

## Research Article

# Tuberculosis in Children with Malignancy

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## Abstract

**Background:** Children with malignancy are at particular risk for tuberculosis (TB) due to immune depression, which is caused by the malignancy and/or the therapy. Nevertheless, there have been limited publications on TB in children with malignancy.

**Objective:** To determine the prevalence of latent TB infection and TB disease among children with malignancy.

**Methods:** We performed a cross sectional study from August 2016 to February 2017 at Dr. Sardjito Hospital, a tertiary hospital in Yogyakarta, Indonesia. All children (0-18 years) who were treated for malignancy in the hospital during the study period were recruited to the study. Children who has been treated or currently being treated for tuberculosis were excluded. All children underwent tuberculin skin test, and those who had one of TB symptoms were investigated further for TB, i.e sputum Xpert MTB-RIF and chest X-ray.

**Results:** A total of 131 children were eligible for the study. Most (120) children did not have any TB symptoms when investigated. Chest X-ray was normal in the majority of the children. Tuberculin skin test was positive in 12 children: five were with acute lymphoblastic leukemia, three with neuroblastoma, one was with acute myeloblastic leukemia, one with non Hodgkin lymphoma, and two were other malignancies. Eleven (8.4%) children were identified to have latent TB infection, and one child was diagnosed with TB disease, that was confirmed by bacteriological examination.

**Conclusion:** TB disease was uncommon among children with malignancies in our setting, but latent TB infection was quite common.

**Keywords:** Malignancy, Tuberculosis, Children

## Introduction

Despite the availability of chemotherapy since the late 1940s, tuberculosis (TB) is still a significant public health concern worldwide. The World Health Organization estimated that 10 million people worldwide had TB disease, in which 1.1 million were in children [1]. Tuberculosis killed 1.5 million people, which makes TB ranks the first as leading cause of death among infectious agents, exceeding HIV infection. Meanwhile, malignancies figure among the leading causes of morbidity and mortality globally, with approxi-

mately 14 million new cases and 8.2 million malignancy related deaths in 2012 [2].

The relationship between TB and malignancy has been acknowledged for many years [3]. Patient with malignancy are at particular risk for TB disease due to depressed cellular immunity, which is caused by the malignancy and/or the therapy. The immune-compromised condition may cause reactivation of latent TB infection or the development of TB disease in recent contact

with an infectious case of TB [4]. It was reported that leukemia and lymphomas are significantly associated with reinfection of mycobacteria [5].

Tuberculosis in children with malignancies is challenging, both for the diagnosis and management. The diagnosis of TB will be more problematic because TB and malignancies may share common symptoms, i.e malaise, weight loss and prolonged fever. The immunodeficiency condition may attenuate clinical symptoms of TB. The result of tuberculin skin test (TST), as an evidence of TB infection, may not reliable due to poor immune response, which leads to false negative result. Long treatment and numbers of pills that should be taken can lead to poor adherence of treatment and higher risk for adverse reactions of the drugs. Prognosis will also be worsened with concomitant disease of TB in children with malignancies.

Despite the risks and problems, there have been limited publications on TB in children with malignancies. We aimed to investigate the prevalence of TB disease and latent TB infection (LTBI) among children with malignancies in Yogyakarta, Indonesia, which is endemic for TB.

## Methods

The study was conducted from August 2016 to February 2017 at Dr. Sardjito Hospital, a teaching and tertiary hospital of Yogyakarta province, Indonesia. All children (0-18 years) who were treated for malignancy in Dr. Sardjito Hospital during the study period were recruited to the study. The child was excluded if had previously been treated or is currently being treated for TB. Written informed consent was obtained from parents. All eligible children underwent history taking, physical examination, and tuberculin skin test (TST). We performed chest X-ray and collected sputum for sputum smear and Xpert MTB/RIF if the child had any of TB symptoms (chronic cough, weight loss, fever > 2 weeks). Based on the results of investigations, the children were diagnosed as having TB disease, latent TB infection or no TB infection or disease (Figure 1).

## Data analysis

The main outcome of this study was the prevalence of latent TB infection and TB disease in children with malignancy that was reported as proportion. Data analysis was conducted using STATA version 12 (Stata Corp., Texas USA).

## Results

A total of 131 children with malignancies were eligible for the study. The majority (68.7%) of the children were with hematologic malignancies, which is acute lymphoblastic leukemia (58.8%),

acute myeloblastic leukemia (6.9%), and chronic myeloblastic leukemia (3.1%). Other malignancies included neuroblastoma (8 children, 6.1%), nephroblastoma (8 children, 6.1%), NHL (3 children, 2.3%), and others malignancies (22 children, 16.8%). The duration of chemotherapy received varied from 0 days to 3 years, with a median of 114 days. History of contact with TB patients was found in five (3.8%) children.

Figure 1: Study procedures.

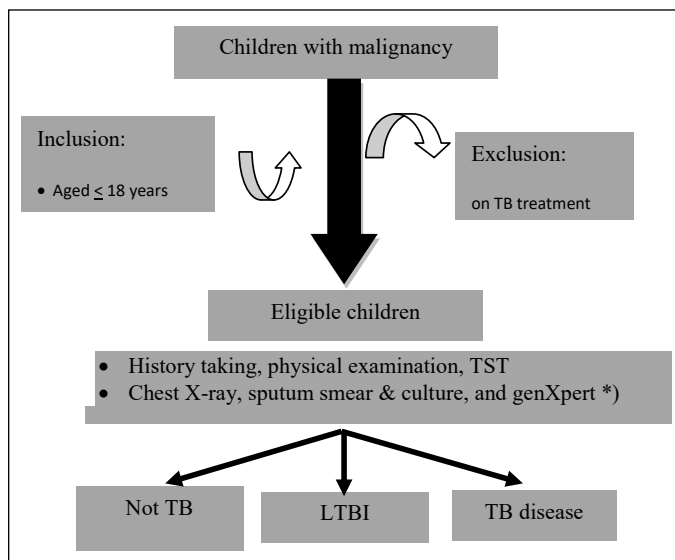
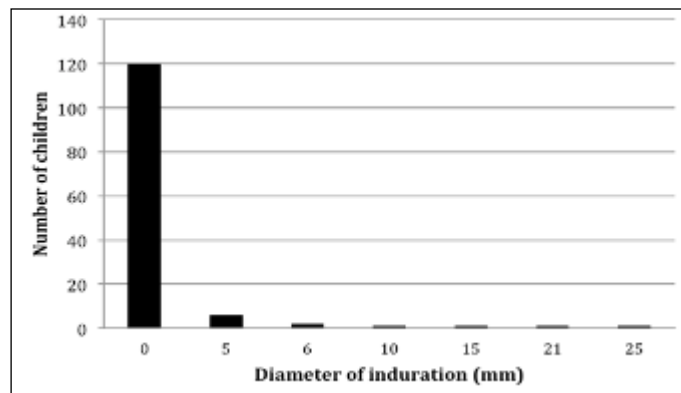


Figure 2: TST induration in children with malignancy.



Most (120) children did not have any TB symptoms when investigated. Among those with symptom, the most common symptom identified was weight loss or inadequate weight gain (45.8%), followed by cough (11.5%), prolonged fever (5.3%) and cervical lymph node enlargement in 4 children (3.1%). Chest X-ray was normal in the majority of the children.

Tuberculin skin test was positive in 12 children, in which most children had a 5 mm induration diameter (Figure 2). Of these

children, five were with acute lymphoblastic leukemia, three were with nephroblastoma, one was with acute myeloblastic leukemia, one was with non Hodgkin lymphoma, and two were other malignancies. Chest X-ray was normal in the majority of the children. Based on the result of investigations, 119 (90.84%) children did not have either TB infection or disease. Eleven (8.4%) children were identified to have TB infection, and one child was diagnosed with TB disease, that was confirmed by bacteriological examination.

### Discussion

Children with malignancy are at risk for TB infection and disease, however our study showed that the majority of the children with malignancy had no TB infection or disease. Prevalence of positive TST in children with malignancy in this study was 9.2%, in which 11 (8.4%) with latent TB infection and one child was identified as having TB disease. A study conducted in Cape Town showed the presence of TB infection in 8.8% of 34 newly diagnosed cancer of children, identified by positive TST. When using interferon gamma release assay of T-SPOT TB, more children (17.6%) had positive result, whereas Quantiferon-TB Gold identified TB infection in the same proportion of the children (8.8%) [6]. A study conducted by Silva et al in Brazil showed that the prevalence of TB in patients with hematologic malignancies was 2.6% with the highest in patients with CLL [5].

Most of the subjects in our study were children with hematologic malignancies (2:1). Nevertheless, there was no difference in the proportion of positive TST between hematologic malignancy and solid tumor (each of 6 subjects). Retrospective studies in the United States with populations of malignant patients of all ages showed that hematologic malignancies have a higher probability of TB diagnosis of 63% than solid tumors (37%) [7,8]. The distinct distribution between the proportion of malignancy type might be caused by several factors namely the age and characteristics of each malignancy are not the same (Table 1).

In the contrary to common bacterial infections, the lower the neutrophil count, the more protective against TB cases. Nevertheless, it could lead to a predisposition to primary TB infection [9,10]. In contrast to these statements, our study showed that of 11 children diagnosed with TB infection, none had neutropenia. Although controversial, previous research had shown that with sufficient quantities of neutrophils, detectable *Mycobacterium* would be eliminated if macrophage and lymphocyte functioned properly [10].

Contact with adult pulmonary TB patients was one of the factors that increase the risk of LTBI in children [11]. There were five chil-

Variable	Total subject	
	n = 131	(%)
Age, mean		
0-4 years	44	(33.6)
5-18 years	87	(66.4)
Sex		
Male	72	(55.0)
Female	59	(45.0)
Nutritional Status		
Underweight	60	(45.8)
Normal or Overweight	71	(54.2)
Type of Malignancy		
Hematology	90	(68.7)
Other malignancies	41	(31.3)
Neutropenia	47	(35.9)
Got BCG vaccination	128	(98.5)
Contact with a TB patient	5	(3.8)

Table 1: Characteristics of the Subjects

dren with close TB contact; one of whom was diagnosed as TB infection. Contacts were obtained from mothers, grandparents and neighbors. Interaction duration of minimum eight hours during the day, almost daily. Research in Canada showed that in the general population of children, 58% of children with positive TST had household contact; while 21% close contact came from neighborhood [12].

A small sample size is one of the limitations of this study, which may not be able to represent all children with malignancy. Another challenge in this study was the limited reference on the population of children with malignancy, so that the sample size calculation was less representative. Determination of immunocompromised conditions could not be done accurately in this study.

### Conclusion

TB disease among children with malignancy in our setting was rare, but the prevalence of TB infection was 8.4%.

### Conflict of Interest

The authors declare that there is no conflict of interest.

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