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Evaluation of Stool for the Diagnosis of Pulmonary Tuberculosis in Under 5 Children

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ABSTRACT
Background: *Tuberculosis (TB) is one of the top ten leading causes of death worldwide. Bangladesh is a both high TB & multidrug resistant TB burden country. Confirmed diagnosis of childhood TB remains challenging for physicians. MT test and Chest X-ray usually has very little diagnostic value for the diagnosis of pulmonary tuberculosis in children who has symptom criteria suggestive of PTB.* ***Objectives:*** *The aim of the study was to compare the Evaluation of Stool for the Diagnosis of Pulmonary Tuberculosis in Under 5 Children.* ***Methods:*** *This cross-sectional study was carried out in the Department of Pediatrics, Sir Salimullah Medical College & Mitford Hospital (SSMC & MH), Dhaka, Bangladesh duringJanuary 2018 to June 2019.A total of 50 patients were participated in the study. Statistical analyses of the results were be obtained by using window-based Microsoft Excel and Statistical Packages for Social Sciences (SPSS-24).* ***Results:****In this study, most of the children 16 (32%) lies between 13 months to 24 months and most of the children 30(60%) were male and 20 (40%) children were female. According to symptoms, where most of the children 39 (78%) presented with Fever, then cough 37 (74%), weight loss 25 (50%) and History of contact was present in 16 (32%) children. Here, 44% of children had positive MT test, 54% children were suggestive of PTB and 46% showed normal X-ray findings.****Conclusion:****Stool is a very good sample and stool Gene Xpert is a relatively easy test for the diagnosis of pulmonary tuberculosis in younger children (below 5 years) if sputum is unavailable.*
Keywords:*Tuberculosis (TB), MT test, Chest X-ray, Stool.*

I. INTRODUCTION

Tuberculosis (TB) remains a major public health problem even after more than 20 years of being declared as a global public health emergency. [1] The World Health Organization (WHO) estimates that tuberculosis remains the second leading cause of death among the infectious diseases after Human immune Deficiency Virus (HIV) and that almost one third of the world's population (2.5 billion people) is infected with mycobacterium Tuberculosis. It is estimated that more than 1.3 million people die each year from TB. [2]

The childhood TB burden is largely due to undiagnosed and late diagnosis of adult TB, which creates a reservoir for transmission to children. [3] Moreover,TB can progress very rapidly in children because of their immatureimmune system. So, rapid detection of TB in children should enable more rapid treatmentand improved outcomes. [4]But the diagnosis of TB in children is not straight-forward as in adult TB patient, hence it requires careful & thorough assessment of all the data derived from a careful history, clinical examination & relevant investigation, e.g., Mantoux test (MT), Chest X-ray, smear microscopy & other investigations.

The MT test is often negative in malnourished children or in other immunocompromised condition and a positive MT only indicates infection with M.Tuberculosis, does not always indicates active disease. [5] Moreover, the reading of the test of tuberculin test requires experience and care. Inexperience can lead to error. So, there may be a large chance of misinterpretation of MT test. [2]

The diagnosis of childhood pulmonary tuberculosis also very difficult by Chest X-ray. Because the X-ray are often nonspecific in children and prone to variable interpretation. [5] There are variable nonspecific

findings may be found which may suggestive of PTB, but does not indicate active disease. Chest X-ray shows very low specificity 52% (54-58) to confirm the diagnosis of pulmonary tuberculosis. [2]

So pulmonary tuberculosis in children cannot be diagnosed just on the basis of MT and Chest X-ray. Respiratory specimen or gastric lavage have to collect to diagnose the pulmonary tuberculosis. AFB can be detected by microscopy test with high specificity (98%) and sensitivity (63%). [2] Culture test is gold standard to detect M.Tuberculosis. But sputum from children is often paucibacillary,as children are less likely to form cavitarylesions in lungs to contain the bacilli. [6]

Children are therefore often treated empirically for TB, based on clinical features, chest X-ray findings, tuberculin skin tests, and contact with an index patient. This approach may lead to both over and under treatment.Previous studies have shown high sensitivity of PCR (Gene Xpert) when induced sputum) and gastric lavage were used. [7, 8] Gene Xpert was therefore endorsed by the World Health Organization as an initial test for diagnosing TB in children. [9]

Therefore stool specimen can detect M.Tuberculosis for the diagnosis of pulmonary tuberculosis in younger children. and sample collection can easily take place in the field or in clinics. [10] Moreover, culture confirmation of disease can take several weeks and disease progresses rapidly in young children. So, rapid diagnostic methods such as PCR (Gene Xpert) MTB/RIF are an important advance. [11]

II. METHODOLOGY

This cross-sectional analytical study was carried out in the Department ofPediatrics, Sir Salimullah Medical College & Mitford Hospital (SSMC & MH), Dhaka, Bangladesh duringJanuary 2018 to June 2019. A total of 50 patients were participated in the study. All the patients less than 5 years of age with clinical features suggestive of pulmonary tuberculosis admitted in Department of Pediatrics, SSMC & MH during the specified period of time.After taking consent and matching eligibility criteria, data were collected from patients on variables of interest using the predesigned structured questionnaire by interview, observation. Statistical analyses of the results were be obtained by using window-based Microsoft Excel and Statistical Packages for Social Sciences (SPSS-24).

III. RESULTS

Table I: Distribution of the patients according to age (n=50)

Age (in months)	Frequency	Percent
1 - 12	12	24.0
13 – 24	16	32.0
25 – 36	6	12.0
37 – 48	11	22.0
49 – 59	5	10.0
Total	50	100.0

Table I shows age distribution of the children, where most of the children 16 (32%) lies between 13 months to 24 months

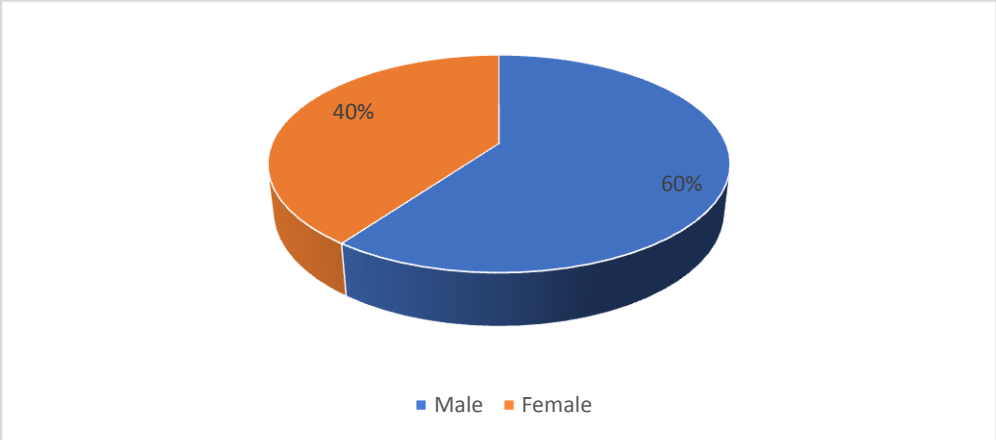

Figure I: Distribution of the patients according to sex (n=50)

This figure shows that most of the children 30(60%) were male and 20 (40%) children were female.

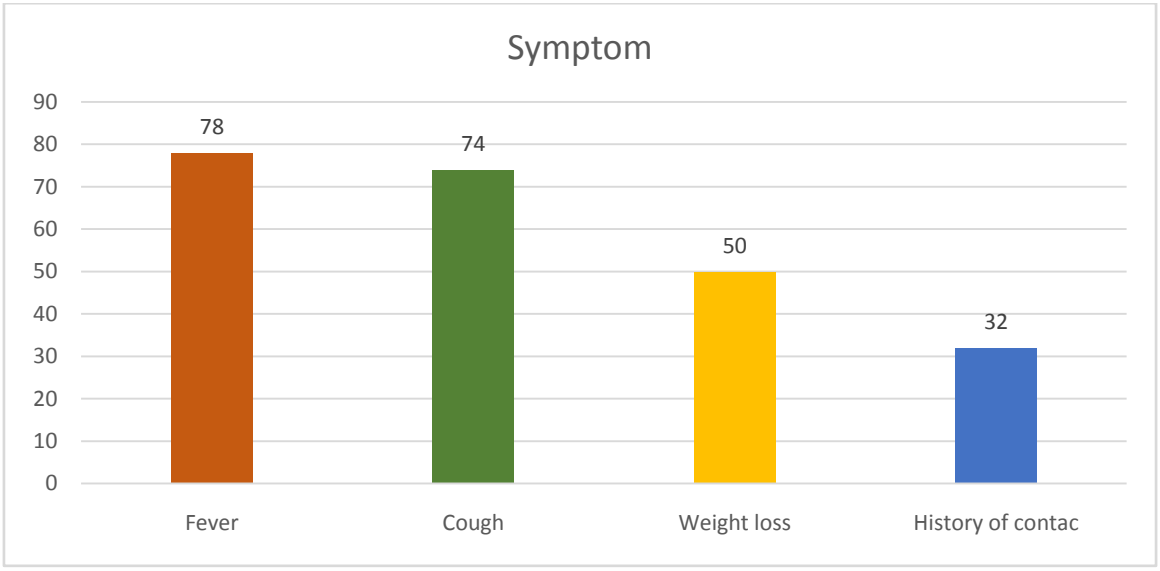

Figure II: Distribution of patients according to the symptoms criteria

Figure II this Bar diagram shows the distribution of patients according to symptoms, where most of the children 39 (78%) presented with Fever, then cough 37 (74%), weight loss 25 (50%) and History of contact was present in 16 (32%) children.

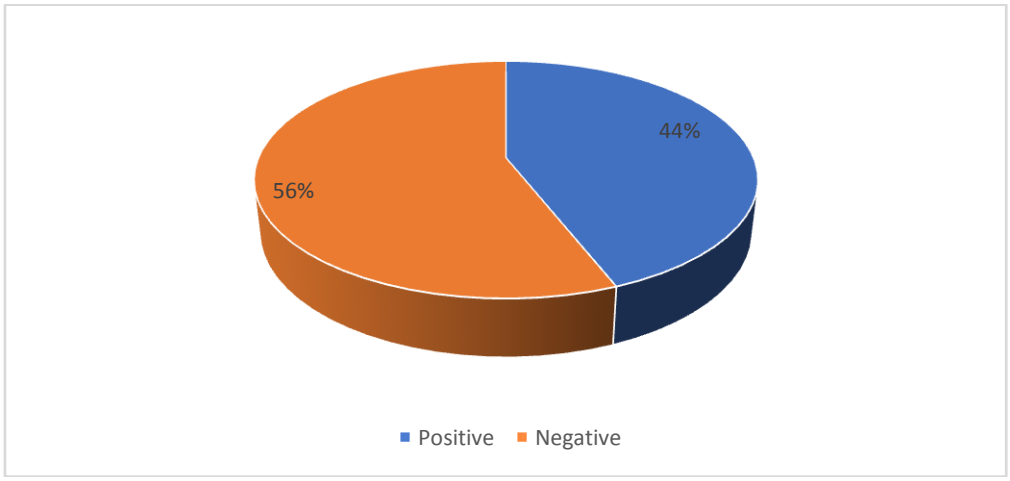

Figure III: Distribution of patients according to MT test (n=50)

Figure III shows that 44% of children had positive MT test.

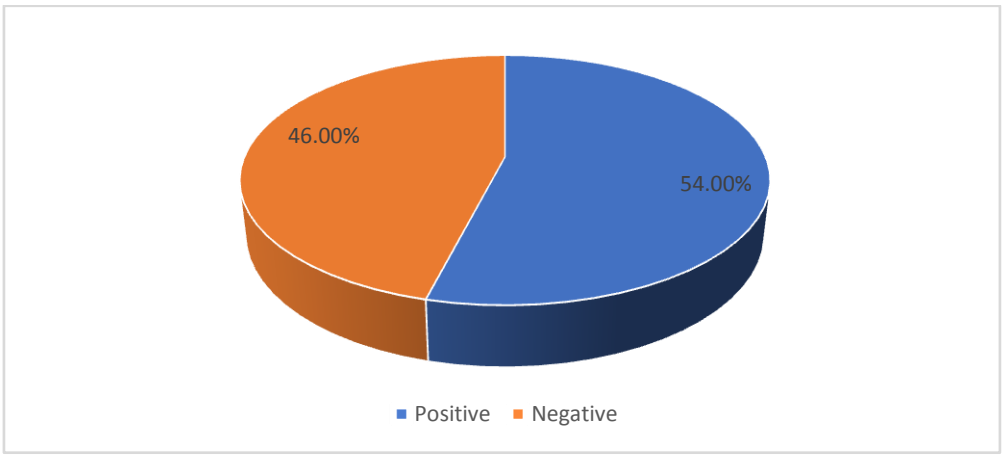

Figure IV: Distribution of the patients according to chest X-ray (n = 50)

Figure IV Shows Chest X-ray of 54% children was suggestive of PTB (as Consolidation, Milliary mottling, patchy opacity etc) and 46% showed normal X-ray findings.

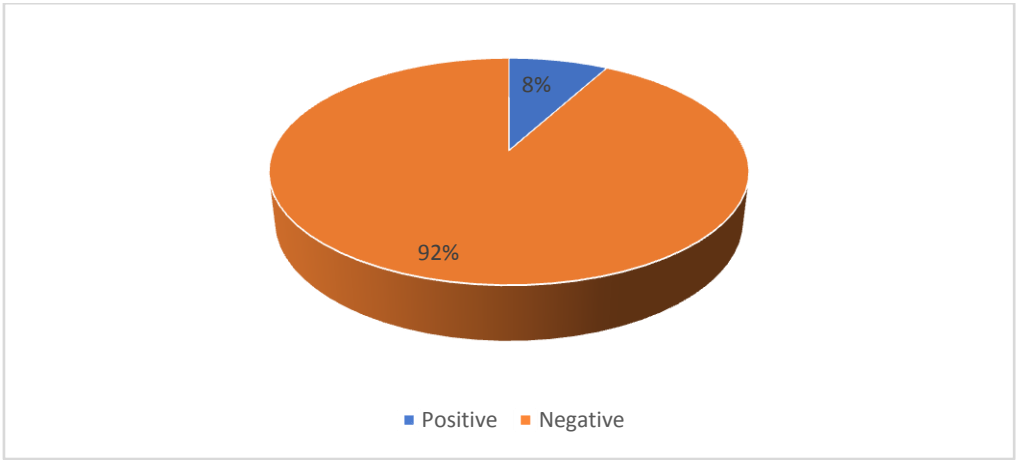

Figure V: Distribution of the patients according to Gene X-pert test of induced sputum (n = 50)

Figure V shows Gene X-pert of Induced sputum could detect M.Tuberculosis in case of 8% children. In 92% cases Gene X-pert could not detect M.Tuberculosis in induced sputum.

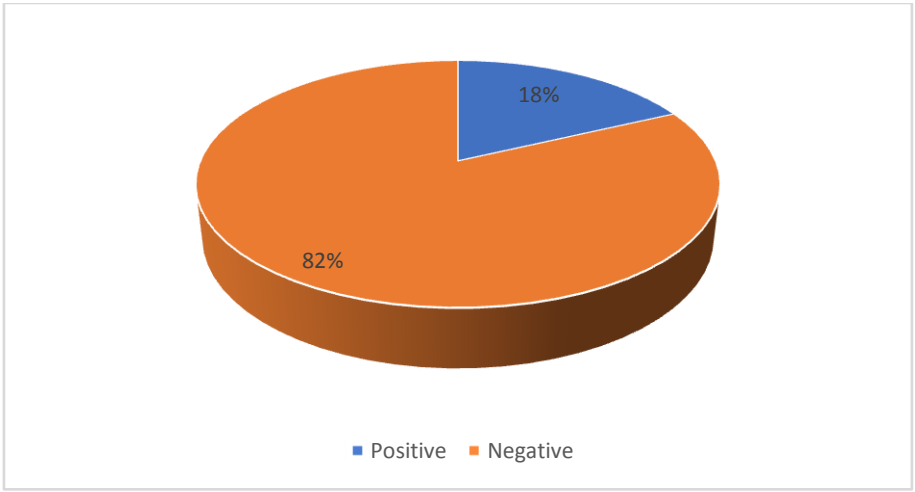

Figure VI: Distribution of the patients according to Gene X-pert test of stool (n = 50)

Figure VI: Shows that M.Tuberculosis was detected by Stool X-pert in 18% of children who were clinically diagnosed as PTB. In 82% of patient stool X-pert could not detect M.Tuberculosis.

Table II: Comparison between clinical criteria and Gene X-pert test of induced sputum in study subjects (n = 50)

Sign & symptom	X-pert test of Induced sputum		p value*
	Positive	Negative	
Fever	4 (10.3)	35 (89.7)	0.563
Cough	4 (10.8)	33 (89.2)	0.561
Weight loss	2 (8.0)	23 (92.0)	0.999
History of contact	2 (12.5)	14 (87.5)	0.584

*Fisher's Exact Test was done to measure the level of significance,
Figure within parenthesis indicates in percentage.

Table II: Showed comparison between clinical symptoms with the X-pert test of induced sputum. Where there was no significant difference between clinical criteria as fever, cough, weight loss & history of contact with X-pert of induced sputum.

Table III: Comparison between clinical criteria & X-pert test of stool in study subjects (n = 50)

Sign & symptom	X-pert test of Induced sputum		p value*
	Positive	Negative	
Fever	9 (23.1)	30 (76.9)	0.177
Cough	7 (18.9)	30 (81.1)	0.999
Weight loss	7 (28.0)	18 (72.0)	0.138
History of contact	6 (37.5)	10 (62.5)	0.022

*Fisher's Exact Test was done to measure the level of significance, Figure within parenthesis indicates in percentage.

This table shows statistically significant result in stool Gene Xpert in those children who had H/O contact (p value 0.02)

Table IV: Comparison between MT test and Gene X-pert test of induced sputum in study subjects (n = 50)

MT test	X-pert test of Induced sputum		p value*
	Positive	Negative	
Positive	3 (13.6)	19 (86.4)	<0.001
Negative	1 (3.6)	27 (96.4)	
Total	4 (8.0)	46 (92.0)	

*McNemar Test was done to measure the level of significance, Figure within parenthesis indicates in percentage.

Table IV shows that statistically significant result in IS Gene Xpert in those children who are MT positive (P value < 0.001)

Table V: Comparison between chest X-ray and Gene X-pert test of induced sputum in study subjects (n = 50)

MT test	X-pert test of Induced sputum		p value*
	Positive	Negative	
Positive	2 (7.4)	25 (92.6)	<0.001
Negative	2 (8.7)	21 (91.3)	
Total	4 (8.0)	46 (92.0)	

*McNemar Test was done to measure the level of significance, Figure within parenthesis indicates in percentage.

Table V shows statistically significant result in IS Gene Xpert in those children whose Chest X-ray were suggestive of PTB (p value < 0.001)

Table VI: Comparison between MT test and Gene X-pert test of stool in study subjects (n = 50)

MT test	X-pert test of Induced sputum		p value*
	Positive	Negative	
Positive	4 (18.2)	18 (81.8)	0.011
Negative	5 (17.9)	23 (82.1)	
Total	9 (18.0)	41 (82.0)	

*McNemar Test was done to measure the level of significance, Figure within parenthesis indicates in percentage.

Table VI shows statistically significant result in stool Gene Xpert in those children who are MT positive (p value <0.011)

Table VII: Comparison between Chest X-ray and Gene X-pert test of stool in study subjects (n = 50)

MT test	X-pert test of Induced sputum		p value*
	Positive	Negative	
Positive	5 (18.5)	22 (81.5)	0.011
Negative	4 (17.4)	19 (82.6)	
Total	9 (18.0)	41 (82.0)	

*McNemar Test was done to measure the level of significance, Figure within parenthesis indicates in percentage.

Table VII: Shows statistically significant result in stool GneXpert in those children whose Chest X-ray were suggestive of PTB (p value <0.001)

Table VIII: Comparison between Gene X-pert test of stool and Gene X-pert test of induced sputum in study subjects (n = 50)

MT test	X-pert test of Induced sputum		p value*
	Positive	Negative	
Positive	2 (50.0)	7 (15.2)	0.180
Negative	2 (50.0)	39 (84.8)	
Total	**4 (100.0)**	**46 (100.0)**	

*McNemar Test was done to measure the level of significance, Figure within parenthesis indicates in percentage.

Table VIII shows that comparison between IS Xpert and stool Xpert is not statistically significant (p value is 0.18)

Table IX: Diagnostic accuracy of stool X-pert compared to X-pert test of Induced sputum (n=50)

Validity test	Value (%)	95% CI
Sensitivity	50.0	9.5-90.4
Specificity	84.8	81.3-88.3
PPV	22.2	4.2-40.2
NPV	95.1	91.2-99.1
Accuracy	82.0	75.5-88.5

Table IX shows comparison between Sensitivity, Specificity, Positive predictive value and negative predictive value of the result of Gene X-pert test of stool specimen with that of induced sputum. Where SEN, SPE, PPV and NPV is 50%, 84.8%, 22.2% and 95.1% respectively with 82% accuracy.

IV. DISCUSSION

Bangladesh is one of the high burden countries of tuberculosis among the 22 high burden countries in the world and majority of the tuberculosis patients are children less than 15 years of age which mainly contribute to pulmonary tuberculosis. Due to the non-specific sign-symptoms of pulmonary tuberculosis in children and as MT test & chest X-ray has very little diagnostic value, most of the children remains underdiagnosed. So, there is a need for rapid, easy way to diagnosis childhood PTB in such settings. National Guideline for childhood TB recommended the use of PCR (Gene Xpert) as an initial test for diagnosis PTB in children. However, due to the difficulty in obtaining suitable specimens for testing diagnosis of PTB in children has generally been low.

This Cross-sectional study was done in the Department of Pediatrics in Sir Salimullah Medical College and Mitford Hospital, Dhaka during the period from January 2018 to June 2019 to evaluate stool for the diagnosis of pulmonary tuberculosis in under 5 children. In this study, according to the clinical presentation majority of the children present with fever 39(78%), followed by cough (74%) and weight loss (50%). Which is similar with the study of Welday et al., 2014, where fever was 88%, cough (84%) and weight loss (45%). [10]

Hasan et al.,2017 showed that in under 5 children contact history was present in 52%, and in this study contact history was present in 16 children that is 32%. [12] In the present study MT test was positive in 22 children (44%) and Chest x-ray suggestive of PTB was in 27 children (54%). But among the 50 children 11 children were confirmed diagnosis of pulmonary tuberculosis by induced sputum and stool PCR (Gene Xpert) and culture that is 22%. The sensitivity of MT test is 75% (22.7-98.7) and specificity is only 58.7% (54.1-60.8). The sensitivity and specificity of Chest X-ray is low that is 50% (9.4-90.6) and 45.7% (42.1-49.2).

In the present study PCR (Gene Xpert) test of induced sputum detected M.Tuberculosis in 4 children out of 50 that is 8% and stool PCR (Gene Xpert) detected MTB in 9 children out of 50, that means 18%. Among the 9 children of stool Gene Xpert positive, the result of Gene Xpert test of IS was also positive in 2 children. That means stool PCR detected M.Tuberculosis solely in 7 children. But it is very unlikely to get more M.Tuberculosis in stool than in induced sputum. It may be due to the collection technique as the children did not allow to collect the induced sputum, it have to collect forcefully, so, there may be inadequate amount of induced sputum to detect M.Tuberculosis, as MTB is paucibacillary in children. But in case of collection of stools there is no such problem as it is a natural process.

In this study there was no significant difference between the result of Gene Xpert test of stool and the Gene Xpert result of IS, where p value was 0.18.A pilot prospective study was done in cape town, South Africa

where 17 children of confirmed tuberculosis were enrolled who had culture positive for M. Tuberculosis. Among them IS Gene Xpert could detect 11/17 (64.7%) and stool Xpert detected 8/17 (47%). The positivity of Gene Xpert results of stool and IS was not statistically significant in the study (p=0.30). [11] In another cross-sectional study in Durban showed that stool GeneXpert was positive in 68% and IS Gene Xpert was positive in 79%, where p value was 0.24, not significant. [13]

The present study detected MTB on stool culture only in 1 patient out of 50 (2%) and no MTB was detected on IS culture. A Cohort study was done in Cape town were showed that Stool culture was positive in 6/37 (16.2%) children with confirmed TB, where sensitivity was 33.3% (95% CI 11.8 to 61.6%). They conclude stool culture for TB diagnosis cannot currently be recommended for the diagnosis of PTB in children. [14]

This present study also compared the clinical sign-symptoms of the patient with the result of X-pert of IS & stool. There was no significant difference between clinical parameter as fever, cough weight loss & history of contact with X-pert test of IS. p value was > 0.5 in all the parameters. No significant difference was between fever, cough & weight loss with X-pert result of stool (p value > 0.05). There was only significant difference between history of contact with stool X-pert (p value = 0.022).

Result of MT and Chest X-ray was also compared with the result of X-pert on IS & stool in this study. Positive MT result was statistically significant with the result of both X-pert on IS and stool, p value was < 0.001 &< 0.011 respectively. Chest X-ray was also significant in compare with X-pert of both IS & stool, p value was < 0.001 in both. Sensitivity, specificity, PPV, NPV of stool PCR (Gene Xpert) were compared with that of induced sputum in this study. Gene X-pert in stool had sensitivity 50% (95% CI 9.5-90.4), specificity 84.8% (95% CI 81.3-88.3), PPV 22.2% (95% CI 4.2 – 40.2), NPV 95.1% (95% CI 91.2-99.1). The study of Hasan et al. 2017 showed that sensitivity, specificity, PPV, NPV of stool X-pert was 81.8% (95% CI 47.8 – 96.8), 97.4 (95% CI 84.6 – 99.9), 81.8% and 97.3% respectively. Another prospective cohort study showed that specificity of stool X-pert was 72.4% (95% CI 52.8 – 87.3) & sensitivity was 75.9% (95% CI 56.5 – 89.7). [15]

This study shows that stool PCR (Gene Xpert) is moderately sensitive (50%), highly specific (84.8%) with high negative predictive value (95.1%) and high accuracy (82%) when compared with that of induced sputum. That means there is less chance of false negative result. So, it can confirm the diagnosis of pulmonary tuberculosis who are clinically highly suggestive of PTB (who fulfill the clinical criteria ≥3 for the diagnosis of PTB).

Limitations of the study

The present study was conducted in a very short period due to time constraints and funding limitations. The small sample size was also a limitation of the present study.

V. CONCLUSION

Only few studies were done on diagnosis of tuberculosis by using stool specimen, but only on adult. To the best of my knowledge, there has not been yet any clinical study done by using stool specimen for the diagnosis of childhood pulmonary tuberculosis. This type of study is diagnosis the pulmonary TB in children easily avoiding those invasive procedures like induced sputum and gastric lavage. Stool is a very good sample and stool Gene Xpert is a relatively easy test for the diagnosis of pulmonary tuberculosis in younger children (below 5 years) if sputum is unavailable.

VI. RECOMMENDATION

This study can serve as a pilot to much larger research involving multiple centers that can provide a nationwide picture, validate regression models proposed in this study for future use and emphasize points to ensure better management and adherence.

ACKNOWLEDGEMENTS

The wide range of disciplines involved in evaluation of stool for the diagnosis of pulmonary tuberculosis in under 5 children research means that editors need much assistance from referees in the evaluation of papers submitted for publication. I would also like to be grateful to my colleagues and family who supported me and offered deep insight into the study.

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