.891	2.437	0.527 to 11.263	0.254

## Discussion

We identified moderate/severe malnutrition as a significant risk factor for miliary TB in children. Similarly, a study in India found that malnutrition was a risk factor for miliary tuberculosis.<sup>4</sup> Also, another study in India found a significant association between nutritional status and the incidence of pulmonary tuberculosis infections.<sup>9</sup> A previous study in Peru also found a significant association between malnutrition and mortality in children with TB.<sup>10</sup> Furthermore, a systematic review of studies in developed countries like the United States, Hong Kong, Finland, and Norway, found a consistent relationship between the incidence of TB and the body mass index (BMI) of the patients, with a 14% increased risk of TB for a decrease of one BMI unit.<sup>11</sup>

The relationship between nutritional status in children and miliary tuberculosis incidence may be explained by Jaganath *et al.* who suggested that nutrient deprivation may have a detrimental effect on Th1 cells, which act as an important component in cell-mediated immune system defense against miliary TB.<sup>12</sup> A previous study reported that cell-mediated immunity is a key factor in host defense mechanisms against the progression of TB infection to active TB disease.<sup>13</sup> Therefore, the compromised cellular immune system in children with undernutrition possibly increases the risk of developing miliary TB

higher prevalence of older pediatric TB patients. A previous study noted that even though an age under 2 years was a risk factor of miliary TB, most children with TB infection in endemic areas were older than 2 years, so there was a higher chance of more children over 2 years suffering from miliary TB.<sup>6</sup> Another study in England and Wales also found more miliary TB in older children, which indicated the possible reactivation of latent disease.<sup>14</sup> Thus, we suggest that miliary TB should be suspected in children of any age. Second, BCG immunization coverage was high in our study. According to a systematic review by Trunz *et al.*, the estimated efficacy of BCG prevention of miliary TB reached 77%, but in Asian countries, there might be an overestimation of the number, due to the inclusion of studies of countries with higher immunization coverage than Asian countries but with lower risk of infection, while Asian countries have higher rate of infection and reinfection despite the high immunization coverage.<sup>15</sup> Moreover, Fine found that the protective effect of BCG was influenced by geographic location, as the protective effect declined in regions closer to the equator.<sup>16</sup> BCG immunization itself should continue to be administered as regulated, but we suggest continuing future study for a better vaccine. Third, the majority of our subjects reported a positive history of contact with TB patients, in contrast to previous studies with more subjects who had no history of contact with TB patients.<sup>8,17</sup>

Therefore, contact tracing is an important task, but the precise relationship between contact and miliary TB needs further study.

A limitation of this study was the use of secondary data which could create a bias in the information we received. We propose future studies with better methodologies, preferably with a prospective design.

In conclusion, moderate/severe malnutrition is a significant risk factor for miliary TB in children. Further study is needed to elucidate the pathogenic mechanism between undernutrition and miliary TB.

### Conflict of interest

None declared.

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