Monaldi Archives for Chest Disease

eISSN 2532-5264 https://www.monaldi-archives.org/

Monaldi Arch Chest Dis 2024 [Online ahead of print]

To cite this Article:
Singla R, Gupta A, Kumar V, et al. **Study of risk factors and clinical management of patients with clinical non-response due to low plasma levels of anti-tubercular drugs.** *Monaldi Arch Chest Dis* doi: 10.4081/monaldi.2024.3036

Study of risk factors and clinical management of patients with clinical non-response due to low plasma levels of anti-tubercular drugs

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Contributions: RS, takes responsibility for the content of the manuscript, including the data and analysis, and the integrity of the data and the accuracy of the data analysis; RS, AG, VK, SA, CPP, AKH, contributed substantially to the study design, data analysis and interpretation; AKH, preformed the plasma levels of anti-TB drugs; AG, VK, AF, DT, MPC, contributed substantially to writing of the manuscript. All the authors have read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest: the authors have no conflict of interest to declare

Ethics approval and consent to participate: research and ethical approval (office letter no. NITRD/RC/2024/2521, letter no. NITRD/EC/2024/7497 respectively) has been obtained from Institutional Research and Ethical Committee.

Patient consent for publication: obtained.

Funding: none.

Availability of data and materials: all data generated or analysed during this study are included in this published article

Abstract

This study was carried out to assess the role of therapeutic drug monitoring of crucial first-line anti-tubercular drugs: rifampicin (R) and isoniazid (H) among 75 non-responding proven drug-sensitive tuberculosis patients on treatment followed by intervention in field conditions. The intervention was done in the form of either an increase in the dosage of R and H in patients with minimally low drug levels or a modification of the regimen in a certain group of patients with significantly low drug levels by augmenting it with three or four second-line drugs in addition to standard first-line drugs. This study also aimed to determine the relationship between the measured plasma concentration of anti-tubercular drugs and various demographic, microbiological, radiological, and malabsorption factors and the presence of co-morbidities affecting them. The study also focused on the clinical impact of the intervention for low plasma levels of anti-TB drugs on TB treatment outcomes. In our study overall, 85.5% of patients had low levels of any drug. In 85.3% of patients, R levels were low, and in 39.1%, H levels were low. On univariate analysis, low body mass index (BMI), hypoalbuminemia, bilateral disease on chest X-rays, and the presence of cavities were found to be significantly associated with low drug levels, while none of the factors were independently significantly associated. Low BMI, pulmonary tuberculosis and disseminated tuberculosis, far-advanced disease and bilateral disease on chest X-ray, presence of cavities, and only low R levels were associated with unfavorable outcomes, with none of the factors found to be significant on multivariate analysis. In our study, it was seen that the treatment outcome was favorable in 59.6% of patients in whom this intervention was done by augmenting the treatment regimen with three/four second-line drugs along with increasing the dose of R and H.

To conclude, various factors may be associated with low plasma levels of anti-tubercular drugs. If such patients show clinical non-response after $\geq$6 months of treatment and have significantly low drug levels, with an absence of drug resistance, their treatment regimen may need augmentation with three/four second-line drugs along with an increase in the dose of R and H, which may lead to a favorable outcome.

Key words: therapeutic drug monitoring, drug resistance, treatment outcome, anti-tubercular drugs.

Introduction

Globally, TB is one of the top 10 causes of death and the leading cause of death from a single infectious agent. Despite the availability of standardized treatment regimens for management of drug sensitive tuberculosis (DST) and drug resistant TB (DR-TB) in India, many patients are suffering from it and the national program of India has geared up for DST based regimen for drug resistant TB. As per Global TB report 2023, globally 10.6 million people developed TB disease and about a quarter of the world's TB cases were reported from India in 2022 [1].

Sometimes despite compliance to treatment, a slower response or no response to treatment is observed. The reasons for slow response are diverse and include extensive disease, comorbidities like diabetes, human immunodeficiency virus (HIV), late initiation of treatment, poor compliance with treatment, inadequate regimen and low plasma levels of anti-TB drugs [2-5]. Low plasma drug levels can be a consequence of malabsorption, inaccurate dosing, altered metabolism, or drug–drug interactions. Therapeutic drug monitoring (TDM) of anti-tubercular drugs (ATD) could improve patient outcomes in patients who are not responding to anti tubercular treatment (ATT) despite demonstrated susceptibility of mycobacteria to these drugs. TDM, especially for ATD, although, not yet popular in India, is well known in clinical pharmacology [2,3,6]. This study was done with an aim to assess the role of TDM among non-responding TB patients where drug resistance had been ruled out followed by intervention in field conditions. This study also aimed to determine the relationship between plasma concentration of anti-tubercular drugs and the factors affecting it such as demographics, microbiological and radiological profile, nutritional status, malabsorption due to GI disease and co-morbidities. We also studied the clinical impact of the intervention for low plasma levels of anti-TB drugs on TB treatment outcome.

Materials and Methods

A retrospective study was conducted to evaluate the occurrence and possible factors associated with low plasma levels of ATD levels in patients of drug sensitive TB who were not responding to treatment despite on appropriate anti-TB treatment/regimen. Among patients with low plasma levels, the dosage of ATDs was increased, or the regimen was modified, and the patients were followed up to assess their response to treatment.

Setting and Patients

The study was carried out at a tertiary referral TB hospital of northern India. A total of 75 drug sensitive TB patients (both pulmonary and extra pulmonary), who were not responding to treatment despite on appropriate regimen, and still showing absence of drug resistance were enrolled. Common causes of non-response such as inadequate dosage of drugs, inaccurate regimen, other causes of immune suppression, resistance to anti-TB drugs, poor drug

compliance etc. were first ruled out. For ruling out malabsorption, D-xylose, plasma IgG and plasma IgA tests were done in all cases and duodenal biopsy was done in selected cases wherever it was possible. Subsequently drug levels of standard anti-TB drugs like rifampicin (R) and isoniazid (H), in plasma of patients were measured.

Study design

Patients were referred by their treating physician to this centre with a concern of a slow clinical response or no response to therapy after more than 3 months, despite patients being compliant and on adequate dosage as per their weight bands. Also, the drug resistance was ruled out by subjecting the most appropriate sample, if available, with genotypic and phenotypic laboratory methods at a national referral laboratory. Research and ethical approval were obtained from Institutional Research and Ethical Committee (office letter no. NITRD/RC/2024/2521, letter no. NITRD/EC/2024/7497 respectively)

All enrolled patients underwent a comprehensive clinical examination and a detailed medical history. All the findings were entered in a clinical data-collection form, including patient demography, duration of signs and symptoms laboratory parameters and findings of chest x-ray [7].

Measurement of drug concentration

Patients were given minimum of 6 doses of ATT for 6 consecutive days on the same time in the morning. On the 7^{th} day morning, patients ingested their usual doses of all medications under direct observation. 3ml of venous blood was drawn, 2-hours post-dosing of the ATT drugs. Blood was collected in green top heparinized vacutainer. The sample was centrifuged to separate the plasma. 10µL of 5% ascorbic acid was added to 1mL of plasma. The separated plasma samples were transported in dry ice to the National Institute for Research in Tuberculosis, Chennai to measure the plasma peak concentrations of rifampicin and isoniazid. Drug levels were measured using high performance liquid chromatography [8]. The normal range of therapeutic level of the drugs was defined as 3 to 6 µg/mL for H and 8 to 24 µg/mL for R [3,9]. Drug concentrations were compared with published reference ranges from studies in human volunteers.

If drug levels were minimally low, we adjusted the doses upward. After a minimum of two weeks of treatment with the new TB drug dosages, plasma drug levels were reassessed to ascertain whether the drug levels have improved and come within the normal therapeutic range.

Treatment augmentation

In certain set of patients who had received treatment with first-line drugs for 6 months or more and had not responded favorably to treatment, though drug sensitive (by genotypic and phenotypic methods) and had significantly low plasma drug levels of standard first-line drugs,

they were declared as treatment failures. Their regimen was augmented with three or four second-line drugs, which are used to treat drug-resistant TB (DR-TB). Given the unique mechanisms of action of these medications, when compared to standard first-line therapy, it was assumed that their use could improve the outcomes when used as adjuvant therapy, in addition to increasing the dose of first-line drugs.

TB treatment outcome

All patients were followed up clinically, radiologically and bacteriologically. TB treatment outcomes (cured/treatment completed, failure, death, or default) were noted at the end of ATT. Cured and treatment completed were taken as favorable outcomes; while default, death, and failure were taken as unfavorable outcomes.

Data analysis

Statistical analyses were performed using SPSS 22.0 (IBM, Chicago, IL, USA). Plasma drug levels were dichotomized into normal if they were within or above the expected range or low if they were below the expected range. Variables were compared between patients with low and normal drug levels using the student *t* test for continuous variables and a chi-square (χ^2) test or Fisher's exact test for categorical variables. A p value of <0.05 was considered statistically significant.

Both univariate and multivariate logistic regression models were used to assess the risk factors independently associated with low drug levels. The influence of various factors on treatment outcome among such patients was also evaluated. Role of interventions, such as only dose increase of first-line drugs or dose increase with augmentation with three or four second-line drugs, on TB treatment outcome was also studied.

Results

A total of 75 patients with 44 (58.7%) having pulmonary TB were enrolled. Out of total, 35 (46.7%) patients were males. The demographic, clinical and radiological profile of patients is given in Table 1. Out of 75 patients, 64 (85.3%) were having low levels of any drug on first TDM and rest 11 (14.7%) were having normal levels. The prevalence of a low plasma concentration of R and H were 59/75 (78.7%) and 30/75 (40%) respectively. The number of patients who received PZA was the lowest since majority had of the patients stopped PZA after 2 months of initiating treatment. In six patients the outcome could not be determined because they did not report back after the first TDM was done. Out of 59 patients having any low levels of drugs, in which dosage was increased, only 28 (47.5%) patients among them reported for repeat TDM. In all these 28 patients repeat levels of R and H were within therapeutic range as per reference values.

On univariate analysis low body mass index (BMI), hypoalbuminemia, bilateral disease on chest x-ray and presence of cavity were found to be significantly associated with low drug levels, while none of the factor was independently associated with low drug levels on multiple logistic regression analysis (Table 2).

Low rifampicin levels were associated with male sex, low body mass index, anemia, hypoalbuminemia, bilateral disease on chest x-ray and presence of cavity on univariate analysis. Multiple logistic regression analysis showed male sex and low BMI were independently associated with low rifampicin levels. (Table 3)

When we compared patients with favorable outcome and unfavorable outcome at end of augmented/revised treatment, low BMI, pulmonary tuberculosis and disseminated TB, far advanced disease on chest x-ray, bilateral disease on chest x-ray, presence of cavity on chest x-ray and only low R levels were associated with unfavourable outcome. However, none of the factors was found to be significant on multivariate analysis. (Table 4).

Discussion

Slow or no response to therapy can result in prolonged infectiousness, extended treatment duration, acquired drug resistance, or recurrence of TB after treatment [10-12]. Cost-effectiveness and cost-utility, lack of population (ethnicity) specific therapeutic ranges of plasma drug levels, requirement of infrastructure and trained manpower are some of the challenges for TDM in India. In the current study 75 patients were enrolled who were not responding clinically and microbiologically, despite showing sensitivity to standard first-line drugs by both genotypic and phenotypic methods. TDM was done with an aim to assess the role of TDM followed by intervention in such patients in field conditions. This study also aimed to determine the relationship between measured plasma concentration of anti-tubercular drugs and the factors affecting them such as demographics, microbiological and radiological profile, nutritional status, malabsorption due to GI disease, co-morbidities.

Overall, 85.5% patients had low levels of any drug with rifampicin (85.3%) followed by isoniazid (39.1%) having low levels. The findings were similar to the other studies done on TDM. In Botswana (30% to 37% had low levels of H, 78% to 84% had low level of rifampicin, but only 1% to 5% had low levels of PZA) [12,13]. In Australia (48% of H levels and 46% of rifampicin levels were below the normal range [14]. In Indonesia 70% of 62 TB patients had low rifampicin concentrations [15].

In the current study low BMI, hypoalbuminemia, bilateral disease on chest x-ray and presence of cavity were the factors found to be significantly associated with overall low drug levels on univariate analysis, but none was having significant independent association. Similarly in some

other studies also, anaemia, hypoproteinaemia, chronic malnutrition and malabsorption were the most common causes for low drug levels in their study [16-20].

In our study low levels of rifampicin were associated with male sex, low body mass index, anemia, hypoalbuminemia, bilateral disease on chest x-ray and presence of cavity. Among these factors male sex and low BMI were found to be independent factors associated with low levels of rifampicin. Low levels of rifampicin were also associated with unfavourable treatment outcome. Many studies have suggested that current dosing of rifampicin may be suboptimal resulting in lower dose/kg, which may or may not affect the treatment outcome [6,21]. Additionally, patients having low BMI usually have low albumin levels resulting in poor drug absorption with more drug being available for hepatic clearance [16,22]. The findings of this study suggest that rifampicin is a main medication to prioritize for early TDM for patients for whom TB therapy is failing. Government of India has considered malnutrition among TB patients as a serious concern and framed a national policy to provide financial aid to all TB patients by transferring cash incentive every month to their accounts till the completion of treatment as an initiative to improve their nutritional status [23].

Patients with TB and HIV co-infection are at an increased risk of significant drug-drug interactions due to intake of large number of drugs and these patients may have reduced drug absorption [13]. Patients with diabetes mellitus (DM) may have gastroparesis, which may lead to delayed and/or reduced drug absorption [6]. Several studies have reported both HIV and DM to be associated with decreased plasma levels of rifampicin and isoniazid [4,5,6,13,23-28]. However, in our study there were only two patients with diabetes and only one patient was HIV positive, hence, their effect could not be studied on drug levels.

The relationship between plasma drug concentrations and TB treatment outcome is difficult to predict. Multiple factors, such as the bacillary load, type of strain, virulence, minimum inhibitory concentration in relation to drug concentrations, drug concentrations at the site of lesion, duration of infection, extent of disease, and the immune status and nutritional status of the subject play a role in treatment outcome in addition to drug concentrations [29]. Few studies have examined whether low drug concentrations of anti-TB drugs affect patient response to TB treatment [6,11,30-32]. Low BMI, PTB and disseminated TB, far advanced disease on chest x-ray, bilateral disease on chest x-ray, presence of cavity on chest x-ray and low levels of rifampicin were associated with unfavourable outcome in our study on univariate analysis but none was having significant independent association.

In our study, low plasma levels of only H were not related to TB treatment response. This finding differs from those of previous studies that showed that H and PZA levels were associated with poorer treatment outcomes [33-35]. Our study observed that only low rifampicin levels were associated with poorer treatment outcome similar to one study from

India and other being systematic meta-analysis [33,34]. However, it has also been observed that not all patients with low plasma levels have poor outcome [27,35,36]. The one reason may be that sufficient follow up was not done in such patients after TB treatment completion to rule out early relapse.

In 59 patients having any low levels of drugs, dosage was increased. However, only 28 (47.5%) patients among them reported for repeat TDM. In all these patients repeat levels of R and H were within therapeutic range as per reference values (Table 5). The studies which had done repeat TDM after adjusting the dosages to achieve therapeutic target levels are very few [21,35]. Financial issues, logistic issues, poor patient compliance for follow up were the main reasons for not doing repeat TDM in these studies including ours.

In 68.1% (47/69) of cases, who had taken drugs for at least 6 months of treatment with first-line drugs and demonstrated drug sensitivity and had significantly low drug levels on first TDM, another intervention was done. This included augmentation of standard drug regimen with three or more drugs from second-line class of anti-TB drugs in addition to increasing the dose of first-line drugs.

In our study it was seen that the treatment outcome was favourable in 28/47 (59.6%) patients in whom this intervention was done.

The strength of this study is that this is the first study from high TB prevalence country, wherein the intervention following the demonstration of low blood levels of anti-TB drugs in non-responding TB patients has been discussed. Despite various logistic challenges, the plasma levels of ATT could be repeated in many patients to guide the intervention. Globally also such studies are limited.

The study had some limitations. The effect of comorbidities like diabetes and HIV on low drug levels could not be assessed due to small number of such patients in this study. Also, repeat measurements could not be performed in all in whose dosages were adjusted. Hence, the estimation of dose adjustment necessary to achieve therapeutic drug levels was incomplete. Being a time-consuming and expensive operation, correlating the clinical response to treatment in TB patients with drug exposure (the area under the concentration-time curve from 0 to 24 hours (AUC 0-24)) for crucial anti-TB medications could not be done. Also, genotypic tests like cytochrome polymorphism and N-acetyltransferase 2 gene mutation tests could not be done as a cause for low drug levels in our study population.

Conclusions

To summarize, the low drug levels, particularly of rifampicin, is an important cause for non-response to treatment despite demonstrated drug sensitivity. Various risk factors associated with low drug levels are low BMI, hypoalbuminemia, bilateral disease on chest x-ray and

presence of cavity. Patients with such risk factors may require higher dose of standard anti-TB drugs from beginning for favourable treatment response. Demonstration of low drug levels, though difficult to predict, are clinically important in determining the success of treatment regimen. It is recommended that the facilities for TDM should be available in the country for non- responders, as it provides objective/key information for the treating physician to make informed dosing decisions. If patient presents before completion of six months and/or have minimally low drug levels, the levels of rifampicin and H may need to be increased to achieve the adequate drug levels. However, if patient presents after receiving six months of treatment and/or have significantly low drug levels, the regimen needs to be augmented with 3 or 4 second-line drugs in addition to increasing the dose of R and H.

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Table 1. Demographic, clinical and radiological profile of 75 tuberculosis patients enrolled for therapeutic drug monitoring.

Variable	Numbers
Age (Mean ± SD years)	29.5 ± 12
Age (Median, IQR) years	28 (21-35)
Male sex, n (%)	35 (46.66%)
History of Previous ATT, n (%)	75 (100%)
Duration of ATT (months) (Median, IQR)	12 (7.7-19.7)
HIV Infected, n (%)	1 (1.33%)
Weight (Mean ± SD) kg	49.96 ±13.39
BMI (Mean ± SD) kg/m^2	19.28 ±3.78
Patients with PTB with or without EPTB n (%)	44 (58.66%)
Patients with EPTB n (%)	31 (41.34%)
Cavity lesions on Chest x-ray n (%) Yes No	 32/44 (72.72%) 12/44 (27.28%)
Cavity lesions n (%) Single Multiple	 5/32(15.62%) 27/32 (84.37%)
Chest x-ray Severity n (%) Mild Moderate Far Advanced	 14/44 (31.82%) 14/44 (31.82%) 16/44 (36.36%)
Extent of disease on chest x-ray n (%) Unilateral Bilateral	 18/44 (40.91%) 26/44 (59.09%)
Serum Albumin (Mean ± SD), g/dl Hypoalbuminnemia n (%)	3.65 ±0.61 32 (42.67%)
Haemoglobin (Mean ± SD), g/dl Anaemia n (%)	11.71 ±1.72 40 (53.3%)
Leucocyte count, $X10^9/L$ (median, IQR)	6570 (8950-5350)

SD, standard deviation; IQR, interquartile range; ATT, anti tubercular treatment; HIV, human immunodeficiency virus; PTB, pulmonary tuberculosis; EPTB, extrapulmonary tuberculosis; anaemia <13gm/dL in males, <12gm/dL in females; hypoalbuminemia <3.5gm/dL.

Table 2. Characteristics of tuberculosis patients with low and normal drug levels (univariate analysis).

Variable	Patients with Low levels (n=64)	Patients with Normal levels (n= 11)	P value
Age	29.5 ± 11.89	26.09 ± 11.77	0.30
Sex Males Females	 33 (51.56%) 31 (48.43%)	 3 (27.27%) 8 (72.72%)	0.136
Duration of ATT in months (range)	12 (8-21.2)	11 (6.5-18.2)	0.26
Type of TB- PTB with/ without EPTB Only EPTB	 38 (59.38%) 27 (42.18%)	 6 (54.54%) 5 (45.46%)	0.5
Low BMI Yes No	 29 (45.31%) 35(54.68%)	 1 (18.18%) 10 (81.81%)	**0.04**
Pulmonary-CXR Unilateral Bilateral	 13/38 (34.2%) 25/38 (65.8%)	 5 /6 (83.3%) 1/6 (16.7%)	**0.034**
Pulmonary-CXR Cavity Yes No	 30/38 (78.9%) 8/38 (21.1%)	 2/6 (33.3%) 4/6 (66.7%)	**0.038**
Pulmonary-CXR Cavity Single Multiple	 4/30 (13.33%) 26/30 (86.66%)	 1/2 (50%) 1/2 (50%)	1.667
Pulmonary-CXR severity Mild Moderate Far Advanced	 11/38 (28.9%) 12/38 (31.6%) 15/38 (39.5%)	 3/6 (50%) 2/6 (33.3%) 1/6 (16.7%)	0.662
Anaemia Yes No	 36/64 (56.25%) 28/64 (43.75%)	 4/11 (36.36%) 7/11 (63.63%)	0.221
Hypoalbuminemia Yes No	 31/64 (48.43%) 33/ 64 (51.5%)	 1/11 (9.09%) 10/11 (90.90%)	**0.0147**

ATT, anti tubercular treatment; TB, tuberculosis; PTB, pulmonary tuberculosis; EPTB, extrapulmonary tuberculosis; BMI, body mass index; CXR, chest x-ray; anaemia, <13gm/dL in males, <12gm/dL in females; hypoalbuminemia, <3.5gm/d; low BMI, <18.5kg/m^2.

Table 3. Factors associated with initially low serum levels of rifampicin (with or without isoniazid) among patients who had their levels measured. (n=75) (univariate analysis).

Variable	Patients with Low levels (n=59)	Patients with Normal levels (n=16)	P value
Age	30.42 ± 12.2	26.3 ± 12.1	0.11
Sex Males Females	 32 (54.23%) 27 (45.77%)	 3 13	**0.02**
Duration of ATT (months)	12.5 (8-22)	10.5 (7.2-16.7)	0.36
Type of TB- PTB with/without EPTB EPTB	 38 (64.40%) 21 (35.60%)	 6 (37.5%) 10 (62.5%)	0.08
Low BMI Yes No	 29 (49.15%) 30 (50.85%)	 2 (12.5%) 14 (87.5%)	**0.009**
Pulmonary-CXR Unilateral (n=44) Bilateral	 13 (29.54%) 25 (56.81%)	 5 (11.36%) 1 (2.27%)	**0.034**
Pulmonary-CXR Cavity Yes (n=44) No	 30 (68.2%) 8 (18.2%)	 2 (4.5%) 4 (9.09%)	**0.038**
Pulmonary-CXR Cavity Single (n=32) Multiple	 4 (12.5%) 26 (81.2%)	 1 (3.12%) 1 (3.12%)	0.28
Pulmonary-CXR severity Mild (n=44) Moderate Far Advanced	 11 (25%) 12 (27.3%) 15 (34.09%)	 3 (6.8%) 2 (4.5%) 1 (2.27%)	-
Anaemia Yes No	 36 (61.02%) 23 (38.98%)	 4 (25%) 12 (75%)	**0.01**
Hypoalbuminemia Yes No	 31 (52.5%) 28 (47.5%)	 2 (12.5%) 14 (87.5%)	**0.0042**

ATT, anti tubercular treatment; TB, tuberculosis; PTB, pulmonary tuberculosis; EPTB, extrapulmonary tuberculosis; BMI, body mass index; CXR, chest x-ray; anaemia, <13gm/dL in males, <12gm/dL in females; hypoalbuminemia, <3.5gm/dL.

Table 4. Factors associated with favorable and unfavorable outcomes among 69 patients who were initiated on the revised regimen after the blood levels (univariate analysis).

Risk factor	Subgroup	Favorable Outcome (n=48)	Unfavorable Outcome (n=21)	P value
Gender	Male	19 (39.6%)	13 (61.9%)	0.087
	Female	29 (60.4%)	8 (38.1%)	
HIV	No	48 (100%)	20 (95.2%)	0.304
	Yes	0	1 (4.8%)	
Smoker	No	47 (97.9%)	19 (90.5%)	0.218
	Yes	1 (2.1%)	2 (9.5%)	
DM	No	47 (97.9%)	20 (95.2%)	0.519
	Yes	1 (2.1%0	1 (4.8%)	
Duration of ATT	<12 months	27 (56.2%)	7 (33.3%)	0.080
	>12 months	21 (43.7%)	14 (66.7%)	
BMI	18.5-22.9	18 (37.6%)	6 (28.5%)	**0.010**
	>23	15 (31.2%)	1 (4.8%)	
	<18.5	15 (31.2%)	14 (66.7%)	
Type of patient	PTB with/without EPTB	21 (43.8%)	18 (85.7%)	**0.001**
	EPTB	27 (56.2%)	3 (14.3%)	
Pulmonary-CXR	Normal	27 (56.2%)	3 (14.3%)	**0.000**
	Unilateral	12 (25%)	4 (19%)	
	Bilateral	9 (18.8%)	14 (66.7%)	
Pulmonary-CXR	Normal	27 (56.25%)	3 (14.3%)	**0.003**
	Cavity Yes	15 (31.25%)	15 (71.42%)	
	Cavity No	6 (12.5%)	3 (14.28%)	
No. of cavity in CXR	No cavity	33 (68.75%)	6 (28.6%)	**0.000**
	Single	5 (10.4%)	0 (0%)	
	Multiple	10 (20.8%)	15 (71.4%)	
Pulmonary-CXR	Normal	27 (56.25%)	3 (14.28%)	**0.003**
	Mild	8 (16.66%)	4 (19.04%)	
	Moderate	8 (16.66%)	5 (23.8%)	
	Severe	5 (10.42%)	9 (42.85%)	
Anaemia	No	26 (54.16%)	5 (23.8%)	**0.020**
	Yes	22 (45.84%)	16 (76.2%)	
Hypoalbuminemia	No	31 (64.6%)	7 (33.3%)	**0.016**
	Yes	17 (35.4%)	14 (66.7%)	
Any Blood drug level	Normal	9 (18.8%)	1 (4.8%)	0.263
	Reduced	39 (81.2%)	20 (95.2%)	
Isoniazid level	Normal	27 (56.25%)	10 (47.62%)	0.769
	Low	18 (37.5%)	9 (42.85%)	
	High	3 (6.25%)	2 (9.53%)	
Rifampicin level	Normal	14 (29.16%)	1 (4.8%)	**0.027**
	Low	34 (70.84%)	20 (95.2%)	
Intervention Done	No action	9	1	**0.031**
	Dose increased	11	1	
	Dose increased +augmentation of regimen	28	19	

HIV, human immunodeficiency virus; DM, diabetes mellitus; ATT, anti tubercular treatment; BMI, body mass index; CXR, chest x-ray; anaemia, <13gm/dL in males, <12gm/dL in females; hypoalbuminemia, <3.5gm/dL; low BMI, <18.5kg/m^2.

Table 5. Comparison of the blood levels of the anti-TB drugs at the baseline and after next TDM where TDM could be repeated (n=28).

Drug	Ist TDM	2nd TDM	P value
Isoniazid (Mean ± SD) (Median, IQR)	3.67 ± 2.44 3.49 (1.41-5.46	6.43 ± 6.0 4.89 (3.2-8.18)	0.049
Rifampicin (Mean ± SD) (Median, IQR)	4.83 3.23 5.06 (2.2-6.7)	10.7 5.1 10.02 (8.66-13.05	0.00001

TDM, therapeutic drug monitoring; SD, standard deviation; IQR, interquartile range.