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RADIOLOGICAL AND GENE-EXPERT PATTERN: IN RELATION WITH TREATMENT OUTCOME OF SENSITIVE AND RESISTANT TUBERCULOSIS

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ABSTRACT: Even if there are so many diagnostic tests available for the detection of tuberculosis, still the diagnosis of TB is a challenging problem in this decade due to differences or non-specificity in symptoms, radiological signs, false negatives, and positives. Chest X-ray can identify the location, area, and morphology of lesions; hence analyzed the pattern and relation of chest X-ray and Gene expert results. This was a retrospective observational study conducted in the Ernakulam district of Kerala, India. The study included both drug-resistant and sensitive patients in two groups from the period 2016-2019 and 2017-2019. The study excluded HIV patients from both groups. Only professionally interpreted data were entered into the study analysis. All privacy and confidentiality were ensured throughout the study under direct observation of the district TB center. The left lung was more affected in DS-TB (76.47%), and the right side was more infected in DR-TB (65%). The predominant infiltration (24.21%), cavity (22.22%), and Non-homogenous opacity (26.47%) were seen in the left middle zone, whereas consolidation (24.63%) was high in the left upper zone. In DR-TB cases, the upper zone had high predominance with non-homogenous opacity leading to 37.89%. When looking into Gene expert, an additional 8% false-negative reporting was identified. The bacterial load in both DS and DR TB was found to be of a medium-severe level. An expert can identify TB using a chest X-ray which allows rapid diagnosis and effective management in many cases, especially when it cannot be confirmed by a bacteriological test.

INTRODUCTION: Tuberculosis (TB) is an infectious disease that is one of the deadly conditions that cause inflammation, tubercle formation, and other growths within the tissue, which may lead to tissue death [1]. Setting a standardized protocol for tuberculosis detection is essential, and as the usage of chest x-ray (CXR) to identify TB has decreased, even where the chest x-ray confirms the case, the final confirmation is made by a culture and gene expert.

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The gene expert is the most trusted and accurate diagnostic test for both tuberculosis and TB resistance towards rifampicin [2-3]**.** Chest X-ray can identify the location, area, and morphology of lesions (cavity, consolidation, pleural effusions, and fibrosis) [2].

The sensitivity and specificity of CXR among smear-negative suspects was 80% and 67% respectively4, whereas the sensitivity and specificity of gene expert was more than 84% and 99% [5]. Even though there are many diagnostic tests available for the detection of tuberculosis, the diagnosis is still a challenging problem in this decade due to differences or non-specificity in symptoms, radiological signs, false negatives, and positives.

The gold standard of diagnosis is culture-based, but that is time-consuming. The CXR can help in a fast diagnosis if the physician is experienced in finding the changes. The rapid tests like gene experts will help both the identification of tuberculosis and resistance towards the rifampicin, which prevented the unnotified cases of resistance [6-7]. The poor specificity and high variability didn't limit the use of CXR as an adjunct to clinical and microbiological tools [8]. Drug-sensitive tuberculosis means the Mycobacterium tuberculosis is sensitive to all drugs used in the treatment, and the drug-resistant indicates that the same bacteria is resistant to any one of the drugs, especially Isoniazid, Rifampicin, and others [9]. Smoking, Alcoholism, existing diabetes, COPD can aggravate tuberculosis. The medication adherence and efficacy can be assessed by a periodical test and CXR [10]. Thus, this study assesses the CXR along with gene experts of both drugs resistant and sensitive cases to find out the pattern of each diagnostic test and how it is related to the treatment outcome in patients.

Methodology: It was a retrospective observational study conducted in the Ernakulam district of Kerala, India. The study was conducted under the State and district tuberculosis center, which includes 8 TB units, and each TB unit consisted of 113 subunits. The protocol was approved initially by the Institutional Human Ethics Committee (IHEC) with the number 012/IHEC/10/2019/NCP.

The State TB cell, District TB Centre, Operational Research (OR) committee, Directorate of health service, Kerala, India, approved the proposed plan of study and granted access to TB data and treatment. Also, the same committees and organizations validated the obtained results. The informed consent forms did not apply to this study because there was no patient interaction and harm. The whole data was obtained from the patient's medical records and treatment providers. The process of data collection was under the supervision of the District TB center, which guaranteed the privacy and confidentiality of patients throughout the study. The study consisted of two groups, *i.e.*, drug-resistant (DR) and drug-sensitive (DS) tuberculosis patients. In the drug-resistant group, all patients who were registered under the district TB center under the norms of the Revised national tuberculosis control program (RNTCP) during 2016-2019 for DR-TB were included. Excluded patients with HIV co-infection. A total of 146 patients satisfied the inclusion criteria set for this study.

In the case of drug-sensitive DS-TB patients registered under RNTCP and who have completed the treatment under the district, during the period 2017 to 2019 with age greater than or equal to 50 years were considered for the study (based on WHO standard population distribution). Using global TB report 2018 and Indian TB Report, the TB estimate of Kerala was calculated, and using Slovin's formula sample size of 383 was determined with a 95% confidence interval (CI), 5% margin of error, and 50% distribution [11-12]. In the study, a total of 532 individuals were enrolled after applying exclusion criteria. The exclusion for DS-TB was to eliminate the subjects with HIV co-infection and those aged below 50 years.

The data collection was based on a study questionnaire that contains basic demographics details, chest X-ray details, and gene expert results. The interpreted Chest X-ray was directly entered into the structured data entry form, and those which only had the X-ray sheet were entered after interpretation by the radiologist or pulmonologist. Each entered data was double-checked to ensure accuracy and authenticity using the records in the District center and concerned TB unit.

The recorded data was updated in the excel 2016 version, and statistical analysis was performed using SPSS version [25]. Data were expressed both in frequency and percentage. A standard deviation was done to measure the spread of data. The relation was identified by using the Pearson correlation with 95% CI.

RESULTS: The mean age of the elderly DS-TB was 61.79 (±8.77), and the mean age of DR-TB was 47.13 (±14.72). The DS-TB had a gender ratio of male to female as 3.4:1, and for DR-TB, it was 3.7:1 with male predominance in both the groups. 77.4% in DS-TB patients and 78.76% in DR-TB patients. In both groups, patients had comorbidities and social habits like diabetes, COPD, Alcoholism, Smoking, *etc.* Also, many of the patients had a previous history of tuberculosis.

Chest X-ray: Among 532 DS-TB patients 68 (11.65%) patients CXR were obtained, which was taken before the initiation of treatment. While comparing the X-RAY pattern observed in **Fig. 1** it was perceived that the left part of the lungs was mostly affected by the disease, with 76.47% reporting and 61.76% of patients showcased right lung infection.

In some cases, both sides were equally affected. The middle and upper zone was predominantly affected by tuberculosis. When it comes to the case of pleural effusion, the right side was found to be highly affected.

Whereas in the case of DR-TB the right side was affected more (65%) than the left, which accounted for 41.66% **Table 1**.

TABLE 1: SIDE OF THE LUNG AFFECTED

	Right lung	Left lung
DS-TB (n= 68)	61.76%	76.47%
DR-TB (n= 120)	65%	51.66%

Based on the 252 different appearance patterns **Table 2** of chest X-RAY (CXR) in 68 patients, 37.69% CXR showed infiltration, 27.38% showed consolidation, 21.42% showed a cavity, and 13.49% showed NHO (Non-homogenous opacity).

The infiltration, cavity, and NHO were seen in the left middle zone, whereas consolidation was more in the left upper zone.

Thus, all active parenchymal lesions in TB were mostly found in the upper-middle zone of the lungs.

TABLE 2: CHEST X-RAY APPEARANCE PATTERN OF DS TB.

Particulars	Infiltrate	Consolidation	Cavity	NHO	Total
Left lower zone	14 (5.52%)	9 (3.57%)	8 (3.17%)	5 (1.98%)	36 (14.28%)
Right lower zone	11 (4.36%)	10 (3.97%)	6 (2.38%)	3 (1.19%)	30 (11.9%)
Left middle zone	23 (9.12%)	15 (5.95%)	12 (4.76%)	9 (3.57%)	59 (23.41%)
Right middle zone	14 (5.52%)	14 (5.52%)	8 (3.17%)	7 (2.78%)	43 (17.06)
Left upper zone	14 (5.52%)	17 (6.74%)	11 (4.36%)	7(2.78%)	49 (19.44)
Right upper zone	19 (7.53%)	4 (1.59%)	9 (3.57%)	3(1.19%)	35 (13.89)
Total	95 (37.69%)	69 (27.38%)	54 (21.42%)	34 (13.49%)	252 (100%)

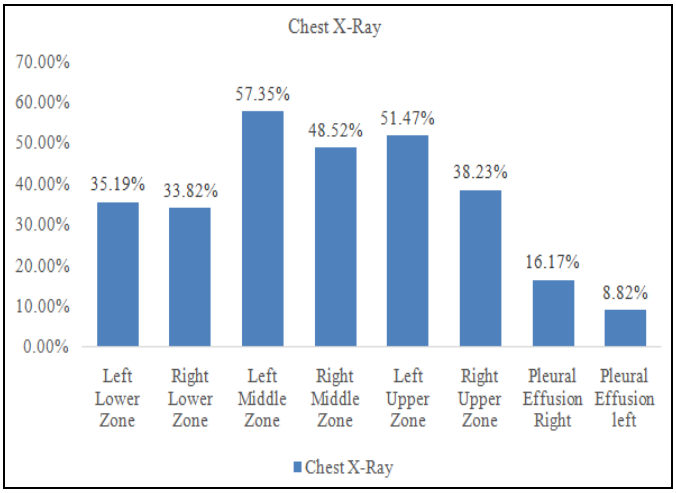

FIG. 1: CHEST X-RAY PATTERN OF DS-TB

Among 146 DR-TB patients, 120 had CXR before the treatment and the pattern observed in CXR **Fig. 2** and **Table 3** indicates the predominance of non-homogenous opacity (NHO) at 37.89% followed by a cavity (19.37%), consolidation (18.5%), infiltrate (8.5%) and reticular nodular shadow (5.7%) respectively. In DR-TB cases, the upper zone had high predominance. The distribution in the right and left lungs were similar in the case of the upper lobe.

The middle and lower lobes have only half of the infection rate than the upper lobe. The right lung showcased more infection (65%) than the left lung (51.66%) **Table 1**.

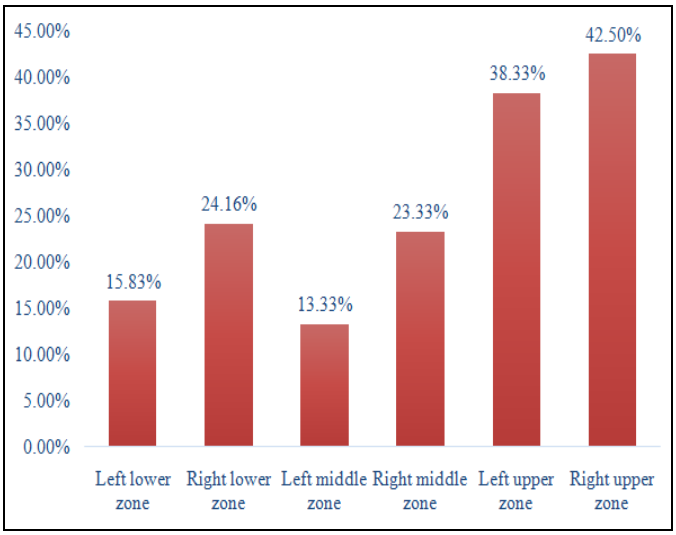

FIG. 2: CHEST X-RAY PATTERN

TABLE 3: CHEST X-RAY PATTERN OF DRUG RESISTANT PATIENT BEFORE TREATMENT

Particulars	Infiltrate	Consolidation	Cavity	NHO	Partial collapse	Opacity	Fibrosis	Reticular nodular shadow	Vestibular shallow
LLZ	6(1.71%)	10(2.8%)	10(2.8%)	14(3.99%)	0	2(0.57%)	0	3(0.85%)	0
RLZ	4(1.11%)	9(2.57%)	9(2.57%)	17(4.84%)	1(0.28%)	3(0.85%)	2(0.57%)	3(0.85%)	0
LMZ	6(1.71%)	9(2.57%)	7(1.99%)	18(5.12%)	1(0.28%)	2(0.57%)	1(0.28%)	4(1.11%)	0
RMZ	4(1.11%)	8(2.28%)	13(3.70%)	19(5.41%)	1(0.28%)	4(1.11%)	1(0.28%)	4(1.11%)	0
LUZ	6(1.71%)	17(4.84%)	16(4.56%)	30(8.54%)	0	3(0.85%)	1(0.28%)	4(1.11%)	0
RUZ	4(1.11%)	12(3.41%)	13(3.70%)	35(9.97%)	4(1.11%)	1(0.28%)	7(1.99%)	5(1.42%)	1(0.28%)
Total	30(8.5%)	65(18.5%)	68(19.4%)	133(37.9%)	7(2%)	15(4.3%)	12(3.4%)	20(5.7%)	1(0.3%)

(LLZ- Left lower zone, RLZ- right lower zone, LMZ- left middle zone, RMZ- right middle zone, LUZ-left upper zone, RUZ- right upper zone, NHO- non-homogenous opacity)

The correlation of CXR with outcome shows significance in DR-TB with a p-value of 0.00. Here a positive correlation was obtained between sides of the lung and outcome. Which describes that the right lung had the most negative outcomes. Also, among lobes, a positive correlation was obtained in DR-TB, which stated that the upper lobe had a negative outcome or if the upper lobe is affected, the chances of a negative outcome are high. In the case of DS-TB, no correlation was found **Table 4**.

Gene Expert: Cartridge-based nucleic acid amplification test (CBNAAT) was previously used to rule out Rifampicin resistance in susceptible patients only, but now it is performed in all TB patients. Obtaining the result of CBNAAT in this study before treatment indicated that most patients with mycobacterium tuberculosis belonged to the group "high" which indicates a high bacterial load. In contrast, 8% of unidentified cases *via* culture/ microscopy/ imaging were identified and diagnosed using the gene expert method.

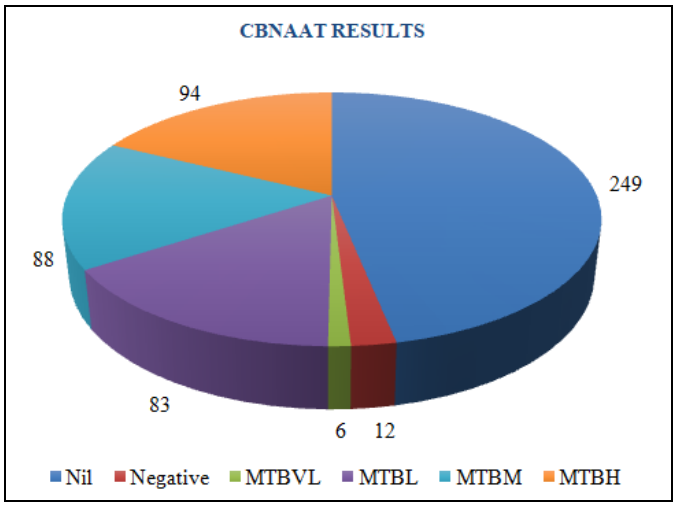

FIG. 3: CBNAAT RESULTS OF DS CASES. ((MTBVI: Mycobacterium tuberculosis Very low MTBL: Mycobacterium tuberculosis low, MTBM: Mycobacterium tuberculosis medium. MTBH: Mycobacterium tuberculosis high)

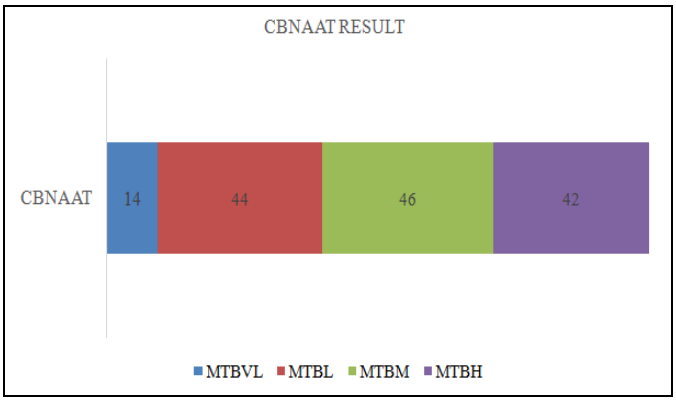

FIG. 4: CBNAAT RESULT OF DR RESISTANT CASES MTBVI: Mycobacterium tuberculosis Very low MTBL: Mycobacterium tuberculosis low, MTBM: Mycobacterium tuberculosis medium. MTBH: Mycobacterium tuberculosis high

TABLE 4: CORRELATION OF CHEST X-RAY WITH THE OUTCOME

	Particulars		Outcome
DR-TB	left/right side of lung	Pearson Correlation	0.311**
		Sig. (2-tailed)	0.000
	Lobes	Pearson Correlation	0.262**
		Sig. (2-tailed)	0.000
DS-TB	left/right side of lung	Pearson Correlation	0.077
		Sig. (2-tailed)	0.280
	Lobes	Pearson Correlation	0.103
		Sig. (2-tailed)	0.168

**. Correlation is significant at the 0.01 level (2-tailed).

TABLE 5: CORRELATION WITH GENE EXPERT MYCOBACTERIUM CONTENT WITH THE OUTCOME OF BOTH DR AND DS TB

Particulars		Outcome
DS-TB	Pearson Correlation	0.023
	Sig. (2-tailed)	0.701
DR-TB	Pearson Correlation	-0.046
	Sig. (2-tailed)	0.577

As per the results of CBNAAT obtained **Fig. 4**, MTB very low 14 (7.08%) was at the lower end, rest all were near equal with MTB low at 30.70% (44), MTB medium at 32.28% (46), and MTB high at 29.92% (42). The result of CBNAAT in this

study indicated that the majority of patients belonged to the MTBM range, showing medium bacterial load, out of which 127 cases were rifampicin-resistant. The correlation study was performed to establish if there is any relationship between the mycobacterium level obtained in gene expert with the outcome of treatment. But no significance was found in both DS and DR TB cases **Table 5**.

DISCUSSION: Gender distribution in both groups showed higher infectivity in males than the female, which means that male is more likely to be infected with tuberculosis due to the higher rate of exposure and having a higher risk of infection which was confirmed via studies from van *et al.*, and Ahuja et al. The radiological examination has an immense role in TB diagnosis and evaluation of therapy. Chest X-RAY is preferred due to its wide availability and its specificity in ruling out location, and the morphology of lesion, *etc.* [13]

The sputum smears sometimes show false negative and false positive; also, in the case of pleural effusion TB, the diagnosis is difficult with the sputum sample. The duration of culture and smear is long, but the chest x-ray rapidly produces the results. An expert in chest X-rays can easily identify the infection and overcome the drawbacks of culture and sputum microscopy [14]. Each stage can be identified based on the cavities, infiltrates, and other observations from the imaging.

The majority of patients were observed to be affected in the left middle zone and left upper zone with least in the right lower zone of lungs, which might be related to relatively reduced lymphatic drainage and increased oxygen tension in this area, factors that facilitate the bacillary replication [15-16]. This study shows drug-sensitive tuberculosis to be more affected in the left middle zone followed by left upper zones and right middle zone. But in the DR-TB, right and left upper zones were affected mostly. Consolidation usually appears in lung apices or superior segments of the upper lobe. They are unlikely to be present in the lower lobe though they may be seen in elderly patients. Lobular consolidation favors TB, while other infections are present with segmental consolidation. Thick-walled cavities are seen in patients during the early stage cavities in the upper lung zone suggest active TB [17]. While comparing with other studies that showed high cavitation and infiltrations, this study showed an increased number of non-homogenous opacity in DR-TB cases and cavitation and infiltration in the DS-TB. Most of these were found in the right upper lobe of the lungs [18]. Among DS-TB patients, Chest X-ray has ruled out many false-negative cases that have provided early detection and helped in providing correct diagnosis, indicating the inevitable technique, which is still a robust platform for detection of TB. In the case of DR-TB, a positive correlation was obtained when the sides of the lungs and lobes correlated with the outcome. Some studies have already stated that cavities are one of the main predisposing factors of treatment failure and recurrence among patients [19-22]. Gene expert or CBNAAT detects the PTB with greater efficacy than microscopy for early diagnosis and detects rifampicin resistance with high specificity, thus enabling the start of therapy early to decrease DRTB [23].

Today the gene expert is a basic test to predict tuberculosis patients, thereby determining resistance to rifampicin. This study indicated an 8% extra identification of TB by using gene expert, which showcased that false-negative result in other studies does not cent percent confirm the presence of the disease. The study also quantifies a load of bacteria in the body in both scenarios, and the load was found to be medium and high. One of the major limitations of the study was the less availability of imaging results along with proper interpretation.

CONCLUSION: In terms of the side of the affected lung left lung was more affected in DS-TB and the right was more infected in DR-TB. The predominance of non-homogenous opacity (NHO) was followed by cavity; consolidation was found in DR-TB. But in DS-TB, infiltration, and consolidation had predominance. When looking into Gene expert additional 8% false-negative cases were identified. The bacterial load in both DS and DR TB was found to be medium-severe level.

An expert can identify TB using a chest X-ray which allows rapid diagnosis of effective management in many cases, especially when cannot be confirmed by bacteriologically.

AUTHOR CONTRIBUTIONS: All authors contributed equally to the study and article.

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CONFLICTS OF INTEREST: There is no conflict of interest.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE: The Institutional ethics committee approved the study via no: 012/IHEC/10/2019/NCP. The Directorate of health services Kerala, State TB cell, and operational research group of tuberculosis research approved the study protocol (281/STC/DHS/2019). The informed consent form was not applicable because direct patient contact or interaction was not required.

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