

# Risk Factors of Extrapulmonary Tuberculosis in Children

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# Risk Factors of Extrapulmonary Tuberculosis in Children

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## Abstract

**Background:** Tuberculosis (TB) continues to result in high morbidity and mortality in children from resource-limited settings. Extrapulmonary TB had several of clinical appearance and complications. Hence it is important to identify the risk factors for early detection and treatment. The objective of this study is to identify factors associated with extrapulmonary TB in children.

**Methods:** Observational study conducted at Dr. Soetomo Hospital, Surabaya, Indonesia. Data was collected from medical records of patients who were diagnosed with extrapulmonary TB, aged 1-18 years old in the period of 2010-2018. Data were collected as risk factors were age, nutritional status, BCG (Bacille Calmette-Guerin) immunization status, contact history with adult TB patients, and HIV (human immunodeficiency virus) infection. Each risk factor was analyzed using Chi-square. Risk factors which were statistically significant ( $p < 0,05$ ) would be analyzed using logistic regression.

**Results:** There were 362 patients diagnosed with extrapulmonary TB. More than a half of them are male (50,6%) and >5 years old (52,8%). Most of them already got BCG immunization (72,9%) and had normal nutritional status (73,9%). Lymphadenitis TB, bone/joint TB and miliary TB were the most extrapulmonary TB in this study. Factors associated with extra pulmonary TB were age (PR 0.51; 95% CI=0.38-0.68;  $p < 0.001$ ), nutritional status (PR 3.14; 95% CI=2.29-4.29;  $p < 0.001$ ), and HIV infection (PR 3.66; 95% CI=2.21-6.06;  $p < 0.001$ ). In multivariate analysis, age, nutritional status, and HIV infection were statistically significant associated with extrapulmonary (Exp(B) 1.921; 0.326; 0.274; respectively  $p < 0.001$ ).

**Conclusion:** Age, nutritional status, and HIV infections are risk factors of extrapulmonary TB in children.

**Keywords:** Extrapulmonary Tuberculosis, Children, Risk Factors

## Introduction

Tuberculosis (TB) is an infectious bacterial disease caused by Mycobacterium tuberculosis (MTB), which commonly infects the lungs, but can harm any tissue.<sup>1</sup> World Health Organization (WHO) assumes that there are 133 new TB cases per 100.000 population.<sup>2,3</sup> TB can spread to extrapulmonary with various percentage

of incidence according to the organs involved. It can be life threatening and cause morbidity and mortality.<sup>4</sup> Meningitis TB in one of extrapulmonary TB that can cause death and disability.<sup>5</sup> The greatest impact of extrapulmonary TB infection in children and immunocompromised individuals is the tendency to develop into severe TB.<sup>6</sup>

WHO providing education to the public about TB transmission and BCG (Bacille Calmette-Guerin) immunization to prevent TB infection.<sup>7</sup> Although BCG immunization has been used as a TB prevention, but there are still doubts about its effectiveness in preventing TB.<sup>8</sup> Contact with adult TB patients is considered to be the risk factor for TB in children,<sup>9</sup> therefore WHO recommends screening household contact with TB patients and providing Isoniazid preventive treatment for children.

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Most of the previous studies are about pulmonary TB, meanwhile studies about extrapulmonary TB in children are limited. Therefore, this study aim is to study the risk factors of extrapulmonary TB in children.

## 2 Method

This study was an observational study conducted at Department of Pediatrics Dr. Soetomo General Hospital, Surabaya, Indonesia. The data was collected from medical records of patients who were diagnosed as extrapulmonary TB in January 2010 until December 2018.<sup>13</sup> Patients aged 1-18 years old, diagnosed with miliary TB, meningitis TB, bone/joint TB, lymphnodes TB, tuberculous pleurisy, cutaneous TB, abdominal TB, reticuloendothelial system TB, renal TB, cardiac TB, and disseminated TB, and received anti tuberculosis drugs in Dr Soetomo General Hospital were included in this study. Some data were collected as risk factors: age, nutritional status (for  $\leq 5$  years old using WHO growth chart,<sup>11</sup> and for  $>5$  years old using CDC growth chart<sup>12</sup>), BCG immunization status, contact history with adult TB patients, and HIV infection. Each risk factor was analyzed using Chi-square and the one which were statistically significant ( $p < 0.05$ ) would be analyzed using logistic regression.

## Results

A total 1438 cases of TB were diagnosed during period of January 2010 until December 2018. Among

the total 1438 cases, 423 cases were excluded because of incomplete data, 653 cases were pulmonary TB, and 362 cases were extrapulmonary TB. Extrapulmonary TB incidence in male patients were slightly greater than in female (50.6%). Most of the patient were  $>5$  years old (52.8%), already got BCG immunization (72.9%) and had normal nutritional status (73.9%). The biggest three of extrapulmonary TB in this study were lymphnodes TB (35.9%), bone/joint TB (22.1%), and miliary TB (20.2%) (Table 1). Based on the age group, miliary TB was the most frequent in  $<2$  years old group, meanwhile lymph nodes TB was the most frequent in  $>2$  years old group (Table 2).

Age was associated with extrapulmonary TB (PR 0.51, CI95% 0,38-0,68,  $p < 0.001$ ), malnutrition and HIV infection children were more likely to have extrapulmonary TB (PR 3.14, CI95% 2.29-4.29,  $p < 0.001$  and PR 3.66, CI 95% 2.21-6.06,  $p < 0.001$  respectively) (Table 3). Our subjects were divided into 3 age groups to determine significant risk factor in each group. This study found that malnutrition and HIV infected children were 2-4 times as likely to have significant risk factors of extrapulmonary TB in all age group (Table 4, 5, 6). In multivariate analysis, age, nutritional status, and HIV infection were statistically significant associated with extrapulmonary (Exp(B) 1.921; 0.326; 0.274; respectively  $p < 0.001$ ) (Table 7).

**Table 1. Characteristic of Subjects**

	Extrapulmonary TB (N=362) n (%)	Pulmonary TB (N=653) n (%)
Gender		
Male	183 (50.6)	330 (50,5)
Female	179 (49.4)	323 (49,5)
Nutritional Status		
Normal	242 (66.9)	564 (86,4)
Malnutrition	120 (33.1)	89 (13,7)
Age		
< 2 year old	78 (21.5)	230 (35,2)
2-5 year old	93 (25.7)	140 (21,4)

**Cont... Table 1. Characteristic of Subjects**

> 5 year old	191 (52.8)	281 (43,0)
TB contact		
Yes	179 (49.4)	392 (53,7)
No	183 (50.6)	338 (46,3)
BCG Immunization		
Yes	246 (72.9)	472 (72,3)
No	98 (27.1)	181 (27,7)
HIV Infection		
Yes	19 (5.2)	110 (16,8)
No	343 (94.8)	543 (83,2)

**Table 2. Extra Pulmonary Tuberculosis Incidence based on Age**

	n (%)	Age		
		< 2 year old (n=78) n (%)	2 – 5 year old (n=93) n (%)	> 5 year old (n=191) n (%)
Meningitis TB	27 (2,7)	15 (19.2)	9 (9.7)	3 (1.6)
Bone/ Joint TB	80 (7,9)	7 (9)	24 (25.8)	49 (25.7)
Lymph Nodes TB	130 (12,8)	22 (28.2)	39 (41.9)	69 (36.1)
Tuberculous pleurisy	6 (0,6)	0	2 (2.2)	4 (2.1)
Cutaneous TB	7 (0,8)	1 (1.3)	0	6 (3.1)
Abdominal TB	22 (2,2)	0	5 (5.4)	17 (8.9)
Reticuloendothelial TB	1 (0,1)	0	1 (1.1)	0
Renal TB	3 (0,3)	0	0	0
Cardiac TB	73 (7,2)	0	0	3 (1.6)
Miliary TB	13 (1,3)	27 (34.6)	11 (11.8)	35 (18.3)
Disseminated TB	27 (2,7)	6 (7.7)	2 (2.2)	5 (2.6)

**Table 3. Risk Factors of Extrapulmonary TB**

Risk Factors	Case n (%)	PR	CI 95%	P value
Age < 2 year old > 2 year old	78 (21,5) 284 (82,1)	0.51	0,38-0,68	<0,001*#
Nutritional status Malnutrition Normal	120 (33,1) 242 (66,9)	3.14	2,29-4,29	<0,001*#
BCG immunization Yes No	264 (72,9) 98 (27,1)	0.97	0,73-1,29	0,883 #
Contact with TB patients Yes No	179 (49,4) 183 (50,6)	1.14	0,88-1,47	0,326 #
HIV infection Yes No	19 (5,2) 343 (94,8)	3.66	2,21-6,06	<0,001*#

<sup>13</sup>  
\*p<0.05 was considered statistically significant

#Chi Square test was used

<sup>14</sup>  
(PR = Prevalent Ratio; CI = Confidence Interval)

**Table 4. Risk Factors of Extrapulmonary TB in age group**

Risk Factor	<2 years old group (n=78)				2-5 years old group (n=93)				>5 years old group (n=191)			
	Case n (%)	PR	CI 95%	P value	Case n (%)	PR	CI 95%	P value	Case n (%)	PR	CI 95%	P value
Nutritional status Malnutrition Normal	25 (32,1) 53 (67,9)	3,55	1,90-6,61	<0,001 *#	24 (25,8) 69 (74,2)	2,89	1,43-5,89	0,004*#	71 (37,2) 120 (62,8)	2,95	1,92-4,53	<0,001*#
BCG immunization Yes No	59 (75,6) 19 (24,4)	1,00	0,55-1,82	1,000#	74 (79,6) 19 (20,4)	0,69	0,37-1,29	0,278#	131 (68,6) 60 (31,4)	1,04	0,69-1,55	0,919#
Contact with TB patients Yes No	40 (51,3) 38 (48,7)	1,04	0,62-1,73	0,897#	42 (45,2) 51 (54,8)	1,53	0,90-2,59	0,141#	94 (49,2) 97 (50,8)	1,05	0,73-1,51	0,851#
HIV infected Yes No	4 (5,1) 74 (94,9)	3,78	1,30-10,94	0,008*#	6 (6,5) 87 (93,5)	4,29	1,72-10,74	0,001*#	9 (4,7) 182 (95,3)	3,16	1,49-6,71	0,002*#

<sup>2</sup>  
\*p < 0.05 was considered statistically significant

#Chi Square test was used

(PR = Prevalent Ratio; CI = Confidence Interval)

**Table 5. Multivariate Analysis of Extrapulmonary TB Risk Factors in Children**

Risk Factors	Exp(B)	CI 95%	P value
Age	1,921	1,41-2,62	<0,001*#
Nutritional status	0,326	0,24-0,45	<0,001*#
HIV infected	0,274	0,16-0,46	<0,001*#
Constant	0,754		

\*p<0.05 was considered statistically significant

#Logistic Regression test was used

(CI = Confidence Interval)

Abbreviations and Symbols

AIDS Syndrome	: Acquired Immune Deficiency
ART	: Antiretroviral Therapy
BCG	: Bacille Calmette-Guerin
BMI	: Body Mass Index
CD	: Cluster of Differentiation
CDC and prevention	: Centers for Disease Control and prevention
CI	: Confidence Interval
HIV Virus	: Human Immunodeficiency Virus
INH	: Isoniazid
MTB	: Mycobacterium Tuberculosis
PR	: Prevalent Ratio
OR	: Odd Ratio
TB	: Tuberculosis
WHO	: World Health Organization

## Discussion

In our study, there were 362 extrapulmonary TB patients. Most of our subjects (52.8%) were over 5 years old, and male patients were slightly more frequent (50.6% vs 49.4%). Saraswati et al mentioned that there was association between TB infection and gender, it might be affected by the sexual hormones and the children's lifestyle,<sup>15</sup> immunity response to vaccine, and immunoglobulin related to gender.<sup>16</sup> Among the 362 extrapulmonary TB patients, 2.7% were disseminated TB, 2.7% were meningitis TB, 1.3% were miliary TB, and 72.9% were already got BCG immunization. Although, BCG immunization can provide protection against disseminated TB infection, but it could not give maximum protection against the other types of TB.<sup>15</sup>

In the age group of <2 years old, the three highest prevalence were miliary TB (34.6%), lymphnodes TB (28.2%), and meningitis TB (19.2%). Wallgren in 1948 stated that hematogenous spread occurred 1-3 months after primary infection would develop into TB meningitis and miliary TB in young children,<sup>17</sup> and WHO estimated that more than 50% of TB cases in children younger than 5 years old were disseminated TB.<sup>2</sup> Meanwhile in age group of 2-5 years old and more than 5 years old, lymphnodes TB had the highest prevalence (41.9% and 36.1%, respectively). Previous study found similar results.<sup>18</sup>

In this study, age was associated with extrapulmonary TB (PR 0.51, CI 95% 0.38-0.68, p<0.001). Marais et al mentioned that children aged less than 1 year old had higher prevalence of disseminated TB compared with children aged 1-2 years old and more than 5 years old,<sup>19</sup> because infants' immunity system were different from adults and it could not function properly. Therefore, infants have 5-10 times greater risk of suffering active and severe TB.<sup>20</sup>

This study found that malnutrition was a significant risk factor for extrapulmonary TB in all ages group (PR 2.89-3.55 p<0.05). Other studies has similar result.<sup>3</sup> Immune mechanism against MTB infection is depend on interaction of monocytes, macrophages, T lymphocytes and cytokines in which inadequate nutrition will reduce its interaction.<sup>21</sup> Malnutrition children have less type 1

cytokines (Interleukin-2 and Interferon- $\gamma$ ) which were primary immunity mediators.<sup>22</sup> Changes of these cell-mediated immune could increase the susceptibility to infection. There are many studies about malnutrition and TB, but it is difficult to prove whether malnutrition or TB that precede one another. Weight loss and malnutrition in TB patients can be caused by decreased food intake or factors due to TB disease itself. Altered metabolism of TB can lead to “anabolic blocks,” where food protein is used more for energy production rather than anabolism.<sup>23</sup>

This study showed that BCG immunization status was not associated with extrapulmonary TB. Previous studies found similar result.<sup>24</sup> There are many factors affecting immune response to BCG vaccine, such as where the immunization is done, maternal immunity factors, late BCG vaccine, and others.<sup>25</sup> The cell wall component of BCG vaccine will occupy macrophage receptors as is done by MTB, therefore BCG immunization has no protective effect if it is given to people who have been already infected or sensitized by MTB. Contact with adult TB patient was not associated with extrapulmonary TB in this study. Many factors affect host defense against pathogens including how MTB induce necrosis by destructing mitochondria inner membranes and preventing plasma membrane repairments which is mediated by lysosomal and Golgi. If MTB cannot be killed by innate immunity response, therefore MTB will replicate and spread.<sup>26</sup>

Among the 362 extrapulmonary TB patients, 5% of our subjects had HIV infection and children with HIV infection were 3-4 times as likely to have extrapulmonary TB. Previous studies stated that HIV infection is associated with TB infection on children.<sup>24</sup> HIV infects T CD4+ and macrophage and MTB also mainly infect macrophage in which to eradicate intracellular microbial pathogens. Therefore, low T CD4+ cells will increase risk of TB infection. TB and HIV are chronic and progressive disease which will impair host protection by promoting an immunoregulatory phenotype characterized by an attenuated T cell response and leads to failure of normal homeostatic control of the inflammatory response.<sup>27</sup>

### Conclusion

Age, nutritional status, and HIV infections are risk factors of extrapulmonary TB. Meanwhile BCG immunization and contact with adult TB patients are not

proven as risk factors.

<sup>12</sup>  
**Ethical Clearance** : Approved by Ethical committee in health research Dr. Soetomo General Hospital Surabaya, 0943/KEPK/II/2019

<sup>2</sup>  
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**Conflict of Interest** : there are no conflict of interest

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