Monaldi Archives for Chest Disease

Monaldi Archives for Chest Disease 2026; 96:3200
doi: 10.4081/monaldi.2025.3200

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

Abdul Wahid,[1] Nafees Ahmad,[2] Fahad Saleem,[2] Amjad Khan,[1] Asad Khan,[2] Faiz Ullah Khan,[3] Farman Ullah Khan[4]

[1]Department of Pharmacy, Quaid I Azam University, Islamabad; [2]Department of Pharmacy Practice, Faculty of Pharmacy and Health Sciences, University of Balochistan, Quetta; [3]Department of Pharmacy, CECOS University of Science and Technology, Peshawar; [4]Faculty of Pharmacy, Department of Pharmacy Practice, Capital University of Science and Technology Islamabad, Pakistan

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 Programmatic Management of Drug-resistant Tuberculosis 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.

Correspondence to: Abdul Wahid, Department of Pharmacy, Quaid I Azam University, Islamabad, Pakistan.
Tel.: 0092-3218020076. E-mail: wahiduob@gmail.com

Introduction

Multidrug-resistant tuberculosis (MDR-TB) is a form of drug-resistant TB where the mycobacteria are 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 276,736 (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 TB [3,4].

A bacteriological conversion occurs when a patient with bacteriologically confirmed TB has at least two consecutive negative cultures [for drug-resistant tuberculosis (DR-TB) and drug-susceptible tuberculosis (DS-TB)] or smears (for DS-TB only), taken on different occasions at least 7 days apart [5]. Sputum culture conversion (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 TB [7]. SCC is used as an early microbiological marker in phase II TB 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 2 months of treatment being an early indicator of positive outcomes in MDR-TB patients [6,8,9]. However, the low sensitivity of SCC at 2 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 2 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 Programmatic Management of Drug-resistant Tuberculosis (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 bacteriology, drug susceptibility testing (DST), negative baseline culture, and lost to follow-up before culture conversion were excluded from the study (Figure 1).

Bacteriology, drug susceptibility testing

All suspected DR-TB 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 (Beckton Dickinson, Franklin Lakes, NJ, USA) at the follow-

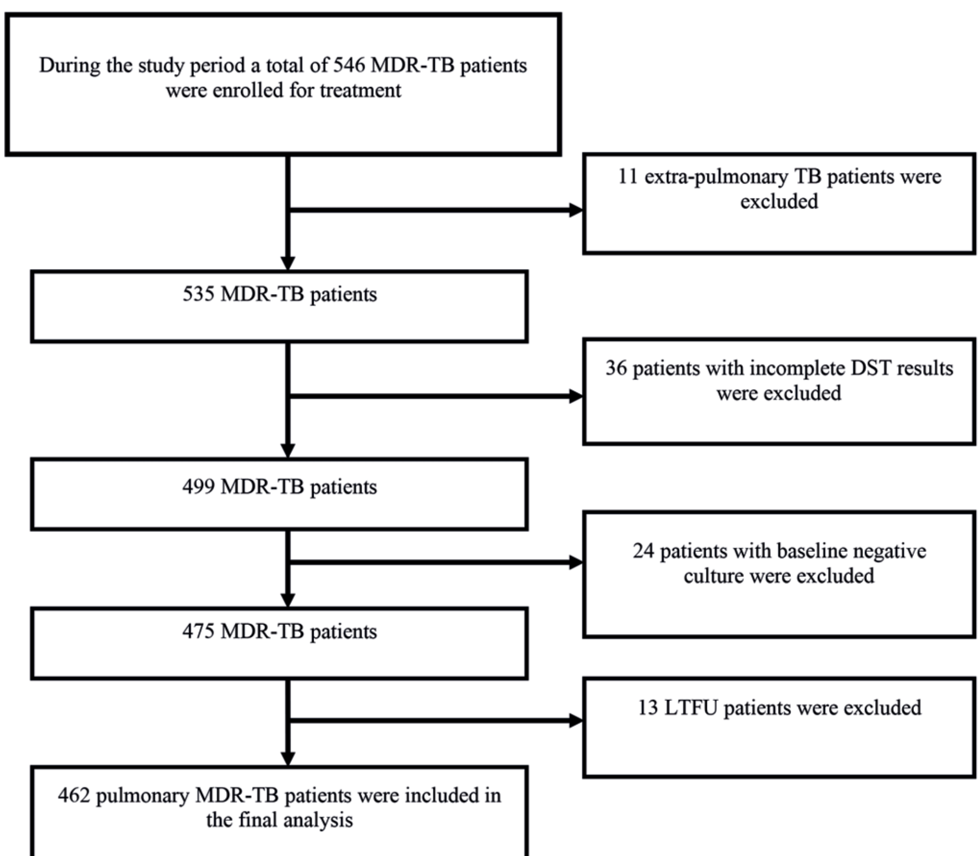


Figure 1. Flow chart of study participants included in the study. DST, drug susceptibility testing; LTFU, lost to follow-up; MDR-TB, multi drug resistant tuberculosis.

ing 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 (Beckton Dickinson, Franklin Lakes, NJ, USA) 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 kanamycin/amikacin/capreomycin + ofloxacin/levofloxacin + ethionamide + cyclosporine + pyrazinamide + 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. After the confirmed results of DST, patients were shifted to individualized and empirical treatment regimens, respectively. The longer treatment regimen 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 SCC was continued for a minimum of 18 months. The SLDs and injectables were provided for a minimum of 6 months and a maximum of 8 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 SCC 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 SCC with cure, odds ratios (OR) were calculated at 95% confidence interval with binary logistic regression, and a p-value less than 0.05 was 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 sputum culture conversion

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 and 78, respectively and the mean age of the patients was 32.36±16.03 years. The majority of patients 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 SCC. The mean time to SCC was 2.34±1.58 months. 151 patients (32.7%) were culture-negative in the first month of treatment, 265 (57.4%) in the second, 361 (78.1) in the third, 386 (83.5%) in the fourth, 412 (89.2%) in the fifth, 416 (90.0%) in the sixth, 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 had cured results and those who did not X^2=28.3, p=0.001 (Figure 2b).

Factors associated with initial sputum culture conversion

In univariate survival analysis, factors such as employment [hazard ratio (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 with p<0.2 were entered into the multivariate survival analysis. The results of the multivariate Cox proportional hazards model revealed that employment (HR=1.438, p=0.013) had a statistically significant association with time to SCC (Table 3).

Diagnostic performance of 1-6-month sputum culture conversion 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<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 statistically significant associations. 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. Whereas specificities were 81.4%, 63.7%, 46.0%, 39.8%, 36.2%, and 35.3%, respectively. The 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 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 out-

Table 1. Socio-demographic and clinical characteristics of study participants of sputum culture conversion.

Variable	Total n (%)	Sputum culture conversion No, n (%)	Sputum culture conversion Yes, n (%)	p
Gender				
Female	248 (53.7)	20 (8.1)	228 (91.9)	0.892
Male	214 (46.3)	18 (8.4)	196 (91.6)	
Age (years)				
<21	149 (32.3)	9 (6.0)	140 (94.0)	0.153
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)				
<40	158 (34.2)	17 (10.8)	141 (89.2)	0.153
≥40	304 (65.8)	21 (6.9)	283 (93.1)	
Employment				
Unemployed	303 (35.1)	16 (5.3)	287 (94.7)	0.001
Employed	159 (34.4)	22 (13.8)	137 (86.2)	
Smoking				
Non smoker	430 (93.1)	35 (8.1)	395 (91.9)	0.806
Active + ex-smoker	32 (6.9)	3 (9.4)	29 (90.6)	
History of TB treatment				
No	97 (21.0)	6 (6.2)	91 (93.8)	0.411
Yes	365 (79.0)	32 (8.8)	333 (91.2)	
History of SLDs used				
No	437 (94.6)	32 (7.3)	405 (92.7)	0.003
Yes	25 (5.4)	6 (24.0)	19 (76.0)	
Baseline sputum smear grading				
Negative	42 (9.1)	2 (4.8)	40 (95.2)	0.085
Scanty+1	274 (59.3)	18 (6.6)	256 (93.4)	
+2+3	146 (31.6)	18 (12.3)	128 (87.7)	
Co morbidities				
No	391 (84.6)	33 (8.4)	358 (91.6)	0.173
Yes	71(15.4)	5 (7.0)	66 (93.0)	
Lungs cavitation				
No	383 (82.9)	29 (7.6)	354 (92.4)	0.260
Yes	79 (17.1)	9 (11.4)	70 (88.6)	
Registration group				
New	96 (20.8)	6 (6.2)	90 (93.8)	0.002
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				
Resistance to HR	230 (49.8)	15 (6.5)	215 (93.5)	0.145
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				
No Resistance	253 (54.8)	17 (6.7)	236 (93.3)	0.195
Resistance to FQ	209 (45.2)	21 (10.0)	188 (90.0)	

TB, tuberculosis; SLDs, second-line anti-TB drugs; FLDs, first-line anti-tuberculosis drugs; HR, isoniazid + rifampicin; HRE, isoniazid + rifampicin + ethambutol; HRZ, isoniazid + rifampicin + pyrazinamide; HREZ, isoniazid + rifampicin + ethambutol + pyrazinamide; HREZS, isoniazid + rifampicin + ethambutol + pyrazinamide + streptomycin; FQ, fluoroquinolone; Scanty: 1-9 AFB (acid fast bacilli)/100 HPF (high power field), +1: 10-99 AFB/100 HPF, +2: 1-9 AFB/HPF, +3: >9 AFB/HPF.

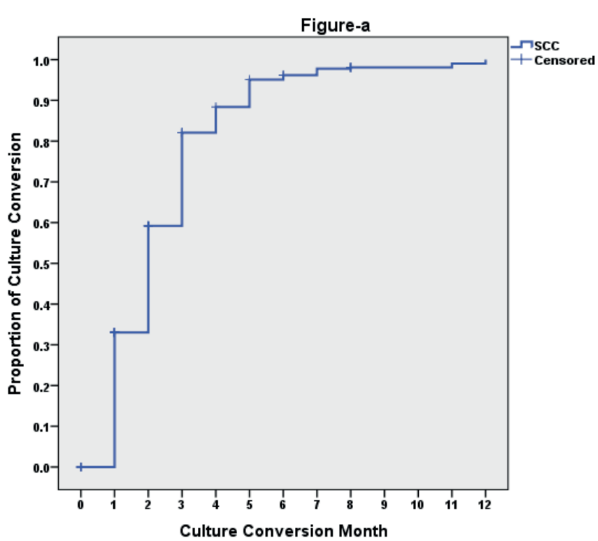
comes [15]. Few studies have been conducted in Pakistan to address these problems [11,13,16]. The current study examined the time to SCC and predictors of early SCC in patients with MDR-TB receiving a longer treatment regimen. This study included a total of 462 patients who were diagnosed and culture-confirmed 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 of 70-90% [15,17-20]. The mean time to SCC was 2.4 months (interquartile range = 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 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 (HREZ) 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, comorbidities, and smoking history were associated with prolong SCC time [31-33].

The time to SCC was found to be strongly associated with treatment outcomes cure. In univariate analysis, SCC at months 1, 2, 3, 4, 5, and 6 had a statistically significant positive association with cure. A stronger association has been observed between SCC and 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 months 1-6. Month 1 showed a low sensitivity of 37.2 % and a high specificity of 81.4% for predicting cure compared to not cure. While month 2 showed sensitivity of 64.1% and specificity of 63.7%, the low sensitivity of SCC at 2 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 also been discussed by Javaid *et al.* [13]. Such misjudgment 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 months (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,

Table 2. Sputum culture conversion and cure among culture converted multidrug-resistant tuberculosis patients (n=462).

Sputum culture conversion	No, n (%)	Yes, n (%)	Cured/SCC (%)
SCC at 1 months	311 (67.3)	151 (32.7)	130/151 (86.1)
SCC at 2 months	197 (42.6)	265 (57.4)	224/265 (84.5)
SCC at 3 months	101 (21.9)	361 (78.1)	300/361 (83.1)
SCC at 4 months	76 (16.5)	386 (83.5)	318 /386(82.3)
SCC at 5 months	50 (10.8)	412 (89.2)	340 /412 (82.5)
SCC at 6 months	46 (10.0)	416 (90.0)	343 /416 (82.4)
Overall SCC	38 (8.2)	424 (91.8)	349/424

SCC, sputum culture conversion.



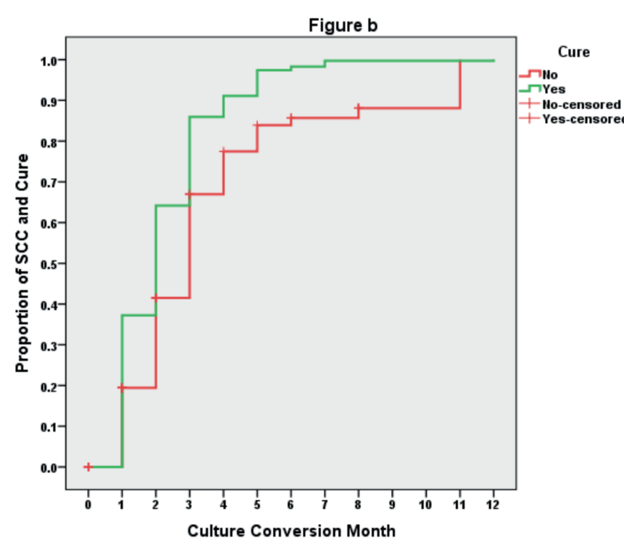


Figure 2. a) Kaplan–Meier survival curve of time to initial sputum culture conversion of 462 multi drug resistant tuberculosis patients; b) Kaplan-Meier survival curve of sputum culture conversion time in cure compared with not cure individuals.

it is suggested 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 after 2 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 2 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*. mentioned that waiting 6 months for SCC might be too long, depending on the patient's overall health [8]. In most cases, doctors would not 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 3 months were 85.9% and 46.0%, and at

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

Variable	Sputum culture conversion No, n (%)	Sputum culture conversion Yes, n (%)	Cox regression HR* (95%CI)	p
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 + ex-smoker	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; HR,hazards ratio; TB, tuberculosis; SLDs, second-line anti-TB drugs; FLDs, first-line anti-tuberculosis drugs; HR, isoniazid + rifampicin; HRE, isoniazid + rifampicin + ethambutol; HRZ, isoniazid + rifampicin + pyrazinamide; HREZ, isoniazid + rifampicin + ethambutol + pyrazinamide; HREZS, isoniazid + rifampicin + ethambutol + pyrazinamide + streptomycin; FQ, fluoroquinolone; Scanty: 1-9 AFB (acid fast bacilli)/100 HPF (high power field).

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

Month of treatment	Cured No (%)	Yes (%)	Univariate analysis* (95% CI)	p	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
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)	(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)	31 318 (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.

4 months were 91.1% and 39.8%. These values were similar to SCC at 6 months, which had a sensitivity of 98.2% and a specificity of 35.3%. Using SCC at 4 months, which has a high PPV of 82.3% and a 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 the entire culture conversion. Very important variables which are associated with delayed SCC and unsuccessful treatment outcomes, occupation, smoking history, comorbidities, and lungs cavitations were lacking the information [15,35].

Conclusions

At 6 months, the association between SCC and cure was much stronger than at 4 and 2 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 did not have information on the cause of death, we could not confirm if all deaths were due to TB. Additionally, because this study was retrospective, we could not 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.

References

1. Nahid P, Mase SR, Migliori GB, et al. Treatment of drug-resistant tuberculosis. An official ATS/CDC/ERS/IDSA clinical practice guideline. Am J Respir Crit Care Med 2019;200:e93-e142.
2. WHO. Global tuberculosis report 2021. Available from: https://www.who.int/publications/i/item/9789240037021.
3. Thiruvalluvan E, Thomas B, Suresh C et al. The psychosocial challenges facing multi drug resistance tuberculosis patients: a qualitative study. SAARC J Tuberc Lung Dis HIV/AIDS 2017; 14:14-21.
4. Magis-Escurra C, Günther G, Lange C, et al. Treatment outcomes of MDR-TB and HIV co-infection in Europe. Eur Respir J 2017;491602363.
5. WHO. Consolidated guidance on tuberculosis data generation and use. Module 1. Tuberculosis surveillance. 2024. Available from: https://www.who.int/publications/i/item/9789240075290.
6. Holtz TH, Sternberg M, Kammerer S, et al. Time to sputum culture conversion in multidrug-resistant tuberculosis: predictors and relationship to treatment outcome. Ann Intern Med 2006; 144:650-9.
7. Fortún J, Martín-Dávila P, Molina A, et al. Sputum conversion among patients with pulmonary tuberculosis: are there implications for removal of respiratory isolation? J Antimicrob Chemother 2007;59:794-8.
8. Kurbatova EV, Cegielski JP, Lienhardt C, et al. Sputum culture conversion as a prognostic marker for end-of-treatment outcome in patients with multidrug-resistant tuberculosis: a secondary analysis of data from two observational cohort studies. Lancet Respir Med 2015;3:201-9.
9. Ige O, Akindele Y, Adebiyi O, et al. Sputum culture conversion among the first cohorts of MDR-TB patients managed in Nigeria at a tertiary care hospital. Eur Respir J 2014;44.
10. Lu P, Liu Q, Martinez L, et al. Time to sputum culture conversion and treatment outcome of patients with multidrug-resistant tuberculosis: a prospective cohort study from urban China. Eur Respir J 2017;49:1601558.

11. Basit A, Ahmed N, Khan AH, et al. Predictors of two months culture conversion in multidrug-resistant tuberculosis: findings from a retrospective cohort study. PloS One 2014;9:e93206.
12. Qazi F, Khan U, Khowaja S, et al. Predictors of delayed culture conversion in patients treated for multidrug-resistant tuberculosis in Pakistan. Int J Tuberc Lung Dis 2011;15:1556-60.
13. Arshad Javaid NA, Ahmad N, Afridi AK, et al. Validity of time to sputum culture conversion to predict cure in patients with multidrug-resistant tuberculosis: a retrospective single-center study. Am J Trop Med Hyg 2018;98:1629-36.
14. NTP. NTP guidlines 2016.
15. Shibabaw A, Gelaw B, Wang SH, Tessema B. Time to sputum smear and culture conversions in multidrug resistant tuberculosis at University of Gondar Hospital, Northwest Ethiopia. PloS One 2018;13:e0198080.
16. Batool R, Khan SW, Imran M, et al. Culture conversion and six months interim outcomes in retreatment cases of pulmonary MDRTB-a six month interim analysis. J Pak Med Assoc 2021;71:2710-6.
17. Yihunie Akalu T, Muchie KF, Alemu Gelaye K. Time to sputum culture conversion and its determinants among multi-drug resistant tuberculosis patients at public hospitals of the amhara regional state: a multicenter retrospective follow up study. PloS One 2018;13:e0199320.
18. Tierney DB, Franke MF, Becerra MC, et al. Time to culture conversion and regimen composition in multidrug-resistant tuberculosis treatment. PloS One 2014;9:e108035.
19. Parmar MM, Sachdeva KS, Dewan PK, et al. Unacceptable treatment outcomes and associated factors among India's initial cohorts of multidrug-resistant tuberculosis (MDR-TB) patients under the revised national TB control programme (2007–2011): evidence leading to policy enhancement. PloS One 2018; 13:e0193903.
20. Velayutham B, Nair D, Kannan T, et al. Factors associated with sputum culture conversion in multidrug-resistant pulmonary tuberculosis. Int J Tuberc Lung Dis 2016;20:1671-6.
21. Liu Q, Lu P, Martinez L, et al. Factors affecting time to sputum culture conversion and treatment outcome of patients with multidrug-resistant tuberculosis in China. BMC Infect Dis 2018; 18:114.
22. Ahmad N, Javaid A, Basit A, et al. Management and treatment outcomes of MDR-TB: results from a setting with high rates of drug resistance. Int J Tuberc Lung Dis 2015;19:1109-14.
23. Falzon D, Gandhi N, Migliori GB, et al. Resistance to fluoroquinolones and second-line injectable drugs: impact on multidrug-resistant TB outcomes. Eur Respir J 2013;42:156-68.
24. Johnston JC, Shahidi NC, Sadatsafavi M, Fitzgerald JM. Treatment outcomes of multidrug-resistant tuberculosis: a systematic review and meta-analysis. PloS One 2009;4:e6914.
25. Javaid A, Shaheen Z, Shafqat M, et al. Risk factors for high death and loss-to-follow-up rates among patients with multidrug-resistant tuberculosis at a programmatic management unit. Am J Infec Control 2017;45:190-3.
26. Wahid A, Ahmad N, Ghafoor A, et al. Effectiveness of shorter treatment regimen in multidrug-resistant tuberculosis patients in Pakistan: a multicenter retrospective record review. Am J Trop Med Hyg 2021;104:1784-91.
27. Hovhannesyan A, Breeze E. Time to sputum conversion in multidrug-resistant tuberculosis patients in Armenia: retrospective cohort study. Global J Med Pub Health 2012;1:24-8.
28. Jabeen K, Shakoor S, Chishti S, et al. Fluoroquinolone-resistant Mycobacterium tuberculosis, Pakistan, 2005-2009. Emerg Infect Dis 2011;17:566-7.
29. Wells WA, Ge CF, Patel N, et al. Size and usage patterns of private TB drug markets in the high burden countries. PLoS One 2011;6:e18964.
30. Megerso A, Deyessa N, Jarso G, Worku A. A retrospective comparative study on median time to sputum culture conversion in multi-drug resistant pulmonary tuberculosis patients in pastoral and non-pastoral settings in southeast Oromia, Ethiopia. Infect Drug Resist 2021;14:5325-33.
31. Ruggles DR, Freyman RL, Oxenham AJ. Influence of musical training on understanding voiced and whispered speech in noise. PloS One 2014;9:e86980.
32. Putri FA, Burhan E, Nawas A, et al. Body mass index predictive of sputum culture conversion among MDR-TB patients in Indonesia. Int J Tuberc Lung Dis 2014;18:564-70.
33. Salindri AD, Kipiani M, Kempker RR, et al. Diabetes reduces the rate of sputum culture conversion in patients with newly diagnosed multidrug-resistant tuberculosis. Open Forum Infect Dis 2016;3:ofw126.
34. Alene KA, Viney K, Yi H, et al. Comparison of the validity of smear and culture conversion as a prognostic marker of treatment outcome in patients with multidrug-resistant tuberculosis. PloS One 2018;13:e0197880.
35. Lv L, Li T, Xu K, et al. Sputum bacteriology conversion and treatment outcome of patients with multidrug-resistant tuberculosis. Infect Drug Resist 2018;11:147-54.

Received: 11 September 2024; Accepted: 17 December 2024; Early view: 24 April 2025.

All 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 declare that they have no competing interests, and all authors confirm accuracy.

Ethics approval and consent to participate: ethical approval was granted by the Research and Ethics Committee of the Faculty of Pharmacy and Health Sciences, University of Balochistan Quetta, and NTP was authorized to perform the study via the letter Ref No: DSA 2901/2020.

Informed consent: this was a retrospective record review; it was impossible to contact all research participants to obtain written or oral consent, and hence the aforementioned institutions authorized a consent waiver.

Patient consent for publication: not applicable.

Availability of data and materials: the data used to support the findings of this study are available from the corresponding author upon request.

Acknowledgments: the authors are thankful to the NTP Islamabad for their support and providing the data.