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Role of Clinical Features and GeneXpert MTB/RIF Assay in Diagnosing Tuberculosis Among Toddler Patients in Surabaya

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Abstract

Tuberculosis (TB) is a leading cause of global morbidity and mortality, mainly in the age of 0-5 years old (toddlers). Several risk factors make toddlers more prone to TB infection. Although it commonly depends on clinical evidence, diagnosis of toddler TB can be done using microbiological confirmation like GeneXpert MTB/RIF Assay. However, this is still challenging to perform due to the low bacterial loads and difficulties in obtaining specimens. While prior studies focused more on the clinical aspects, this study will determine both the clinical and microbiological profiles of toddler TB patients at Dr. Soetomo General Academic Hospital Surabaya. This study was conducted using a retrospective approach. Samples were obtained using a total sampling technique from electronic medical records from January 2018 to September 2023. Variables collected include age, gender, type of TB, BCG vaccination status, history of household contact, nutritional status, symptoms, and GeneXpert MTB/RIF examination specimens and results. Among 125 toddler TB patients, the majority being female (57%), between the ages of 1–2 (45%), had BCG vaccination (86%), and without a history of household contact (63%). Most of the samples were malnourished (56%) and had cough as the symptom (62%). In GeneXpert MTB/RIF examination, gastric aspirate was the most collected specimen (52%) and the most common result found was negative (70%). In addition, two toddler patients were found to have DR-TB. In conclusion, while GeneXpert MTB/RIF assay predominantly resulted in negative, clinical features become the essential evidence to establish a diagnosis of tuberculosis among toddler patients.

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INTRODUCTION

Tuberculosis (TB) is a chronic, infectious disease caused by the species *Mycobacterium tuberculosis* (MTB).[1] Children aged 0-5 years old, also known as toddlers, have a higher risk of experiencing severe disease and mortality due to TB.[1] In 2022, it is estimated that 1-1.2 out of 7.5 million children in the world had progressivity from latent to active TB, more than half of it happened in toddlers.[2] Previous studies stated that in the range of 0-18 years old, TB is commonly found in the age of 0-4 years old due to the immunity system that has not been fully developed.[3,4]

Globally, only 42% of children under five with TB were diagnosed, compared with 70% of adults.[5] Diagnosis of TB can be established clinically or bacteriologically. As for the clinical signs and symptoms, a previous study showed that the majority of TB patients aged toddlers were dominated by males, had a history of household contact, and showed some symptoms such as chronic cough, fever, and lymphadenopathy.[6] Another study explained that the majority of toddler patients who were infected with TB had malnutrition and had not been vaccinated with BCG.[7] In general, toddlers tend to develop nonspecific symptoms similar to other diseases in the age group.[2]

The World Health Organization (WHO) recommends the utilization of rapid molecular tests using GeneXpert MTB/RIF as a screening and diagnostic tool for TB.[2] The result can be shown in two hours, which is shorter in duration than specimen culture, with 100% sensitivity and 95% specificity.[8] In a previous study, it was found that the most collected specimens in the GeneXpert MTB/RIF examination are gastric aspirate, sputum, cerebrospinal fluid, and tissue biopsy, respectively.[9] However, in toddlers, GeneXpert MTB/RIF results often show negative due to the paucibacillary characteristics of the microorganism. In specimen collection, toddlers also had difficulties in producing sputum, making toddler TB more difficult to diagnose and often ignored.[10]

There have not been many studies in Indonesia that discuss the GeneXpert MTB/RIF specimens and results specific to this highest-risk population. However, its sensitivity is lower than that of culture and clinical evidence (48%), making its application in children limited.[11] Based on the explanation above, this study aimed to determine the role of clinical features and GeneXpert MTB/RIF assay in diagnosing TB among toddler patients.

MATERIALS AND METHODS

This was a descriptive study using a retrospective approach. Data were collected from electronic medical records of toddler TB patients at Dr. Soetomo General Academic Hospital Surabaya. Samples in this study were toddlers (age 0-5 years old) who had been diagnosed positive for TB, either clinically or bacteriologically, and given TB treatment. Variables collected consist of age, gender, types of TB, nutritional status, history of household contact, BCG vaccination, symptoms, drug regimen, and the specimen and result of GeneXpert MTB/RIF examination. The inclusion criteria for this study were toddler TB patients in the range of January 2018 to September 2023. The exclusion criterion was patients with incomplete medical records according to the variables of this study. Technique used in this study was total sampling for the medical records of the patient that meet the inclusion criteria. Data were then processed using Microsoft Excel 2019 and presented in frequency distribution tables.

RESULTS AND DISCUSSION

This research was conducted from October 2023 to April 2024 at Dr. Soetomo General Academic Hospital Surabaya, East Java. A total of 125 medical records of toddler TB patients were obtained using total sampling technique according to inclusion and exclusion criteria, as shown in Figure 1. Based on domicile, 64 patients (51%) were from Surabaya and 61 patients (49%) were from outside Surabaya. This represents the role of Dr. Soetomo General Academic Hospital as a tertiary or referral hospital for TB patients.

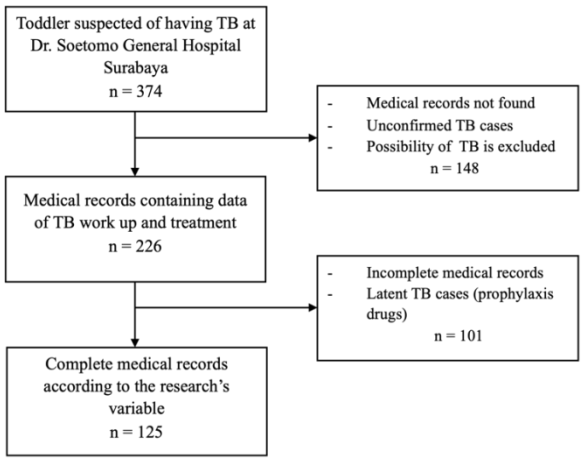

Figure 1. Inclusion and Exclusion Diagram

Figure 2 shows the annual sample amount, which indicates a fluctuation, yet relatively the same from 2018 to 2021. In 2022, there was a drastic surge compared to the year before, reaching the number of 35 samples. The amount kept rising in the period of January–September 2023 with a total of 47 patients. This event might be affected by several factors, such as data transfer from manual to electronic medical records and the COVID-19 pandemic which may affect people's health seeking behavior.

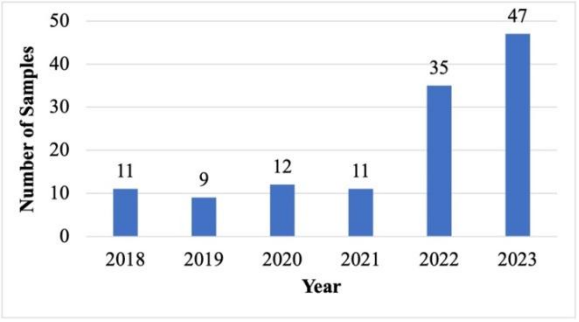

Figure 2. Annual Distribution of Research Samples

Table 1. Clinical characteristics of toddler TB patients

Characteristics	N (%)
Age (n=125)	
<1 years old	31 (25)
1-2 years old	57 (45)
3-5 years old	37 (30)
Gender (n=125)	
Male	54 (43)
Female	71 (57)
Type of TB (n=125)	
Pulmonary	108 (86)
Pulmonary Only	77 (71)
Pulmonary and Extrapulmonary	31 (29)
Extrapulmonary	17 (14)
Bone and Joint TB	8 (47)
Meningitis TB	5 (29)
Lymphadenopathy TB	2 (12)
Abdominal TB	1 (6)
Skin TB	1 (6)
Nutritional Status (n=125)	
Severely Wasted	39 (31)
Wasted	27 (22)
Normal	52 (42)
Possible Risk of Overweight	3 (2)
Overweight	4 (3)
Obese	0 (0)
BCG Vaccination History (n=125	
Yes	108 (86)
No	17 (14)
Contact History (n=125)	
Yes	46 (37)
No	79 (63)
Symptoms	
Cough (n=125)	79 (62)
Weight loss / difficult to gain weight (n=125	50 (39)
Fever (n=125)	64 (50)
Night Sweats (n=125)	4 (3)
Short of Breath (n=125)	32 (25)

Samples were children between the ages of 0 and 60 months old, which then divided into three age groups: <1 year old, 1-2 years old, and 3-5 years old. In this study, most of the subjects were between the ages of 1 and 2 (45%). A study among children aged 0-14 years old in Indonesia revealed the highest amount of TB occurs in the age 1-5 years old.[10] Similar to that, another study found that pediatric TB patients were dominated by patients aged 1-5 years old (52%).[6] Children has a higher mortality and progressivity risk from latent infection to active disease, particularly for those aged under 2, having immunocompromise disease, or with malnutrition.[2,5] The high incidence of toddler TB could be the effect of immature immune system, which affect body's susceptibility to infection.[6] The immune cells in toddlers are inadequately functioning and predominated with Th2, compared to those in older children which are predominated by lymphocytes and Th1. Furthermore, there is a lesser amount of specific CD4+ T cells for MTB ESAT-6 (Early Secretion Antigen Target-6) in toddlers, mainly 0-3 years old, compared to older children (age 3-15 years old).[12]

According to gender, this study found that most toddler patients at Dr. Soetomo General Academic Hospital were female (57%). Prior study in the same hospital showed similar results, with a greater number of females in patients aged 0-4 years old.[3] Meanwhile, a study in Kediri, East Java discovered a higher number in male pediatric TB patients (56%).[6] This phenomenon might be influenced by several factors such as contact history, hormones, and body physiology. At toddler age, estrogens hormone, which acts as a protective factor to improve body immunity, cytokine, and macrophages, has not fully developed. Female tend to have weaker Th1 cells and fewer T CD8 and NK cells, which then makes the inflammation response become more massive.[13] However, a study stated that the greater probability of males developing TB than females were non-significant. Gender can be regarded as a risk factor after a child reach the age of puberty, by the role of sexual hormones in immunological dimorphism. In older age, males are then become more susceptible to TB due to increase exposure to outside world.[14]

Based on the Ministry of Health Republic of Indonesia, patients with pulmonary and extrapulmonary manifestation is classified as pulmonary TB.[15] This study found a higher frequency of pulmonary TB (86%), which linear to the result from prior study in the same hospital within the period of 2013-2017.[3] This primarily occurred due to the role of lungs as the *port d'entrée* of TB. *Mycobacterium tuberculosis* has a high affinity to oxygen and easily transmitted through droplet to enter the alveoli.[16] Bone and joint TB were the most found cases among extrapulmonary TB. This result is similar with a study in Beijing, whereas a study in Italy found peripheral lymphadenopathy TB dominated extrapulmonary cases (34.09%).[17,18] Bone and joint TB in toddlers originate from a primary infection site, typically the lungs or lymph nodes, which disseminates through the bloodstream.[19]

In this study, nutritional status was measured by the parameter of weight and height according to the anthropometric index of the WHO Child Growth Standard.[20] Apparently, from Table 1, most of the samples had normal nutritional status (42%). However, referring to the classification of malnutrition from the WHO, it was found that 56% of the samples had malnutrition. The WHO defined malnutrition as a condition with deficiency, overload, or imbalance of

energy intake and/or nutrition. This includes weight-to-height measurement which resulted in <-2 SD (wasting) or >+2 SD (overweight) based on WHO Child Growth Standard Median.[21] The outcome was different with another study in Sidoarjo, East Java, which found more toddler TB patients with normal nutritional status (32%) than poor nutritional status (27.2%).[16] Adequate nutrition might reinforce the immune system of the body, however this does not absolutely prevent toddler from getting infected with TB.[6] Tuberculosis and malnutrition correlated reciprocally. Malnutrition can increase severity and prolong recovery time from TB. This occurs due to an alteration in immune function, mainly in the interaction between macrophages and T-lymphocytes.[22] In addition, malnutrition can alter drug absorption and its further mechanism, which may cause treatment failure and downstream effects on treatment toxicity.[23] On the other hand, TB cause an increase in basal metabolic rate (BMR) to preserve body function, which then lead to weight loss. At the same time, TB patients often experience a decrease in appetite and gastrointestinal disorder, resulting in malnutrition.[22,24]

As much as 86% of the patients have received BCG vaccination. This result is similar with previous study in Jakarta which showed 80.6% of pediatric TB patients have been vaccinated.[25] In contrast, another study discovered only a small number of pediatric patients (30.8%) with history of BCG vaccination.[26] BCG vaccination has a variety of effectivity, ranging from 0-80%, this explains the probability of getting infected with TB despite having vaccinated before.[27,28] BCG vaccination could prevent the occurrence of severe TB, such as meningitis and miliary TB, and reduce the infection rate of MTB.[29] In young children, BCG vaccination can promote effective containment of the bacteria and protection against TB by increasing Th1 response towards MTB.[30]

Contact history remain an important factor in cases finding. Toddlers can only get infected by TB from a close contact history with either active or latent TB patient, hence it is required to perform history tracing from family and people nearby. In this study, the majority of the samples did not have any contact history (63%). This finding is similar to a study in Jakarta which discovered contact history in only 15.4% of pediatric patients.[26] Conversely, another study found contact history in most of pediatric TB patients (66%).[31] A study in a public health center in Surabaya mentioned that history of contact developed a higher likelihood of TB infection ($p<0.001$).[32] Incidence of toddler TB occurs not only by a single factor of contact history, but it is also influenced by other internal and external risk factors.[10]

Clinical symptoms that appeared the most among patients was cough (62%), followed by fever (50%) and weight loss/difficulty in gain weight (39%). The result was similar to a preceding study by Firnadi on children and adolescent TB patient at Dr. Soetomo General Academic Hospital.[3] Toddlers tend to develop unspecific symptoms that commonly mistaken as other diseases. However, clinical symptoms still become an important factor to establish a diagnosis of TB by using scoring method.[33] The least common symptom found was night sweats, it is linear to another study by Silva which discovered night sweats in only 10.9% of child TB patients.[34]

GeneXpert MTB/RIF Assay is a WHO recommendation for the screening and diagnostic testing of TB.[35] Culture confirmation remains a gold standard for diagnosing TB; however, it requires a longer

Table 2. Specimens and results of GeneXpert MTB/RIF assay

Specimens	Age (years)	GeneXpert MTB/RIF Results			N (%)
		MTB Detected		MTB Not Detected	
		RIF Sensitive	RIF Resistant		
Gastric Aspirate	0	6	0	15	21 (32)
	1-2	4	0	26	30 (46)
	3-5	6	1	7	14 (22)
	Total	**17 (25)**		**48 (75)**	**65 (52)**
Sputum	0	3	0	3	6 (20)
	1-2	4	0	10	14 (47)
	3-5	2	0	8	10 (33)
	Total	**9 (30)**		**21 (70)**	**30 (24)**
Tissue Biopsy	0	0	0	2	2 (13)
	1-2	1	0	3	4 (27)
	3-5	4	1	4	9 (60)
	Total	**6 (40)**		**9 (60)**	**15 (12)**
Cerebrospinal Fluid	0	0	0	1	1 (9)
	1-2	4	0	4	8 (73)
	3-5	1	0	1	2 (18)
	Total	**5 (45)**		**6 (55)**	**11 (9)**
Feces	0	1	0	0	1 (33)
	1-2	0	0	1	1 (33)
	3-5	0	0	1	1 (33)
	Total	**1 (33)**		**2 (67)**	**3 (2)**
Pericardium Fluid	0	0	0	0	0 (0)
	1-2	0	0	0	0 (0)
	3-5	0	0	1	1 (100)
	Total	**0 (0)**		**1 (100)**	**1 (100)**
Total		**38 (30)**		**87 (70)**	**125**

time to grow.[36] In this study, gastric aspirate was the most commonly used specimens (86%), which is in line with a 2018 study in Cipto Mangunkusumo Hospital, Jakarta.[37] GeneXpert MTB/RIF has a high sensitivity and specificity to detect MTB in gastric aspirate specimens of toddler patients.[38] Toddlers are usually facing difficulties in producing sputum, thus gastric aspirate is more frequently used than other specimens.[39]

From the examination, 70% of the specimens resulted in "MTB Not Detected" or MTB negative (Table 2). This was likely due to paucibacillary characteristics of MTB in toddlers. Moreover, toddlers commonly show difficulty in sputum expectoration and tend to swallow sputum during cough.[40] Results of GeneXpert MTB/RIF can be influenced several factors including specimen collection, processing, and storage.

Among 125 samples, two samples were found to have Drug-Resistant Tuberculosis (DR-TB) from the detection of resistance to rifampicin in the examination. From medical records, one patient was written to have Rifampicin-Resistance Tuberculosis (RR-TB) and the other had Multi Drug Resistance Tuberculosis (MDR-TB). Annual pediatric MDR-TB cases are estimated to reach the number of 30,000, yet only less than 5% are confirmed microbiologically.[41]

Rapid molecular test using GeneXpert MTB/RIF can also identify bacterial load using semiquantitative method. Measurement unit was indicated by cycle threshold (Ct) value, which is inversely related to bacterial load inside a specimen. This study found most specimens with very low level of bacteria, which means that the bacteria were found

during Ct >28 (Table 3). Low Ct value indicated a higher number of bacterial loads, and correlates with an increase in clinical severity of the patients.[42] Even with a low volume of specimen, rapid molecular test can still detect MTB DNA and bacterial amount inside specimen.[43] In order to obtain MTB isolates and avoid false-negative result, GeneXpert MTB/RIF is better to be performed together with MTB culture.[40]

Table 3. Bacterial load of the specimens (n=38)

Bacterial Load (based on Cycle threshold (Ct))	**Total N (%)**
Very Low (>28)	12 (31)
Low (22-28)	6 (15)
Medium (16-22)	3 (8)
High (<16)	0 (0)
No Data	17 (46)

The discussions above implied the importance of clinical evidence (signs and symptoms) in TB workup and diagnosis, despite commonly appearing nonspecific. In this study, since most of the patients had negative results in GeneXpert MTB/RIF Assay, most TB patients were diagnosed clinically rather than bacteriologically. As stated in a prior study, clinical signs and symptoms, patient history, and radiography are crucially essential for identifying TB in children, especially when the diagnostic test resulted in negative.[5]

STRENGTH AND LIMITATION

The strength of this study was comprehensive data of TB cases in specific high-risk population, especially the utilization of GeneXpert MTB/RIF as an early screening and diagnostic tool. The limitation of this study were some incomplete medical records which may potentially influence the accuracy of this study's findings. These findings may also differ in other settings or other healthcare system.

CONCLUSIONS

While GeneXpert MTB/RIF assay predominantly resulted in negative, clinical features become the essential evidence to establish a diagnosis of tuberculosis among toddler patients.

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ETHICAL CLEARANCE

The research protocol was approved by Ethics Commissions of the Faculty of Medicine, Universitas Airlangga, Surabaya, with grant number 1495/LOE/301.4.2/X/2023.

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CONFLICT OF INTEREST

All authors have no conflict of interest.

AUTHOR CONTRIBUTION

This study was designed by all authors. Reviewing the literature was done by SAP. Data collection was done by SAP and RAS. Data were analyzed by SAP, RJS, and RAS. Drafting manuscript was done by SAP and SPP. All authors have given approval for publication of this manuscript.

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