Original Article

Gene X-pert Positivity and its Relation with Tuberculin Skin Test (TST) in Tuberculosis Suspected Children Visiting Tertiary Care Pediatric Center of Nepal

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ABSTRACT

Background: Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, is among the top ten leading causes of death worldwide. Pulmonary TB is the most common form of TB and is easily transmitted through aerosol droplets. Gene- X-pert MTB/RIF can perform rapid detection of *M. tuberculosis* (MTB) and its resistance to rifampicin. Mantoux tuberculin skin test (TST) is used to determine whether a person is infected with *M. tuberculosis* by measuring the size of induration 72 hours after inoculation. The main objective of the study was to observe the relation of the mantoux test with Gene X-pert test for detection of tuberculosis.

Method: We reviewed the data of the patients who underwent Gene X-pert testing in Kanti children's Hospital (KCH) in the last two years. The Mantoux test and the Gene X-pert data were collected with sociodemographic data of children. The data were collected and the frequency tables were prepared and analyzed. The descriptive analysis was done using the frequency table.

Results: Among 622 TB-suspected children, 46 (7.4%) were Gene X-pert positive. Mantoux TST results were available in 249 cases, with 87 (34.9%) testing positive (≥10 mm induration). Of these, only 12.6% (n=11) were also Gene X-pert positive. The Mantoux test showed a sensitivity of 44%, specificity of 66.1%, PPV of 12.6%, and NPV of 91.4% against Gene X-pert. Gene X-pert testing was more frequently performed in males (63.7%), but positivity was higher in females (58.7%). Mantoux positivity was slightly more common in males (59.8%) than females (40.2%). Most TB suspects and Gene X-pert positive cases were from Bagmati province (46.1% and 52.2%, respectively), followed by Madhesh. Brahmin/Chhetri and Janajati ethnic groups were the most represented among both TB suspects and confirmed cases.

Conclusion The Mantoux test showed low sensitivity (44%) and poor positive predictive value (12.6%) compared to Gene X-pert, limiting its role in pediatric TB diagnosis. It should not be used alone for screening or treatment decisions. Gene X-pert remains crucial for accurate confirmation of TB in children.

Key words: Gene X-pert; Mantoux test; Tuberculin skin test; Tuberculosis.

Article Information

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INTRODUCTION

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, is among the top ten leading causes of death worldwide, with an estimated 1.2 million TB deaths and an additional 0.2 million deaths resulting from TB Human Immunodeficiency Virus (HIV) co-infection. Approximately 10 million new TB cases are emerging every year, but only 7 million are being notified, among them, 0.2 million are rifampicin resistant/ multidrug resistant (MDR) [1]. However, in the Nepali scenario, it showed that there were an estimated 45,000 cases with a range of 39,000 to 50,000, which is approximately 152 cases per 100,000 population. The report in 2019 showed that there were 31,064 incident TB cases notified, which is 106 notifications per 100,000 population [2].

Smear microscopy, culture sensitivity testing, and chest radiography are the conventional methods for TB detection, with smear microscopy being a cheap diagnostic tool but with low sensitivity, and culture sensitivity being the gold standard [3–6]. Although, TB can affect any part of the body like the brain, spine, intestine, the lymph node, pulmonary TB is the most common form of TB and it gets easily spread with aerosol droplets. On the other hand, extra pulmonary TB, with its low infectious potential, receives less attention but has got more diagnostic challenges due to diverse clinical manifestations leading to diagnostic delay and carrries greater potential for morbidity and mortality [7–9]. Using the nucleic acid amplification technique, Gene- X-pert Multi Drug resistant Tuberculosis (MTB/RIF) can do rapid detection of Mycobacterium tuberculosis and its resistance to rifampicin within 2 hours [10,11].

The Mantoux Tuberculin Skin Test (TST) is performed with the intradermal injection of 0.1 ml tuberculin Purified Protein Derivative (PPD). The interpretation of the Mantoux test is done by measuring the induration produced by Mycobacterium tuberculosis by measuring the size of induration 72 hours after inoculation. An induration ≥15 mm is considered positive in people with no known risk factors, whereas ≥5 mm induration indicates positivity only in people living with HIV, recent contact with infectious TB, chest X-ray finding suggestive of previous TB, organ transplants, and those on immunosuppressive therapy. In children younger than 5 years, people with low body weight (<90% of ideal body weight), and those suffering from certain disease conditions like diabetes, severe kidney disease, drug abuse, from countries with high rates of TB, or in high risk working settings (lab, nursing homes, homeless shelter; an induration of ≥10 mm is sufficient to mark a positive result [12].

This study aims to find the Gene X-pert positivity among the children who were suspected to have tuberculosis on clinical, radiological, and Mantoux TST grounds; and to compare its prevalence according to gender, ethnicity, and geographical location.

METHODOLOGY

This study is a retrospective study, which is done in the only tertiary pediatric care center. We have reviewed the available data of the patients who were suspected to have either pulmonary or extra-pulmonary tuberculosis and underwent Gene X-pert testing in the last two years, starting from Aug 2021 to Jul 2023. The variables like place of origin, sex, ethnicity, and Mantoux test result were encrypted. The patient's identity was anonymized. Those records were collected by MS Excel, which were later transcribed to statistical software IBM SPSS 20.0 and analyzed further. The frequency tables were prepared, and the percentage of different variables was calculated individually. The descriptive analysis was done.

RESULTS

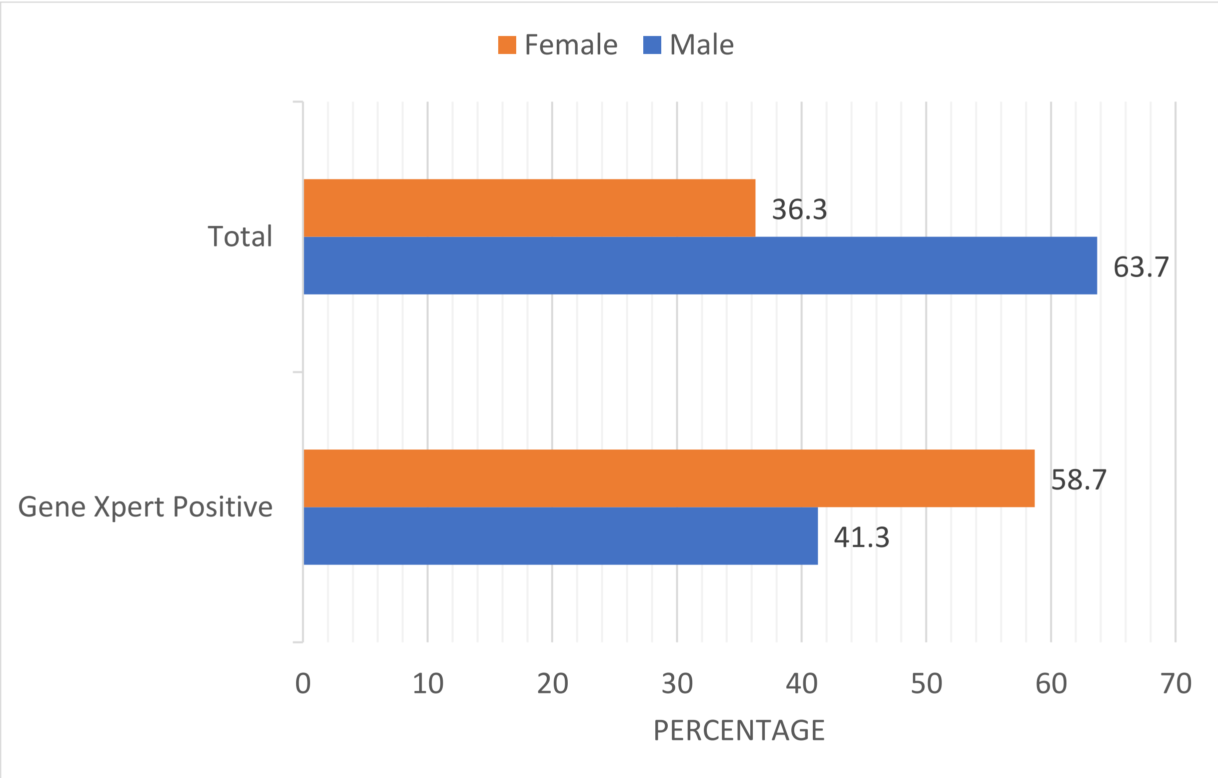
There were total of 622 requests made for Gene X-pert testing with the suspicion of tuberculosis, among them 7.4% (n=46) came out to be positive while 92.6 % (n=576) showed the report of MTB not detected. The Mantoux tuberculin skin test report was available only in 249 among them 34.9% (n=87) showed a positive TST result (induration size ≥10 mm) while 65.1% (n=162) had negative results (induration <10 mm). Out of the 87 TST-positive individuals, only 12.6% (n=11) were also Gene X-pert positive, indicating a positive predictive value (PPV) of 12.6%**.** In contrast, 148 individuals were both TST negative and Gene X-pert negative, resulting in a negative predictive value (NPV) of 91.4%**.** Taking Gene X-pert as the reference standard, the Mantoux test demonstrated a sensitivity of 44.0% (11 true positives out of 25 Gene X-pert positives) and a specificity of 66.1% (148 true negatives out of 224 Gene X-pert negatives). A 2×2 contingency table using Gene X-pert results as the reference standard to calculate the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the Mantoux tuberculin skin test (TST) is shown the table 1

Table 1: Diagnostic Performance of Mantoux Test against Gene X pert (n=249)

	Gene Xpert Positive	Gene Xpert Negative	Total
Mantoux Positive	11 (True Positive)	76 (False Positive)	87
Mantoux Negative	14 (False Negative)	148 (True Negative)	162
	25	224	249

The number of samples sent for Gene X-pert is almost double in case of male in comparison to female; 63.7% (n=396) vs 36.3% (n=226) but the Gene X-pert positivity rate is opposite as female contribute more percentage of positivity as compared to male; 58.7% (n=27) vs 41.3% (n=19). On the other hand, Mantoux positivity was slightly more common among boys (59.8%, n=52) than girls (40.2%, n=35), roughly reflecting the distribution of TB suspects by gender. Sex-wise distribution of Gene Xpert positive and TB suspected cases is shown in the figure 1.

Figure 1: Sex-wise distribution of Gene Xpert positive and TB suspected cases in percentage



The highest number TB suspects were from Bagmati province; 287 (46.1%) while Sudurpaschim province contributes to the least number; 28 (4.5%). Gene X-pert sample was sent from two foreign nationals with the suspicion of tuberculosis. The Brahmin/Chhetri and Janajati ethnic group were in leading position for the number of TB suspects as they contribute 36.8% (n=229) and 32.8% (n=204) of the cases sent for Gene X-pert testing respectively. The Province and ethnicity wise distribution of TB suspects is given in the table-2.

Table-2: Demographics distribution of TB suspects (n=622)

Variables	No. of TB suspects	Percentage
Province		
Koshi	40	6.4%
Madhesh	113	18.2%
Bagmati	289	46.4%
Gandaki	45	7.2%
Lumbini	65	10.5%

Karnali	42	6.8%
Sudurpaschim	28	4.5%
Ethnicity		
Dalit	77	12.4%
Janajati	204	32.8%
Madhesi	83	13.3%
Muslim	14	2.3%
Brahmin/Chhetri	229	36.8%
Others	15	2.4%

Among the total 46 Gene X-pert positive tuberculosis cases, 52.2% (n=24) were from Bagmati province followed by Madhesh province accounting 15.2% (n=7). Janajati and Brahmin/ Chhetri constitute the highest percentage of TB cases with equal contribution of 37% whereas Muslim ethnicity contribute the least with 4.3%. Province and ethnicity wise distribution of TB cases with Gene X-pert positivity is comparable with TB suspects cases which is presented in the table-3.

Table-3: Distribution of TB cases (n=46)

Province	Frequency	Percent
Koshi	4	8.7%
Madhesh	7	15.2%
Bagmati	24	52.2%
Gandaki	2	4.3%
Lumbini	2	4.3%
Karnali	4	8.7%
Sudurpaschim	3	6.5%
Ethinicity		
Dalit	6	13.0%
Janajati	17	37.0%
Madhesi	4	8.7%
Muslim	2	4.3%
Brahmin/Chhetri	17	37.0%
Others	0	0.0%

Similar to prevalence of TB suspect and gene X-pert positive TB case of different province, Bagmati province contribute for the highest number of mantoux TST positive cases, 62.0% (n=54) followed by Madhesh province, 10.3% (n=9). Brahmin/ Chhetri contribute to 40.2% (n=35) of Mantoux TST positive cases which is followed by Janajati 34.5% (n=30). The geographical and ethnicity wise prevalence of mantoux TST positive cases follows the distribution pattern of TB suspect and Gene X-pert positive tuberculosis cases and this is presented in the table-4.

Table-4: Province wise distribution of Mantoux TST positive cases (n=87)

Variables	Frequency	Percentage
Province		
Koshi	5	5.7%
Madhesh	9	10.3%
Bagmati	54	62.0%
Gandaki	6	6.9%
Lumbini	6	6.9%
Karnali	3	3.4%
Sudurpaschim	4	4.6%
Ethinicity		
Dalit	12	13.8%
Janajati	30	34.5%
Madhesi	8	9.2%
Muslim	1	1.1%
Brahmin/Chhetri	35	40.2%
Others	1	1.1%

DISCUSSION

Gastric aspirate or sputum Gene Xpert is considered the gold standard for the rapid diagnosis of tuberculosis in the modern era, as it detects the presence of *Mycobacterium tuberculosis* and rifampicin resistance with high sensitivity and specificity [1]. In settings with a strong clinical suspicion of TB—especially in pediatric populations where bacteriological confirmation is often difficult—radiographic findings and supportive biochemical tests can aid in making a presumptive diagnosis and initiating anti-tubercular therapy [2,3]. Although there may be discordance between Gene Xpert results and the Mantoux tuberculin skin test, the Mantoux test can still be valuable in initiating prophylactic therapy, particularly in high-risk children with clinical or epidemiological evidence of TB exposure [4,5].

This diagnostic yield of gastric aspirate gene X-pert in pediatric population is less compared to sputum gene X-pert done in adult population. The Gene X-pert positivity rate in our study was 7.4%, which is consistent with studies such as Shrestha et al. reporting 6.8% and Gurung et al. with 5.9% [13,14]. Similarly, Roma et al. reported a positivity rate of 10.6% among children suspected of TB in a Nepalese tertiary care hospital, and Kabir et al. found a 12.4% positivity rate in a Bangladeshi cohort of suspected TB cases.[15,16] This is closely aligned with the pooled positivity rate of 8.7% reported by Detjen et al. in a meta-analysis of pediatric Gene X-pert studies.[17] In contrast, studies in adult populations show a much higher positivity rate, often exceeding 25% [18]. Detjen et al. in their meta-analysis highlighted that despite advances, no single test can detect TB reliably in all pediatric cases, underscoring the need for multimodal diagnosis [17].

Gene Xpert testing has proven superior to smear microscopy, with detection of tuberculosis in up to 28.57% of smear-negative cases.[19] Other research has reported lower detection rates within the smear-negative population, at 21.5% and 11.4% [20,21].

The discordance between the Mantoux tuberculin skin test (TST) and Gene X-pert was notable in our data. Among the 87 Mantoux-positive children, only 12.6% had a Gene X-pert-confirmed TB diagnosis. The positive predictive value (PPV) of TST was low (12.6%), while the negative predictive value (NPV) was high (91.4%). Using Gene X-pert as the reference, the sensitivity and specificity of Mantoux were 44% and 66.1%, respectively. These findings contrast with higher Mantoux sensitivities reported by Roma et al and White & Bandi [15,22], but align with others emphasizing the limitations of TST in high-burden, BCG-vaccinated populations.[23] Factors such as prior BCG vaccination, cross-reactivity with non-tuberculous mycobacteria, and immunosuppression could influence TST accuracy, leading to both false positives and negatives [7].

Importantly, Mantoux TST was not performed in all Gene X-pert-positive cases. Among the 25 Gene X-pert-positive children with available TST results, 44% were TST positive, again underscoring limited concordance between the two diagnostic methods. These results suggest that while TST can assist in identifying candidates for prophylactic therapy, it has a limited role in the bacteriological confirmation of active TB, especially when compared to Gene X-pert. [23]

Gender-based analysis revealed that more boys underwent Gene X-pert testing than girls (63.7% vs. 36.3%), possibly reflecting sociocultural healthcare-seeking disparities. However, positivity rates were higher among girls (58.7%), echoing findings from other regional studies where female TB patients were under-tested but more likely to have active disease once evaluated.[13] In contrast, Mantoux positivity was slightly more common among boys, which may mirror the greater number of tests performed in this group.

Provincial distribution showed the majority of TB suspects and confirmed TB cases originated from Bagmati Province, likely due to the proximity of Kanti Children's Hospital to this region. This pattern also held for Mantoux positivity. Ethnically, Brahmin/Chhetri and Janajati groups had the highest numbers of TB suspects and confirmed cases. These trends may reflect demographic composition and access to tertiary care rather than inherent ethnic susceptibility.

CONCLUSION

This study highlights the diagnostic limitations of the Mantoux tuberculin skin test in pediatric tuberculosis when compared to Gene X-pert as the reference standard. The Mantoux test showed low sensitivity (44%), suggesting that more than half of true TB cases might be missed if diagnosis relies solely on TST. Furthermore, the positive predictive value (PPV) was only 12.6%, indicating that a significant proportion of TST-positive children did not have microbiologically confirmed TB.

These findings reinforce the inadequacy of using the Mantoux test alone for definitive diagnosis and support the incorporation of more specific molecular diagnostics like Gene X-pert in routine clinical practice. In high TB burden and BCG-vaccinated populations like Nepal, Mantoux should be interpreted cautiously and used primarily for screening or prophylactic decisions, rather than as a sole diagnostic tool.

Limitation: This retrospective study was done using the secondary data retrieved from record which has had only patchy information and only little information could be retrieved aggregating the all data.

Author Contributions: TB and RHC conceptualized and designed the research. CKB, RKB, RS, and PT collected the data. RHC, SA, and TB analyzed and interpreted the data. All authors were involved in drafting and reviewing the manuscript for important intellectual content. All authors approved the final version of the manuscript for submission and agreed to be accountable for all aspects of the work.

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Ethical Approval: **Consent/Assent:** Informed written consent was not applicable as the study was conducted retrospectively using anonymized secondary data.

Name of Registry and Registration number: Not applicable.

Data Availability Statement: The data supporting the findings of this study are available from the corresponding author upon reasonable request

Conflicts of Interest: The authors declare no conflict of interest, financial or non-financial.

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Layman summary: This study explored how two tests—the Gene X-pert and the Mantoux tuberculin skin test—compare when diagnosing tuberculosis (TB) in children suspected of having the disease. The Gene X-pert test is a newer method that can detect TB bacteria quickly and accurately, while the Mantoux test is a traditional skin test. Researchers found that the Mantoux test often missed TB cases and also gave false alarms. This means it's not reliable on its own for diagnosing TB in children. The Gene X-pert test was found to be much more accurate. The study highlights the importance of using better diagnostic tools like gene X-pert to ensure children get the right treatment early tools like Gene X-pert to ensure children get the right treatment early.

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