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Comparison of Characteristics and Clinical Outcomes of Children with Confirmed Tuberculosis and Unconfirmed Rapid Molecular Test Examination

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ABSTRACT

Background: Making a confirmation of TB diagnosis by bacteriological examination is difficult in children. Currently, the GeneXpert examination is better than AFB examination. However, obtaining a representative specimen is quite difficult in children cause some TB cases are established clinically.
Objective: To analyze the comparison of characteristics and clinical outcomes of children with confirmed tuberculosis by GeneXpert examination with clinical TB.
Method: A case-control study to evaluate the clinical characteristics and outcomes of TB patients aged 0-18 years who underwent GeneXpert examination at Dr. M Djamil Padang from July 2017 to June 2022.
Results: A total of 153 subjects consisted of 24% confirmed TB through GeneXpert examination and 76% were clinical TB. It was found clinical presentations more frequent in confirmed TB than clinical TB in complaints; fever and cough more than 2 weeks, malaise, contact history, did not have BCG immunization, lymph nodes enlargement, radiological features, and prolonged ESR, except for findings rales. Most subjects have recovered of chest X-ray in both groups.
Conclusion: Clinical presentations is more common in confirmed TB than clinical TB except for rales.

Keywords: TB, confirmed TB, clinical TB, clinical characteristic, clinical outcome

INTRODUCTION

Tuberculosis (TBC) is a crucial health problem both in the national or international society. Tuberculosis is known as the second cause of death in the world after the *human immunodeficiency virus* (HIV). Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis* (M.tb), and WHO has determined that one third of the world's population is infected with this bacteri.[1,2] About 70% of tuberculosis infections attacks lungs and the rest are

extrapulmonary, but these findings may vary between one and another country. It is estimated that there were 9.0 million new TB cases in 2013, of the 9 million new TBC cases, 1 million of them were known to be children aged under 15 years.[3]

The diagnosis of pulmonary tuberculosis can be established by clinical manifestations, physical examination, radiographic and bacteriological abnormalities. Based on the American Thoracic Society (ATS) and WHO, a definite diagnosis of pulmonary tuberculosis can be established by finding *Mycobacterium tuberculosis* in sputum or lung tissue culture. However, not all sputum examination came out positive. This may be due to lung disease not related to the bronchi or because the patient is unable to expel phlegm properly. Examination to establish the diagnosis of TB that has long been used around the world is AFB (Acid Resistant Bacilli) in sputum specimens, but the sensitivity and specificity are still low.[4,5]

AFB examination with a light microscope has weaknesses and limitations, which are only able to detect microbacterium if the number of germs is at least 5000 germs/mL. Because of this weakness in AFB examination, causes the need for a fast diagnostic tool, with high sensitivity and specificity.4 Advances in molecular biology have helped increase the ability to detect mycobacterium, namely the invention of the GenXpert MTB RIF Molecular Rapid Test (TCM) tool. Through this new method, WHO has targeted to be able to detect 70% of positive confirmed TB cases and successfully treat 85% of cases. The advantage of this molecular rapid test method is that it can determine resistance to Rifampicin.[6]

Many studies have stated that the examination using the M.tb molecular detection method can be used in children. It is known that the bacteriological diagnosis of TB in children is very difficult, because the clinical picture of TB in children is not specific and X-ray images of children's lungs are difficult to interpret. There are difficulties in carrying out bacteriological confirmation, as well as difficulties in obtaining representative sputum samples.[5,7] However, with the sputum induction method, this sampling has begun to be carried out regularly, so that there are more opportunities to obtain diagnosis with a bacteriological confirmation.[5,7]

RSUP Dr. M.Djamil has had an examination machine for GeneXpert MTB/RIF since 2016. In accordance with the path of diagnosing TB in children issued by the TB Sub-Directorate of the Indonesian Ministry of Health, all pediatric patients suspected of having TB must have their sputum sample examined to obtain a bacteriological diagnosis. RSUP Dr.M.Djamil which is a level 3 referral hospital, accepts patients with suspected tuberculosis with various conditions, ranging from moderate, severe and different comorbidities, and come from various regions and social-economics level. To date, the factors associated with the positive result of GeneXpert MTB/RIF in pediatric TB cases at Dr. M. Djamil is unknown.

In reference to this situation, the writer intended to look for clinical differences and outcomes, as well as factors associated with positive GeneXpert MTB/RIF results.

MATERIALS & METHODS

This study is an analytic case-control study to evaluate the clinical characteristics and outcomes of patients with tuberculosis confirmed by the GeneXpert MTB/RIF survey compared with unconfirmed results. The research was conducted at Dr.M.Djamil Hospital Padang. The time of the research was carried out from September 2022 - November 2022.

The populations of this study were all pediatric patients under the age of 18 who were suspected of having tuberculosis infection and took the GeneXpert MTB/RIF rapid molecular test. The research sample was obtained by collecting data on pediatric patients with tuberculosis who met the inclusion and exclusion criteria. Sample

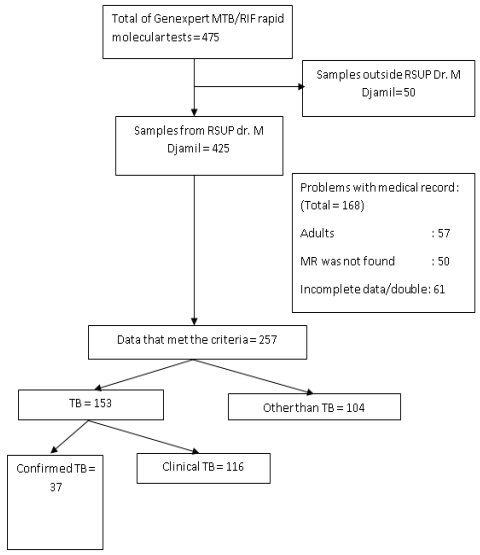
data were obtained from the medical records of patients who had the Gene-Xpert MTB/RIF rapid molecular test from July 2017 to June 2022. The sampling technique used in this study is convenience sampling by utilizing data documented in medical records. The inclusion criteria were children aged 0-18 years who were suspected of having TB and all children diagnosed with TB who had TCM examinations and all pediatric patients diagnosed with tuberculosis with incomplete clinical data and drug-resistant pulmonary TB were excluded. Research permission was obtained from the Research Ethics Committee (REC) of the Faculty of Medicine, Andalas University, Padang.

STATISTICAL ANALYSIS

The data obtained was processed and displayed in the form of tables and graphs. Numerical data were presented in the form of central tendency, namely mean, standard deviation, minimum and maximum values, while categorical data were presented in the form of frequency and percentage tables. Bivariate analysis was analyzed by chi-square method and multivariate analysis was analyzed by binary logistic regression. Data were analyzed using the Statistical Package for the Social Sciences (SPSS) program. The analysis used was univariate analysis, namely the numerical variables are presented in the form of central tendency (mean, SD, median, minimum, and maximum). In the other hand, Tables of frequency and distribution are used to present the categorical variables.

RESULT

The total of GeneXpert MTB/RIF rapid molecular test was 475 tests, 50 of which were carried out with samples requested from outside RSUP dr. M Djamil Padang. And there were 168 adult subjects, duplicate data and medical records were not found. A total of 257 data were examined, obtained as many as 153 research subjects consisting of 37 confirmed TB subjects and 116 clinical TB subjects.



The characteristics of pediatric patients who underwent the GeneXpert MTB/RIF rapid molecular test can be seen in table 1.

Table 1. The characteristics of patient who had the GeneXpert MTB/RIF rapid molecular test

Characteristics	Total (n=257) (f,%)
Gender	
- Male	135 (52,5)
- Female	122 (47,5)
Age	
- 0-5 years old	78 (30,3)
- 5-12 years old	72 (28)
- 12-18 years old	107 (41,6)
Nutritional status	
- Severe	55 (21,4)
- Poor	89 (34,6)
- Good	106 (41,2)
- Overweight - No data	7 (2,7) 7 (2,7)
Vaccine BCG	126 (49)
TB + contact history	
- Present	39 (15,2)
- Not present	171 (66,5)
- Unclear	47 (18,3)

Domicile	
- West Sumatera	202 (79)
- Outside West Sumatera	54 (21)
- No Data	1 (0,4)
TB diagnosis	153 (59,5)
- Confirmed TB	37 (24,1)
- Clinical TB	116 (75,8)

Table 1 shows the differences in age, sex, nutritional status, BCG vaccine history, contact history, and domicile of all patients who underwent the GeneXpert MTB/RIF rapid molecular test. Based on the table, it was found that male sex, age group 12-18 years, and good nutritional status were the highest percentages of the total subjects. Nearly half of the subjects had a history of getting BCG immunization, most of them had no contact history and came from West Sumatra Province.

Comparison of the characteristics of pediatric tuberculosis patients with confirmed and non-confirmed rapid molecular test examinations can be seen as follows.

Table 2. Comparison of the characteristics of pediatric tuberculosis patients with confirmed and non-confirmed rapid molecular test examinations

Characteristics	MTb detected (f, %)	MTb not detected (f, %)	p-value	OR (95% CI)
Gender			0,610	
Male	16 (43,2)	62 (53,4)		
Female	21 (56,8)	54 (46,7)		
Age (years)			0,028*	
0-5	8 (21,6)	41 (35,3)		0,44 (0,18-1,13)
6-12	5 (13,5)	35 (30,2)		0,28 (0,09-0,81)*
12-18	24 (64,9)	49 (38,9)		Ref
Fever > 2 weeks			0,021*	
Yes	30 (81,1)	61 (52,5)		3,10 (1,25-7,38)*
No	7 (18,9)	55 (47,5)		Ref
Cough > 2 weeks			0,035*	
Yes	30 (81,1)	62 (53,4)		2,86 (1,15-7,13)*
No	7 (18,9)	44 (37,9)		Ref
Malaise			<0,001*	
Yes	22 (59,5)	25 (21,5)		4,40 (1,98-9,77)*
No	15 (40,5)	81 (69,8)		Ref
TB + contact history			0,120	
Present	14 (37,8)	23 (19,8)		2,67 (0,95-7,46)
Not Present	15 (40,5)	59 (50,1)		1,28 (0,49-3,36)
Unclear	8 (21,6)	34 (29,3)		Ref
History of BCG immunization, Scar (+)			0,981	
Present	14 (38,9)	49 (42,2)		0,92 (0,42-1,99)
Not Present	22 (61,1)	65 (56,0)		Ref
Nutritional status			0,894	
Severe	11 (31,4)	30 (25,9)		1,11 (0,43-2,83)
Poor	13 (37,1)	42 (36,2)		1,15 (0,47-2,83)
Good	11 (31,4)	49 (42,2)		Ref
Overweight	0	1 (0,9)		N/A
Physical examination				
Crackles	21 (56,8)	87 (75,0)	0,001*	0,23 (0,09-0,54)*
Lymphnode enlargement	14 (37,8)	26 (22,4)	0,050*	2,44 (1,07-5,56)*
Chest X-ray				
Suggestive TB	28 (75,7)	77 (66,3)	1,000	0,98 (0.41-2,37)
Bronchopneumonia	6 (16,2)	13 (11,0)	0,572	1,42 (0,49-4,11)
Pleural effusion	3 (8,1)	2 (1,7)	0,122	4,32 (0,69-26,99)
In normal limit	0	8 (6,9)	N/A	Ref
ESR			0,026*	
<10 mm/hour	2 (5,4)	28 (24,1)		Ref
>10 mm/hour	35 (94,6)	80 (68,9)		5,53 (1,24-24,69)*
Tuberculin test			1,000	
Positive	5 (22,7)	19 (23,5)		0,96 (0,31-3,00)
Negative	17 (77,3)	65 (76,5)		Ref
Associated disease				
Malignancy	3 (8,1)	10 (8,6)	1,000	
Autoimmune	1 (2,7)	9 (7,8)	0,287	
Infection	16 (43,2)	35 (30,1)	0,363	

Others	2 (5,4)	14 (12,1)	0,351	
MTB detected				
Low detected	24 (64,9)			
Intermediete detected	7 ((18,9)			
High detected	3 (8,1)			
No data	3 (8,1)			
Samples Type				
- Sputum	37 (100)			
- Gastric juice	0 (0)			
- CSF	0 (0)			

***p<0,05 significant; N/A, not account; Ref, reference**

Table 2 shows that there were differences in age, fever for more than 2 weeks, cough for more than 2 weeks, malaise, crackles, lymphnode enlargement, and ESR with pediatric tuberculosis patients confirmed by rapid molecular test examination with those which not confirmed (p <0.05). Sequentially significant risk opportunities are ESR > 10 mm/hour with OR = 5.53 (95% CI 1.24-24.69), malaise with OR = 4.40 (95% CI 1.98-9.77), fever more than 2 weeks had OR = 3.10 (95% CI 1.25-7.38), cough more than 2 weeks OR = 2.86 (95% CI 1.15-7.13), lymph node enlargement with OR = 2.44 (95 CI 1.07-5.56), and rank with OR = 0.23 (95% CI 0.09-0.54).

Comparison of the clinical outcomes of pediatric tuberculosis patients with confirmed and non-confirmed rapid molecular test examinations can be seen as follows:

Table 3. Comparison of the clinical outcomes of pediatric tuberculosis patients with confirmed and non-confirmed rapid molecular test examinations

Clinical Outcomes	MTb detected (f, %)	MTb not detected (f, %)	p-value
Chest X-ray			0,041*
Recovered/ in normal limit	7 (19,1)	8 (7,4)	
Unknown/ was not examined	30 (80,9)	85 (92,6)	
Final outcome			0,622
Died	7 (18,9)	15 (20,5)	
Recovered	18 (48,6)	61 (79,5)	
Did not finish the treatment	0 (0)	2 (9,1)	
Unknown	12 (32,4)	38 (25)	

***p<0,05 significant; N/A, not account; Ref, reference**

Table 3 shows that there were differences in chest X-rays with recovered results from pediatric tuberculosis patients confirmed by molecular rapid test examination with those not confirmed (p <0.05), with OR = 6.81 (95% CI 1.25-37.06).

Bivariate selection is carried out to determine candidate variables that can be continued for multivariate modeling, with the condition that p <0.25. The results of the bivariate selection can be seen as follows:

Table 4. Bivariate selection

Variables	p-value
Characteristics	
Gender	0,610
Age (years)	0,028*
Fever > 2 weeks	0,021*
Cough > 2 weeks	0,035*
Malaise	<0,001*
Malignancy	1,000
Autoimmune	0,287
Infection	0,363
Others	0,351
TB + contact history	0,120*
History of BCG immunization, Scar (+)	0,981
Nutritional status	0,894
Crackles	0,001*
Lymph node enlargement	0,050*
Suggestive TB	1,000
Bronchopneumonia	0,572
Pleural effusion	0,122*

ESR	0,026*
Tuberculin test	1,000
GeneXpert MTB/RIF rapid molecular test	N/A
Clinical outcomes	
Chest X-ray	0,041*
Drug resistance	0,571
Final outcome	0,622

Table 4 shows that based on bivariate selection, it is known that the variables included in the multivariate modeling are age, fever for more than 2 weeks, cough for more than 2 weeks, malaise, contact history, rales, lymph node enlargement, pleural effusion, ESR and chest X-ray clinical outcomes. Multivariate modeling can be seen as follows.

Table 5. Multivariate modeling

Variables	B	S.E.	Wald	p-value	OR (95% CI)
Age (0-5 years old)	-0,741	0,650	1,303	0,254	0,48 (0,13-1,70)
Age(6-12years old)	-1,302	0,687	3,591	0,058	0,27 (0,07-1,05)
Fever > 2 weeks	0,977	0,639	2,340	0,126	2,66 (0,76-9,29)
Cough > 2 weeks	0,410	0,623	0,433	0,510	1,51 (0,45-5,11)
Malaise	1,383	0,569	5,915	0,015*	3,99 (1,31-12,16)*
TB + contact history	0,626	0,695	0,812	0,368	1,87 (0,48-7,29)
Crackles	-1,343	0,586	5,244	0,022	0,26 (0,08-0,82)*
Lymph node enlargement	1,075	0,586	3,363	0,067	2,93 (0,93-9,24)
Pleural effusion	1,175	1,523	0,595	0,440	3,24 (0,16-64,09)
ESR	2,203	0,913	5,826	0,016	9,05 (1,51-54,16)*
Clinical outcomes of chest x-ray (recovered)	0,945	1,224	0,596	0,440	2,57 (0,23-28,29)
Clinical outcomes of chest x-ray (in normal limit)	-0,675	0,942	0,512	0,474	0,51 (0,08-3,23)

p<0,05 significant

Table 5 shows that the most influential factor between the characteristics and clinical outcomes of pediatric tuberculosis patients confirmed by molecular rapid test examination is ESR with OR = 9.05 (95% CI 1.51-54.16) followed by malaise with OR = 3.99 (95 % CI 1.31-12.16).

DISCUSSION

There were 257 samples of children with diagnosis of tuberculosis who underwent the GeneXpert MTB/RIF rapid molecular test from July 2017 to June 2022. There were 153 subjects diagnosed with TB with 37 samples (24%) of whom had confirmed TB and 116 samples (76%) were clinical TB. It is known that the bacteriological diagnosis of TB in children has difficulties in obtaining representative sputum samples.[5,8] Clinical TB was found to be higher than GeneXpert MTB/RIF rapid molecular test confirmed TB. Research conducted by Monika Agrawal et al. at the Oncquest Laboratory in India reported that out of 170 samples, there were 42 samples (24.7%) with a positive GeneXpert test.[9] This was also in line with the study conducted by Mulengwa et al, which obtained 297 (26.8%) TB was confirmed by GeneXpert MTB/RIF rapid molecular test from 1110 samples in the group of children and adults.[10] The study conducted by Swaminathan found 201 (7.6%) TB confirmed by bacteriological examination of 2652 TB cases.[11] Studies conducted by Rina Triasih et al obtained 4 confirmed GeneXpert MTB/RIF rapid molecular test samples from 21 TB patients in children suspected TB. [12] TB endemic areas in South Africa.[13] In the age group less than 5 years there are subjects who are still aged 7 months and 8 months, but not because of congenital TB because they do not meet the criteria for congenital TB, namely lesions that appear in the first week of life, primary liver complex or caseous hepatic granuloma, tuberculous infection of the placenta or genital tract infection, the possibility of postnatal transmission has been excluded.[14] It was found that the female sex was more than the male sex in the GeneXpert MTB/RIF rapid molecular test confirmed TB group, but in the clinical TB group the number based on gender was the same.

Based on statistical analysis, there was no relationship between clinical TB or GeneXpert confirmed TB based on gender. Research from Xiaoshan Peng et al found 50.9% of TB sufferers in female children. A study by Mulengwa et al also stated that the number of female patients was more than male in both the clinical TB and GeneXpert MTB/RIF rapid molecular test confirmed TB groups in children and adults. However, these two studies stated that there was no significant relationship in TB cases based on gender.[10,15] However, Noviarisa et al's research on TB patients in children at RSUP dr. M Djamil Padang from 2014 to 2016 found only a third of the patients were female.[16]

Based on the age group, it was found that the group of children aged over 12 years was the largest group who had TB, both GeneXpert MTB/RIF rapid molecular test confirmed and clinical TB. There are difficulties in carrying out bacteriological confirmation in TB patients in children, namely the difficulty in obtaining representative sputum samples.[5,7] This is because the number of *Mycobacterium tuberculosis* in the bronchial secretions of pediatric patients is less because the location of primary pulmonary TB tissue damage is located in the hilar lymph nodes and peripheral lung parenchyma and the difficulty of collecting specimens because of minimal sputum production and cough symptoms are rare in children.[17] Study by Mulengwa et al found 8 TB confirmed bacteriological examination from 23 TB patients under 15 years of age.[10] Study by Swaminathan et al. in children aged 6 months to 12 years, it was 34%.[11] Meanwhile, a study conducted by Noviarisa et al on TB in children aged 0-15 years found that the largest population was in the 5-9 year age group, namely 40%.[16] This is in line with the study conducted by Xiaoshan Peng who found that the average age of children with confirmed TB was 7.1 years.[15]

Fever, cough and malaise are symptoms that are often found in TB disease, both in GeneXpert MTB/RIF rapid molecular test confirmed TB and clinical TB. The frequency of fever for more than 2 weeks, cough for more than 2 weeks, and malaise was higher in GeneXpert MTB/RIF rapid molecular test confirmed TB than in clinical TB. Based on this study, malaise is one of the factors that most play a role in the characteristics and clinical outcomes of pediatric tuberculosis patients with confirmed molecular rapid test examination. Fever for more than 2 weeks, cough for more than 2 weeks, malaise for more than 2 weeks and weight loss or difficulty gaining weight fever is the main complaint of TB infection.[18] The study conducted by Singh et al found complaints of fever, cough, malaise and weight loss in the TB group confirmed by bacteriological examination with M.tb bacterial culture and those that were not confirmed with the frequency of complaints were more frequently found in the TB group. Confirmed TB.[19] A study conducted by Swaminathan et al found symptoms of fever and cough for more than 2 weeks with or without respiratory tract infection as symptoms that are often found in bacteriologically confirmed TB.[11] Report of Rina Triasih et al. complaints of fever and cough are the main complaints when a patient is diagnosed GeneXpert MTB/RIF rapid molecular test confirmed.[12] Noviarisa's research also said fever, cough were complaints that were often found in TB apart from difficulty of gaining weight.[16]

The frequency of contact history of confirmed TB is more than clinical TB. However, no significant association was found between contact history with GeneXpert MTB/RIF rapid molecular test confirmed TB and clinical TB. A history of close contact with TB sufferers is an important point in clinical TB enforcement in children.[18] A study from Xiaoshan Peng et al stated that 88.4% of TB cases claimed to have no history of exposure to previous TB sufferers.82 A study conducted by Swaminathan et al stated 22, 8% of confirmed TB children have a history of

contact with previous TB sufferers.[11] Similarly, research from Noviarisa et al stated that 43.9% had a history of known contact with TB sufferers. Most children with TB infection come from low socioeconomic status which is related to the level of education and low understanding of parents about the transmission of M. TB germs so that it can increase the risk of TB infection in children.[16,20] The study conducted by Singh et al obtained a history of close contact in 31.3% TB confirmed bacteriologically by culture examination of M.tb bacteria and 38.4% of TB not confirmed bacteriologically by culture examination of M.tb bacteria.[19] Research conducted by Jagarnath et al in Uganda and Erkens et al in the Netherlands also found a small portion of the study population had a history of close contact, sequentially 20% and 7%. However, this study stated that it is important to investigate contacts with TB sufferers to identify TB cases, screening and carry out preventive therapy to increase the effectiveness of prevention and efficiency of M.tb. infection management costs. [21–23]

Most of the GeneXpert MTB/RIF rapid molecular test confirmed TB population and clinical TB have a history of not receiving BCG immunization. This is not related to a study conducted by Jaganath et al., in which 80% of the population received BCG immunization with positive scars.[21] Research from Xiaosha Peng et al stated that 24.6% of TB were confirmed to have received the BCG vaccine previously, 43.9% did not receive BCG immunization, while the rest is unknown. History of previous BCG immunization.[15] Research conducted by Jitendra et al showed that 81.3% of cases of TB infection were children who received BCG immunization.[24] BCG protect against TB infection, although its protective ability can differ for each individual.[25] Studies conducted by Singh et al obtained a positive scar picture in 86.3% of TB confirmed bacteriologically by culture of M.tb bacteria and 91.1% of TB not bacteriologically confirmed by culture of M.tb.[19]

The majority of children have a nutritional status with the impression of malnutrition and malnutrition at the initial diagnosis of TB infection, both GeneXpert MTB/RIF rapid molecular test confirmed TB and clinical TB. However, no significant relationship was found between confirmed TB and clinical TB in nutritional status. TB infection is often associated with nutritional problems, especially malnutrition.[26] A study conducted by Noviarisa et al found that 82.8% and 10.1% of children had nutritional status with the impression of malnourished and malnutrition at the initial diagnosis of TB.[16] Study by Swaminathan et al. it was found that 41% of children with TB infection experienced weight loss.[11] Conditions of nutritional disorders increase the risk factors for respiratory tract infections including TB infection. Improving nutritional status will also improve immunity against TB infection.[27]

Physical examination in both groups revealed crackles in the majority of samples in both groups. Crackles are more common in clinical TB than GeneXpert MTB/RIF rapid molecular test confirmed TB. There was a significant relationship between the two groups with the findings of crackles on physical examination. The findings of crackles on physical examination are not always found in TB infection in children. Crackles can also appear due to comorbid disease such as pneumonia in children. The initial appearance of the acute phase of TB disease is indistinguishable from pneumonia. The study by Roya-Pabon et al found TB to be the most common differential diagnosis or co-infection in pneumonia.[28]

Lymph node enlargement was found in GeneXpert MTB/RIF rapid molecular test confirmed TB and clinical TB. It was found that 37.8% of TB were confirmed with enlarged lymph nodes and 20% of clinical TB had enlarged lymph nodes. The physical examination that is most often found in TB infection is lymph node enlargement. [7,29] Research by Jaganath et al found lymphadenopathy cases as much as 28% of

all TB cases in children.[21] Another study conducted by Swaminathan et al found lymphadenopathy cases by 47% of 201 TB cases were confirmed. [11] Research by Noviarisa et al at Dr. M Djamil General Hospital found lymph node enlargement in 11.6% of 198 TB cases in children.[16] Study by Singh et al found lymph node enlargement in 27.4% TB confirmed bacteriologically by culture M.tb bacteria and 29.2% in TB not bacteriologically confirmed by culture of M.tb bacteria. Radiological images also show the presence of enlarged perihilar lymph nodes on a chest X-ray image of a child suffering from pulmonary TB.[19]

Result of suggestive of TB was found on chest X-ray examination in both groups, 75.7% in confirmed TB and 76% in clinical TB. Other features found on the chest X-ray are bronchopneumonia, pleural effusion and chest X-ray images within normal limits. TB in children does not give a specific picture on chest radiographs.[28] Diagnosis of TB through radiological imaging is not easy because the characteristics found in TB can resemble other diseases. Conversely, a normal chest X-ray cannot rule out a clinical diagnosis of tuberculosis in a patient if other investigations support it. Therefore, except for miliary tuberculosis, chest radiograph alone cannot diagnose tuberculosis. Nonetheless, chest x-ray examination is useful in making the diagnosis, evaluating treatment and detecting TB infection.[7,30-32] There are several general features that indicate pulmonary tuberculosis. These radiographic features include hilar or paratracheal gland enlargement with or without infiltrates, segmental or lobar consolidation, miliary, calcification with infiltrates, atelectasis, cavities, pleural effusion, and increasing tuberculoma. The most common radiological abnormalities found in children include enlarged lymph nodes (90-95%), especially on the right paratrachea in the hilus.[33] A study by Noviarisa et al found a picture suggestive of TB in 92.4% of TB cases in children at dr. M Djamil Padang in 2014-2016.[16]

ESR values were found to be prolonged in the majority of TB cases in both groups. A higher frequency of ESR was obtained in the GeneXpert MTB/RIF rapid molecular test confirmed TB group compared to clinical TB. Based on this study, prolonged ESR is the most important factor in the characteristics and clinical outcomes of pediatric tuberculosis patients confirmed by molecular rapid test. The blood test that is often used in diagnosing TB infection is the ESR. ESR is often found to be increased in active TB patients, but a normal ESR cannot rule out pulmonary TB.[34] Research by Min et al found an increase in ESR in cases of latent TB with a cut-off value of 31 mm/hour. 100 Research by Yousuf et al also showed an increase in ESR in 87% of TB was confirmed bacteriologically by examining M.tb culture with an average value of 77.7 mm/hour in pulmonary TB.[35] This was also supported by the results of a study by Yaranal et al., who found an increase in ESR in 99% of TB cases. [36]

Negative tuberculin test were found in the majority of the population in both groups. There was no significant and significant difference regarding the value of the tuberculin test between clinical TB and GeneXpert MTB/RIF rapid molecular test confirmed TB in this study. The tuberculin test is an additional test to detect tuberculosis infection in children. The sensitivity and specificity of this examination are very high, especially in determining the presence or absence of tuberculosis infection in children. However, the drawback of the tuberculin test is that it cannot differentiate between latent and active TB infection, and false-negative results can occur due to anergy. In addition, the tuberculin test can give false positive results due to cross-reactivity with Bacillus Calmette Guerrin (BCG) and other mycobacterial infections. [7,37] A positive tuberculin test result only indicates infection and does not indicate the presence or absence of tuberculosis. Conversely, a negative result does not necessarily rule out a TB diagnosis.[18] In addition to false

positive results, the tuberculin test will also show false negative results in cases of immunodeficiency, immunosuppression, malnutrition, and examination errors.[38] WHO has recommended the tuberculin test as the main diagnostic test and should not be replaced by the interferon test. The tuberculin test in children has a sensitivity and specificity of 86% and 92%.[18,38,39] Different form research by Xiaoshan Peng et al., found 64,9% cases of TB in paediatric had positive tuberculin test result.[15] Research by Swaminathan et. al., also obtained positive result in 79% of TB was confirmed bacteriologically in children.[11] Jaganath et al also obtained positive tuberculin test results in 65% of TB cases in children.[27]

There were 48 subjects (31%) out of 153 subjects who did not have tuberculin test data. The group that was not tested for tuberculin consisted of 16 subjects (43%) in the confirmed TB group and 32 patients (28%) in unconfirmed TB who did not have tuberculin test data. The study by Xiaoshan Peng et al found 15.7% of the total cases did not have tuberculin test data, 2.1% of which were TB confirmed by GeneXpert MTB/RIF rapid molecular test.[15] Studies from Jaganath et al and Swaminathan et al had 35% and 21% respectively the subject did not have tuberculin test data. [11,21] In contrast to Singh et al, they carried out a tuberculin test on all of their study subjects.[24]

Common co-morbidities found in this study were infections-related diseases as well as malignancies and autoimmune diseases in both GeneXpert MTB/RIF rapid molecular test confirmed TB and clinical TB. However, no relationship was found between TB infection and the types of comorbidities that occurred. A study conducted by Swaminathan et al found that recurrent respiratory infections often occur in TB patients.[11] In addition to malignancy and autoimmune disease, children are in an immunocompromised condition, so they have a higher risk of developing TB infection compared to the general population. In immunocompromised children, it is necessary to investigate TB and perform TST. [40-43] Other immunocompromised conditions that can increase the risk of TB infection are HIV infection.[16]

All GeneXpert MTB/RIF rapid molecular test confirmed TB subjects used sputum specimens. GeneXpert MTB/RIF rapid molecular test can also use lung and extra-pulmonary specimens. Specimens that have been tested include pleural fluid, lymph node biopsies, ascitic fluid, cerebrospinal fluid, pericardial fluid, skin biopsies, and urine specimens.[44-47] Test results for GeneXpert MTB/RIF rapid molecular extra-pulmonary test specimens have sensitivity 52.1% with a specificity of 100% each.[46] GeneXpert MTB/RIF rapid molecular test using lung specimens such as sputum has better sensitivity. Specimens used for GeneXpert such as sputum and also BAL (Bronchoscopy and Bronchoalveolar Lavage). Research conducted by Monika Agrawal et al. at the Oncquest Laboratory in India reported that out of 170 samples, there were 42 samples (24.7%) with a positive GeneXpert test. The GeneXpert MTB/RIF TCM test in a study with sputum and BAL specimens with a sensitivity of 100% and 81.4%, with a specificity of 90% and 93.4%.[9] Mulengwa et al.'s study obtained 297 subjects of all ages who were examined for the GeneXpert MTB/RIF rapid molecular test, all use sputum specimens with sensitivity and specificity above 90% even though the sputum is was mixed with saliva and blood.[10] Stool is one of the specimens that have been used as GeneXpert MTB/RIF rapid molecular test specimens. The use of stool specimens can also aid in the bacteriological diagnosis of TB, several studies have examined the sensitivity or specificity of the GeneXpert MTB/RIF rapid molecular test when using stool samples. Nicol et al reported that the GeneXpert MTB/RIF rapid molecular fecal test detected MTB in only 47% of samples from children with culture-confirmed pulmonary TB. Meanwhile Walters et al

reported that GeneXpert MTB/RIF rapid molecular test analysis with stool specimens accurately detected MTB in 75% of samples.[44,48,49]

Comparison of Clinical Outcomes in Pediatric Patients with Confirmed and Unconfirmed Rapid Molecular Test Examination

Both the GeneXpert MTB/RIF rapid molecular test confirmed TB group and clinical TB which had controlled at Dr. M Djamil Padang until the completion of treatment had cured clinical outcomes. However, 29.8% of the TB group had GeneXpert MTB/RIF rapid molecular test confirmed and 25% of the clinical TB group continued treatment at other hospitals, so their condition was not known when they finished treatment. There were 2 children in the clinical TB group who did not complete treatment. And as many as 7 confirmed TB cases and 15 cases of clinical TB died due to other comorbidities. The cause of death in both groups was sepsis, pneumonia and cerebral edema. Statistical analysis of clinical outcomes showed no clinically significant relationship between the two groups.

Research conducted by Noviarisa et al at dr M Djamil Hospital Padang in 2014-2016 found that 54.5% of subjects recovered after 6 months of treatment, 15.2% of subjects recovered with additional treatment, and 6.6% of subjects died, while the remainder continued treatment elsewhere or dropped out of treatment.[16] Mortality rates of TB in children will increase if they do not receive adequate management and in HIV infection. If the children received appropriate treatment of TB, they will have as good clinical outcomes as adult patients despite experiencing drug resistance.[50] A meta-analysis study by Jenkins et al found that the mortality rate for TB infection in children was very low, namely 0.9% after 1980 and has improved compared to decades before, even though the TB infection was accompanied by HIV infection.[51] A study by Erkins et al found 42% of subjects recovered after treatment, 4% stopped treatment on their own, 1% died of TB disease, 1% died of other diseases, and 2% unknown condition after treatment.

The radiological appearance after the chest X-ray examination of most of the study subjects was unknown. This is because chest x-ray examination was not always done after TB treatment is finished or the subject continues treatment at another hospital. While the subject underwent a chest X-ray examination when the treatment was finished, all of which showed a chest X-ray picture within normal limits. Chest X-ray examination is not only useful in making a diagnosis, but also for evaluating treatment. Post-treatment chest X-ray examination is carried out if post-treatment symptoms are still found or there are sequelae after treatment. Radiological images can assess changes in TB inflammation or picture of the sequelae of TB infection. Chest X-ray examination for evaluation is used to assess treatment response by comparing it with the previous chest X-ray picture with the conclusion of the chest X-ray picture of active TB or recovering from TB. While the description of TB sequelae can be in the form of bronchiectasis, bronchial wall thickening, and atelectasis/collapse.[31,32,52]

There are several limitations to this research. These limitations include that there is still a lot of required data that cannot be found in the medical record so that the number of samples obtained is not too large or not all of the required variable data is listed in the medical record. In addition, because a number of subjects did not continue treatment at Dr. M Djamil so that the clinical outcomes of the subjects after treatment were unknown and the relationship between variables in the statistical analysis was not significant.

CONCLUSION

Based on this research, we can conclude that 153 patients out of 257 subjects were diagnosed with TB. Subjects diagnosed with TB were divided into 2 groups, namely 24%

TB confirmed by GeneXpert MTB/RIF rapid molecular test and 76% were clinical TB. Clinical presentation features were found more frequently in confirmed TB than clinical TB except on crackle examination. Most of the subjects had clinical outcomes recovered in both groups with chest X-ray images within normal limits. There were a number of subjects who did not continue treatment at Dr. M Djamil Padang so that the clinical outcome is not known.

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