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Time to sputum culture conversion as a predictor of cure in multidrug-resistant tuberculosis patients: a multicenter retrospective cohort study in Pakistan

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Abstract

This study aimed to evaluate how the time to sputum culture conversion (SCC) predicts cure and to identify factors associated with delayed SCC and cure among multidrug-resistant tuberculosis (MDR-TB) patients receiving longer treatment regimens of 18-24 months. This multicenter retrospective cohort study was conducted at eight programmatic management units. A total of 462 patients with confirmed pulmonary MDR-TB were enrolled at eight PMDT sites between January 2017 and August 2018 with available treatment outcomes till 30th June, 2020. Survival analysis was done using the Kaplan-Meier curve, and Cox proportional hazards model and binary logistic regression were performed to determine factors associated with time to SCC and cure. Statistical significance was set at $p<0.05$. A total of 424/462 (91.8%) patients achieved SCC, with a cure rate of 75.5%. The mean time to SCC was 2.4 months (interquartile range = 1-3 months). Factors such as employment [hazard ratio (HR)=0.654, p=0.001], sputum smear grading score +2+3 (HR = 0.638, p=0.014), resistance to first-line drugs HREZ (HR=0.716, p=0.014), and resistance to second-line drugs, fluoroquinolones (HR=0.698, p 0.001) were significantly associated with SCC. In the current study, the cure rate was 75.5% (349/462). In the binary logistic regression, month 1 [odds ratio (OR)=2.601, p 0.001), month 2 (OR=3.14, p 0.001), month 3 (OR=5.219, p 0.001), month 4 (OR=6.788, p 0.001), month 5 (OR=21.512, p 0.001), and month 6 (OR=31.806, p 0.001) had a statistically significant association with cure. In predicting cure, the overall sensitivities of SCC at 1, 2, 3, 4, 5, and 6 months were 37.2%, 64.1%, 85.9%, 91.1%, 97.4%, and 98.2%, respectively, and the specificities were 81.4%, 63.7%, 46.0%, 39.8%, 36.2%, and 35.3%, respectively. Interestingly, the combined sensitivity and specificity of SCC at 3 and 4 months in predicting cure were similar to those observed at 5 and 6 months.

Key words: drug resistant-TB, longer treatment regimen, MDR-TB, Pakistan, sputum culture conversion, tuberculosis.

Introduction

Multi-drug resistant tuberculosis (MDR-TB) is a form of drug-resistant TB where the mycobacteria is resistant to the two most effective and inexpensive first-line drugs, isoniazid and rifampicin [1]. MDR-TB is more difficult to treat because it requires prolonged use of second-line drugs (SLDs), which are less effective and often cause adverse effects and poor outcomes [1]. According to the World Health Organization (WHO) report, in 2021, about 10.6 million people worldwide contracted TB, resulting in 1.3 million deaths. Among those cases, around 410,000 involved MDR/RR strains of Mycobacterium tuberculosis (MTB). Pakistan is ranked as the 5th highest TB burden country and annually contributes to nearly 5.8% of new cases of TB worldwide. Out of the 573,000 new cases estimated for 2020, a total of 276736 (48%) were notified [2]. MDR-TB treatment is provided and monitored throughout the country by the National Tuberculosis Control Program (NTP) and the Global Fund. MDR-TB is more difficult to treat and has a lower success rate than susceptible tuberculosis [3,4].

A bacteriological conversion occurs when a patient with bacteriologically confirmed TB has at least two consecutive negative cultures (for DR-TB and DS-TB) or smears (for DS-TB only), taken on different occasions at least 7 days apart [5]. SCC is usually the primary goal in MDR-TB treatment, guiding therapy adjustments, transitioning patients from the intensive to continuation phase, and determining treatment outcomes [6]. SCC is the primary and most consistent sign of anti-TB therapy; it indicates non-infectiousness and effectiveness in the treatment of pulmonary tuberculosis (PTB) [7]. SCC is used as an early microbiological marker in phase II tuberculosis treatment trials due to its assumed predictive value for end-of-treatment outcomes [8]. Several studies investigating the association between SCC and treatment outcomes in MDR-TB patients have found that the time to SCC is strongly associated with treatment success, with SCC achieved after two months of treatment being an early indicator of positive outcomes in MDR-TB patients [6,8,9]. However, the low sensitivity of SCC at two months in predicting MDR-TB treatment outcomes is concerning, as many treatments that lead to good long-term results may not meet the SCC criteria at two months [8,10]. Although SCC is important in MDR-TB treatment, our review of the literature found that very few studies from Pakistan have explored the predictors of delayed SCC in MDR-TB patients [11,12] or examined the link between SCC at different time points and treatment outcomes [13]. Since early detection of a patient's non-response to MDR-TB treatment could allow doctors to adjust medications and prevent treatment failure, this study was conducted to assess the factors associated with time to SCC and cure, as well as the sensitivity, specificity,

positive predictive value (PPV), and negative predictive value (NPV) of SCC at 1, 2, 3, 4, 5, and 6 months of treatment.

Materials and Methods

Study design, setting and population

This was a retrospective cohort study using the NTP Pakistan database. The MDR-TB patients who were treated with conventional or longer treatment regimen from the following eight PMDT units: i) Lady Reading Hospital (LRH) Peshawar ii) Saidu Teaching Hospital (STH) Swat iii) Medical Teaching Institute (MTI) Mardan iv) Rawalpindi Leprosy Hospital (LRH) Rawalpindi v) District Head Quarter (DHQ) Hospital Faisalabad vi) Nishter Hospital (NH) Multan vii) Sheikh Zaid Hospital (SZH) Rahimyar Khan and viii) Jinnah Hospital Lahore (JHL). All the patients who were diagnosed, culture confirmed, for MDR-TB and who were registered in their respective PMDT units from January 2017 to August 2018 with available treatment outcomes till 30th June 2020 were included in the study

Patients with extrapulmonary MDR-TB, incomplete DST, negative baseline culture, and lost to follow-up before culture conversion were excluded from the study (Figure 1).

Bacteriology, drug susceptibility testing (DST)

All suspected DRTB cases reported to the study sites were evaluated using two sputum samples for acid-fast bacilli, with Ziehl-Neelsen staining and the Xpert MTB/RIF (Cepheid) test. Following positive results from smear microscopy and rapid DST, sputum samples were sent to Provincial TB reference laboratories for further sputum culture and DST. The DST was conducted using the Agar proportion method on enriched Middlebrook 7H10 medium (BBL; Beckton Dickinson) at the following concentrations (WHO, 2012): rifampicin (1 µg/mL), isoniazid (0.2 µg/mL), streptomycin (2 µg/mL), ethambutol (5 µg/mL), ofloxacin (2 µg/mL), amikacin (4 µg/mL), kanamycin (5 µg/mL), capreomycin (4 µg/mL), and ethionamide (5 µg/mL). The DST for pyrazinamide was performed at a concentration of 100 µg/mL using a Mycobacterial Growth Indicator Tube (Becton Dickinson) according to the manufacturer's instructions. DST was performed at baseline and repeated as necessary, while acid-fast bacilli culture and sputum smears were conducted on a monthly basis

Treatment protocol

Upon positive sputum smear microscopy and rapid DST, presumed MDR-TB patients underwent baseline laboratory tests, including a complete blood count, screening for human immunodeficiency virus and hepatitis, liver, kidney, and thyroid function tests, random blood glucose, electrolytes, and urinalysis. Once the screening tests at baseline were completed, MDR-TB patients were enrolled to be treated with a longer treatment regimen according to the NTP guidelines [14]. All MDR-TB patients were treated with KM/AM/CM + OFX/LFX + ETH + cyclosporine (CS) + PZA + vitamin B6, except for those who had previously used SLDs. Patients who had previously used SLDs were treated with the same regimen along with para-amino salicylic acid (PSA). After the confirmed results of DST, patients were shifted to individualized and empirical treatment regimens, respectively. The LTR was modified based on the DST results of patients, which comprised four effective or likely effective SLDs + PZA and vitamin B6. All drugs were administered at their maximum prescribed dosages, which were determined by the patients' body weights. Treatment of all patients after sputum culture conversion (SCC) was continued for a minimum of 18 months. The SLDs and injectables were provided for a minimum of six month and a maximum of eight months after SCC. All patients were assessed monthly and treated as outpatients. To ensure treatment adherence, patients were monitored by trained treatment supporters. A trained PMDT Home Directly Observed Treatment Linkages (HDL) facilitator had continuous visits to the patients' homes to develop links between the patients and the PMDT unit and District TB officers. All the drugs used in the treatment were free of cost, along with free food ration and convincing allowance to the patient and the supporter.

Data collection

The NTP receives DR-TB data from respective PMDT units across the country through an electronic nominal recording and reporting system (ENRS) on a monthly basis. A data collection form was designed and used to extract patients' sociodemographic, microbiological, and clinical data from the ENRS shared with NTP.

Statistical analysis

SPSS version 23 was used for data analysis. Chi-square and Fisher's exact tests were used to determine the association between variables where appropriate. The time to initial sputum culture conversion was calculated using the Kaplan–Meier method, and the log-rank test was used to analyze differences between the groups. To identify factors associated with the time to SCC,

survival analysis using the Cox proportional hazards model was performed. Sputum cultures that were not converted before the last follow-up were censored. To estimate the association of 1 month to 6 months of sputum culture conversion with cure, odds ratios (ORs) were calculated at 95% CIs with binary logistic regression, and a p-value less than 0.05 were considered significant. We also evaluated the sensitivity, specificity, PPV, and NPV of SCC at 1, 2, 3, 4, 5, and 6 months for predicting treatment outcomes. Receiver operating characteristic curves were plotted to visualize the effect of different time points for SCC on the balance between sensitivity and specificity.

Results

Socio-demographic and clinical characteristics of study participants of SCC

In total, 462 patients were included in the study and evaluated. Baseline sociodemographic and clinical characteristics of the patients included in the final analysis are presented in Table 1. The Minimal and maximal age of patients was (5-78) respectively and mean age of the patients was 32.36 ± 16.03 years, the majority of them were male (53.7%), had a history of previous TB treatment (87.2%), no history of SLD use (94.6%), and did not suffer from concurrent co-morbidity (58.0%).

Time to sputum culture conversion and cure rate

A total of 424/462 (91.8%) patients achieved sputum culture conversion (SCC). The mean time to SCC was 2.34 $\pm$ 1.58 months. 151 patients (32.7%) were culture-negative in the first month of treatment, 265 (57.4%) in the second month, 361 (78.1) in the third month, 386 (83.5%) in the fourth month, 412 (89.2%) in the fifth month, 416 (90.0%) in the sixth month, and 38/462 (8.2%) did not achieve SCC, as shown in Table 2 and Figure 2a. The cure rate in this study was 75.5 %, and the observed rate of SCC was significantly greater among patients who had a final outcome cure than among those who did not. The time to initial SCC was also significantly different between those who cured results and those who did not X^2 =28.3, p-value= 0.001 (Figure 2b).

Factors associated with initial sputum culture conversion

In univariate survival analysis, factors such as employment (HR = 0.654, p = 0.001), active and ex-smoker (0.684, p=0.050), history of previous SLD use (HR = 0.728, p = 0.178), sputum smear grading scanty+1 (HR = 0.765, p = 0.117), +2+3 (HR = 0.638, p = 0.014), resistance to first-line drugs HRZ (HR = 0.801, p = 0.072), HREZ (HR=0.716, p= 0.014), and resistance to second-line

drugs such as fluoroquinolones (HR= 0.698, p 0.001) were significantly associated with SCC. All variables in the univariate analysis had a p-value <0.2 were entered into the multivariate survival analysis. The results of the multivariate Cox proportional hazards model revealed that employment (hazard ratio [HR] = 1.438, p=0.013) had a statistically significant association with time to SCC (Table 3).

Diagnostic performance of 1–6-month SCC in predicting cure

In the current study, the cure rate was 349/462 (75.5%). In binary logistic regression month 1 (OR=2.601, p-value= <0.001), month 2 (OR=3.14, p-value= <0.001) month 3 (OR=5.219, p-value= <0.001) month 4 (OR=6.788, p-value= <0.001) month 5 (OR=21.512, p-value= <0.001) month 6 (OR=31.806, p-value= <0.001) had statistically significant association. In predicting cure, the overall sensitivities of sputum culture conversion at 1, 2, 3, 4, 5, and 6 months were 37.2%, 64.1%, 85.9%, 91.1%, 97.4%, and 98.2%, respectively. Whereas specificities were 81.4%, 63.7%, 46.0%, 39.8%, 36.2%, and 35.3%, respectively. The positive predictive values (PPV) at 1, 2, 3, 4, 5, and 6 months were 86.0, 84.5, 83.1, 82.3, 82.5, and 82.4, respectively, and the negative predictive values (NPV) at 1, 2, 3, 4, 5, and 6 months were 29.5, 36.5, 51.4, 59.2, 82.0, and 86.9, respectively, as shown in Table 4.

Discussion

Routine sputum culture monitoring is crucial for successful MDR-TB management, as SCC consistently predicts therapeutic efficacy and time to SCC is an early predictor of treatment outcomes [15]. Few studies have been conducted in Pakistan to address these problems [11,13,16]. The current study examined the time to SCC and predictors of early SCC in patients with MDR-TB receiving a longer treatment regimen. This study included a total 462 patients who were diagnosed and culture-confirmed pulmonary MDR-TB. It examined the expected value of SCC at various time points for the purpose of predicting the cure. Overall, the findings of this study were that 424/462 (91.8%) patients achieved SCC which is better than other studies range 70-90% [15,17-20]. The mean time to SCC was 2.4 months (IQR = 1-3 months) which is in the upper range of 2-3 months reported in previous studies [13,21]. All the factors correlated with delayed SCC were common in patients with unsuccessful treatment results in the current study, including resistance to fluoroquinolones, baseline sputum smear, and a resistant to all FLDs. We observed significantly delayed SCC in individuals who were resistant to fluoroquinolones, as well as a high probability of death and treatment failure [22-25]. Susceptibility to fluoroquinolones has been

widely associated with cure and early SCC in MDR-TB patients [26,27]. The non-prescription selling, over-the-counter availability, and inappropriate prescribing of fluoroquinolones by physicians are significant contributors to the rise in fluoroquinolone resistant MDR-TB strains in Pakistan [28,29]. In our study, resistance to FLDs (RHEZ) was linked with delayed SCC, whereas another study conducted by Anila Basit et al. observed an association between resistance to FLDs and culture conversion in Pakistan [11]. Some other research studies are deficient in terms of information on resistance to FLDs and cultural conversion [12,16,30]. Other variables such as occupation, co morbidities, and smoking history were associated to prolong SCC time [31-33].

The time to SCC was found to be strongly associated with treatment outcomes cure. In Univariate analysis SCC at month 1, 2, 3, 4, 5, and 6 had a statistically significant positive association with cure. Stronger association has been observed of SCC with successful outcomes from 3-6 months in other studies [8,10,13]. In this study we have evaluated the sensitivity and specificity of SCC at month1-6, month-1 showed a low sensitivity of 37.2 % and a high specificity of 81.4% for predicting cure compared to not cure. While at months 2 showed sensitivity of 64.1% and specificity of 63.7%, due to the low sensitivity of SCC at two months of treatment (64.1 %), 35.9% with final cure would be misjudged as treatment failures if it were employed as a proxy marker for final outcomes which has been also discussed by Javaid et al. [13]. Such misjudge may result in an underestimation of a regimen's overall therapeutic efficacy, the substitution of useful drugs, the termination of potentially effective regimens [8,10], and the addition of unnecessary drugs. The high sensitivity of SCC at 5 months (97.4 %) and 6 month (98.2%) in the current study shows that treatment that failed to produce SCC at this time point was unlikely to cure. However, due to the low specificity (35.3 %) at 6 months, suggests that 64.7 % with subsequent unsuccessful outcomes would be misjudged as cured hence exaggerating the regimen's effectiveness. The results of this study show that while achieving SCC (Sputum Culture Conversion) after two months can give some confidence in the treatment's success, it may not be a strong enough indicator due to its low sensitivity. Failing to reach SCC at two months might be too soon to decide if the regimen is working or needs to be changed, unless the patient's condition is getting worse. Kurbatova et al. [8] mentioned that waiting six months for SCC might be too long, depending on the patient's overall health. In most cases, doctors wouldn't wait that long before considering a change in regimen. In most circumstances, professionals would not wait 6 months before reevaluating and modifying the patient's regimen. In our study, the sensitivity and specificity of SCC at three months were 85.9% and 46.0%, and at four months were 91.1% and 39.8%. These values were similar to SCC at six months, which had a sensitivity of 98.2% and a specificity of 35.3%. Using SCC at

four months, which has a high positive predictive value (PPV) of 82.3% and a negative predictive value (NPV) of 59.2%, can help doctors decide on regimen effectiveness earlier, which has also been discussed in other studies conducted elsewhere [13,34]. The study's significant limitation is its retrospective approach and inability to evaluate entire culture conversion. Very important variables which are associated with delayed SCC and unsuccessful treatments outcome, occupation, smoking history, co morbidities and lungs cavitations [15,35] were lacking the information.

Conclusions

At six months, the association between SCC and cure was much stronger than at four and two months of treatment. However, the low sensitivity of SCC at 1 and 2 months, and the low specificity at 5 and 6 months, suggest that none of these markers is perfect for predicting cure in patients with MDR-TB. Patients who eventually had poor treatment outcomes often missed the chance to switch to a more effective regimen. Since the combined sensitivity and specificity of SCC at 3 and 4 months were similar to those at 5 and 6 months, using SCC at month 3 or 4 as a marker for predicting cure could help doctors make decisions about regimen effectiveness earlier. The strengths of this study include its large sample size and the fact that it included patients with varying levels of disease severity and drug resistance. Even though the study covered eight different sites, patients with MDR-TB from a wide geographical area were treated. However, because we didn't have information on the cause of death, we couldn't confirm if all deaths were due to tuberculosis. Additionally, because this study was retrospective, we couldn't assess how the ADRs or changes in regimen impacted SCC and overall treatment outcomes. Another limitation of the study that the authors should consider is that the study included patients treated between 2017 and 2018, and the treatment of MDR-TB has evolved significantly since then.

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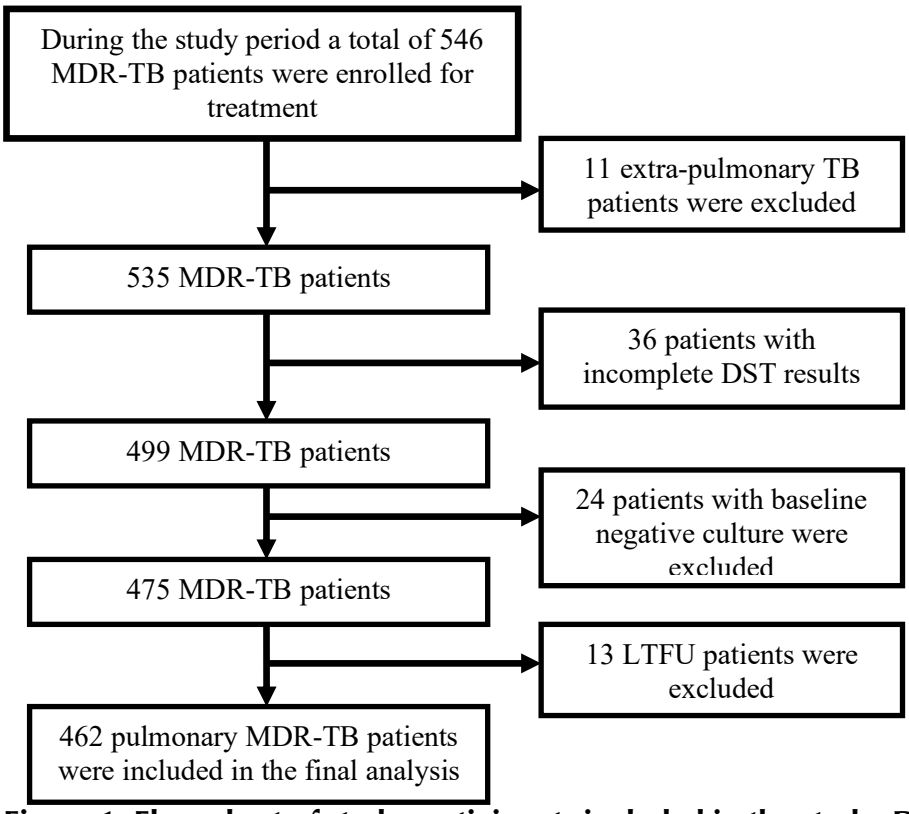

Figure 1. Flow chart of study participants included in the study. DST, drug susceptibility testing; LTFU, lost to follow-up; MDR-TB, multi drug resistant tuberculosis.

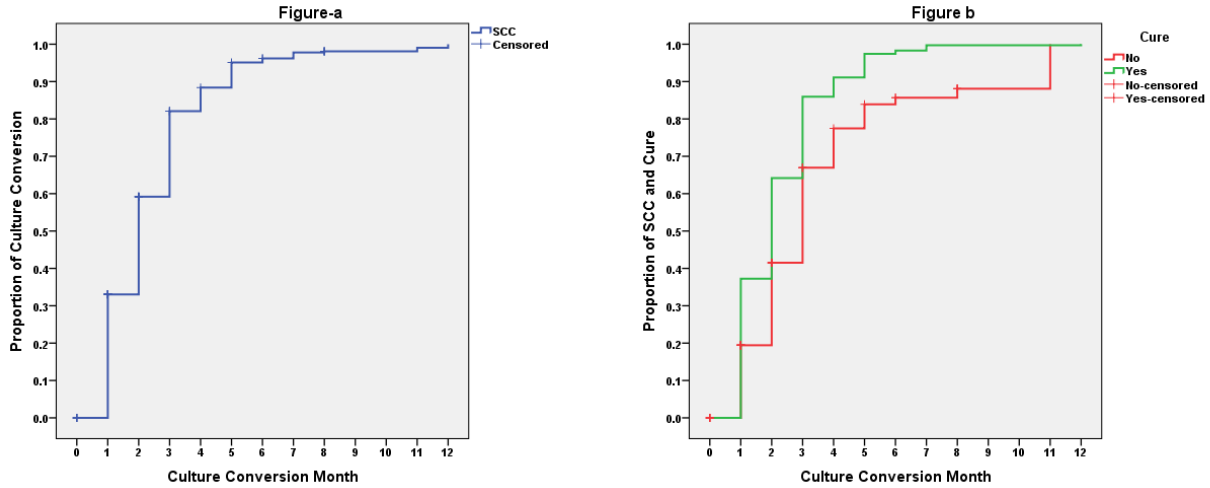

Figure 2. a) Kaplan–Meier survival curve of time to initial sputum culture conversion of 462 MDR-Tb patients; b) Kaplan–Meier survival curve of sputum culture conversion time in cure compared with not cure individuals.

Table 1. Socio-demographic and clinical characteristics of study participants of SCC.

Variable	Total No (%)	Sputum Culture Conversion		p
		No, N (%)	Yes, N (%)	
Gender				0.892
Female	248 (53.7)	20 (8.1)	228 (91.9)	
Male	214 (46.3)	18 (8.4)	196 (91.6)	
Age (years)				0.153
< 21	149 (32.3)	9 (6.0)	140 (94.0)	
21-40	177 (38.3)	12 (6.8)	165 (93.2)	
41-60	104 (22.5)	12 (11.5)	92 (88.5)	
> 60	32 (6.9)	5 (15.6)	27 (84.4)	
Baseline body weight (Kg)				0.153
<40	158 (34.2)	17 (10.8)	141 (89.2)	
40	304 (65.8)	21 (6.9)	283 (93.1)	
Employment				**0.001**
Unemployed	303 (35.1)	16 (5.3)	287 (94.7)	
Employed	159 (34.4)	22 (13.8)	137 (86.2)	
Smoking				0.806
Non smoker	430 (93.1)	35 (8.1)	395 (91.9)	
Active + Exsmoker	32 (6.9)	3 (9.4)	29 (90.6)	
History of TB treatment				0.411
No	97 (21.0)	6 (6.2)	91 (93.8)	
Yes	365 (79.0)	32 (8.8)	333 (91.2)	
History of SLDs used				**0.003**
No	437 (94.6)	32 (7.3)	405 (92.7)	
Yes	25 (5.4)	6 (24.0)	19 (76.0)	
Baseline sputum smear grading				0.085
Negative	42 (9.1)	2 (4.8)	40 (95.2)	
Scanty+1	274 (59.3)	18 (6.6)	256 (93.4)	
+2+3	146 (31.6)	18 (12.3)	128 (87.7)	
Co morbidities				0.173
No	391 (84.6)	33 (8.4)	358 (91.6)	
Yes	71(15.4)	5 (7.0)	66 (93.0)	
Lungs Cavitation				0.260
No	383 (82.9)	29 (7.6)	354 (92.4)	
Yes	79 (17.1)	9 (11.4)	70 (88.6)	
Registration Group				**0.002**
New	96 (20.8)	6 (6.2)	90 (93.8)	
Failure	215 (46.5)	9 (4.2)	206 (95.8)	
Relapse	113 (24.5)	19 (16.8)	94 (83.2)	
Last to Follow up	25 (5.4)	4 (16.0)	21 (84.0)	
Transferred in	13 (2.8)	0 (0.0)	13 (100)	
Resistance to FLDs				0.145
Resistance to HR	230 (49.8)	15 (6.5)	215 (93.5)	
Resistance to HRE	38 (8.2)	4 (10.5)	34 (89.5)	
Resistance to HRZ	110 (23.8)	15 (13.6)	95 (86.4)	
Resistance to HREZ	79 (17.1)	4 (5.1)	75 (94.9)	
Resistance to HREZS	5 (1.1)	0 (0.0)	5 (100.0)	
Resistance to SLDs				0.195
No Resistance	253 (54.8)	17 (6.7)	236 (93.3)	
Resistance to FQ	209 (45.2)	21 (10.0)	188 (90.0)	

FLD: first line anti-TB drugs, MDR-TB: multidrug resistant TB, SCC: sputum culture conversion, Scanty: 1–9 AFB (Acid fast bacilli)/100 HPF (High power field), SLD: Second line anti-TB drugs, +1: 10–99 AFB/100 HPF, +2: 1–9 AFB/HPF, +3: > 9 AFB/HPF.

Table 2. Sputum culture conversion and cure among culture converted multidrug resistant TB patients (N=462)

Sputum culture conversion	No (%)	Yes (%)	Cured /SCC (%)
SCC at One months	311 (67.3)	151 (32.7)	130/151 (86.1)
SCC at Two months	197 (42.6)	265 (57.4)	224/265 (84.5)
SCC at Three months	101 (21.9)	361 (78.1)	300/361 (83.1)
SCC at Four months	76 (16.5)	386 (83.5)	318 /386(82.3)
SCC at Five months	50 (10.8)	412 (89.2)	340 /412 (82.5)
SCC at Six months	46 (10.0)	416 (90.0)	343 /416 (82.4)
Overall SCC	38 (8.2)	424 (91.8)	349/424

NA: not available, SCC: sputum culture conversion.

Table 3. Predictors of time to sputum culture conversion in multidrug resistant TB patients.

Variable	SCC		COX Regression HR* (95%CI)	p
	No, N (%)	Yes, N (%)		
Gender				
Female	20 (8.1)	228 (91.9)		
Male	18 (8.4)	196 (91.6)	0.907 (0.749-1.098)	0.316
Age (years)				
< 21	9 (6.0)	140 (94.0)		
21-40	12 (6.8)	165 (93.2)	0.984 (0.785-1.234)	0.889
41-60	12 (11.5)	92 (88.5)	0.856 (0.657-1.115)	0.248
> 60	5 (15.6)	27 (84.4)	0.837 (0.837-1.912)	0.265
Baseline body weight				
<40	17 (10.8)	141 (89.2)		
40	21 (6.9)	283 (93.1)	0.981 (0.800-1.203)	0.854
Employment				
Unemployed	16 (5.3)	287 (94.7)		
Employed	22 (13.8)	137 (86.2)	0.654 (0.531-0.805)	**0.001**
Smoking				
Non smoker	35 (8.1)	395 (91.9)		
Active + Exsmoker	3 (9.4)	29 (90.6)	0.684 (0.468-1.000)	0.050
History of TB treatment				
No	8 (13.6)	51 (86.4)		
Yes	30 (7.4)	373 (92.6)	0.857 (0.639-1.149)	0.303
History of SLDs used				
No	32 (7.3)	405 (92.7)		
Yes	6 (24.0)	19 (76.0)	0.728 (0.459-1.156)	0.178
Baseline sputum smear grading				
Negative	2 (4.8)	40 (95.2)		
Scanty+1	18 (6.6)	256 (93.4)	0.765 (0.548-1.069)	0.117
+2+3	18 (12.3)	128 (87.7)	0.638 (0.447-0.912)	**0.014**
Co morbidities				
No	33 (8.4)	358 (91.6)		
Yes	5 (7.0)	66 (93.0)	0.963 (0.740-1.253)	0.778
Lungs Cavitation				
No	29 (7.6)	354 (92.4)		
Yes	9 (11.4)	70 (88.6)	0.868 (0.672-1.122)	0.280
Registration Group				
New	6 (6.2)	90 (93.8)		
Failure	9 (4.2)	206 (95.8)	0.946 (0.738-1.213)	0.661
Relapse	19 (16.8)	94 (83.2)	1.053 (0.788-1.407)	0.725
Last to Follow up	4 (16.0)	21 (84.0)	0.871 (0.540-1.403)	0.569
Transferred in	0 (0.0)	13 (100)	0.684 (0.382-1.224)	0.201
Resistance to FLDs				
Resistance to HR	15 (6.5)	215 (93.5)		
Resistance to HRE	4 (10.5)	34 (89.5)	0.867 (0.604-1.246)	0.441
Resistance to HRZ	15 (13.6)	95 (86.4)	0.801 (0.629-1.020)	0.072
Resistance to HREZ	4 (5.1)	75 (94.9)	0.716 (0.549-0.934)	**0.014**
Resistance to HREZS	0 (0.0)	5 (100.0)	0.911 (0.375-2.212)	0.836
Resistance to SLDs				
No Resistance	17 (6.7)	236 (93.3)		
Resistance to FQ	21 (10.0)	188 (90.0)	0.698 (0.575-0.847)	**0.000**

CI: Confidence interval, FLD: First line anti-TB drugs, HR*: Hazards ratio, kg: Kilogram, MDR-TB: Multidrug resistant TB, SCC: Sputum culture conversion, Scanty: 1–9 AFB (Acid fast bacilli)/100 HPF (High power field), SLD: Second line anti-TB drugs.

Table 4. Association of sputum culture conversion at different time points with cured

Month of treatment	Cured		Univariate analysis* (95% CI)	p	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
	No (%)	Yes (%)						
1- month								
Did not convert	92 (29.6)	219 (70.4)	2.601 (1.544-4.380)	**<0.001**	37.2 (32.2-42.5)	81.4 (72.7-87.8)	86.0 (79.2-90.9)	29.5 (24.6-35.0)
Converted	21 (13.9)	130 (86.1)						
2- month								
Did not convert	72 (36.5)	125 (63.5)	3.147 (2.024-4.894)	**<0.001**	64.1 (58.8-69.1)	63.7 (54.0-72.4)	84.5 (79.4-88.5)	36.5 (29.9-43.7)
Converted	41 (15.5)	224 (84.5)						
3- month								
Did not convert	52 (51.2)	49 (48.5)	5.219 (3.237-8.414)	**<0.001**	85.9 (81.7-89.3)	46.0 (36.6-55.6)	83.1 (78.7-86.7)	51.4 (41.3-61.4)
Converted	61 (16.9)	300 (83.1)						
4-month								
Did not convert	45 (59.2)	31 (40.8)	6.788 (4.007-11.500)	**<0.001**	91.1 (87.5-93.7)	39.8 (30.8-49.4)	82.3 (78.1-85.9)	59.2 (47.3-70.1)
Converted	68 (17.6)	318 (82.4)						
5- month								
Did not convert	41 (82.2)	9 (18.0)	21.512 (10.011-46.228)	**<0.001**	97.4 (94.9-98.7)	36.2 (27.5-45.9)	82.5 (78.4-85.9)	82.0 (68.0-90.9)
Converted	72 (17.5)	340 (82.5)						
6-month								
Did not convert	40 (87.0)	6 (13.0)	31.806 (12.806-76.621)	**<0.001**	98.2 (96.1-99.2)	35.3 (26.7-45.0)	82.4 (78.3-85.9)	86.9 (73.0-94.5)
Converted	73 (17.5)	343 (82.5)						

CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value; * Univariate binary logistic regression analysis.