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Factors Affecting Time to Sputum Culture Conversion and Treatment Outcome of 160 Patients with Multidrug-Resistant Tuberculosis in Tertiary Care Centres, Chennai

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Abstract: ***The aim of the present study was to investigate the relationship between treatment outcomes of multidrug-resistant tuberculosis (MDR-TB) patients and sputum culture conversion. Factors affecting the time of the culture conversion throughout the whole course of the treatment have rarely been investigated. This study was performed in tertiary care centres, Chennai. MDR-TB patients were consecutively enrolled between December 2017 and March 2018. A prospective cohort study was carried out to identify the factors associated with initial culture conversion. Survival analysis was performed using Cox proportional hazards model to compute estimates for time to sputum culture conversion and rate ratios, respectively. Initial sputum culture conversion was reported in 139 out of 160 cases. In all, 139 MDR-TB patients with treatment outcomes were enrolled. Median time to culture conversion among those who converted was 91.5 days (interquartile range, 34.0–110.8 days). After multivariable analysis, smoking (HR = 0.44; 95% CI: 0.23–0.83), drinking (HR = 0.41; 95% CI: 0.21–0.81), ofloxacin resistance (HR = 0.43; 95% CI: 0.24–0.76) and sputum smear grade > 1 (HR = 0.51; 95% CI: 0.31–0.83) were less likely to have culture conversion. Treatment success was observed in 84 patients.***

Keywords: Multidrug-resistant tuberculosis, Risk factors, Sputum culture conversion, Treatment outcome

1. Introduction

Tuberculosis (TB) now exceeds human immunodeficiency virus (HIV) as the infectious disease responsible for the greatest number of deaths globally [1]. In addition, multidrug-resistant tuberculosis (MDR-TB), patients resistant to rifampicin (INH) and isoniazid (RMP), hampers the prevention and control of tuberculosis. Due to poor effectiveness and elevated costs in treatment of MDR-TB patients, they may endure longer infectious periods than those with drug-susceptible TB [2]. Early identification and diagnosis of MDR-TB patients are essential to further prevent the spread of MDR-TB and provide comprehensive and successful treatment. Definition of treatment outcome of MDR-TB patients according to WHO 2013 guidelines 5 are,

1) Cured: patient who has completed MDR-TB treatment, is culture-negative in the last month of treatment and has been culture-negative during the preceding 11 months of treatment.
2) Treatment completed: patient who completed MDR-TB treatment but did not meet the definition for cure or failure due to lack of bacteriologic results.
3) Treatment failure: defined as more than one positive culture in the last 12 months of treatment, with a minimum of five cultures performed during the last 12 months, or if patient is persistently culture-positive and a clinical decision has been made to terminate treatment early.
4) Death: defined as patient who dies for any reason during the course of MDR-TB treatment.
5) Treatment default: defined as patient whose MDR-TB treatment was interrupted for two or more consecutive months.

Culture conversion was defined as three negative consecutive cultures taken at least one month apart after treatment initiation.[7] All data from these patients including clinical profile and treatment outcome was entered. Statistical analysis was done by using mean method and results were expressed in terms of percentages. Univariate analysis of treatment outcome data was done to know predictors of treatment success of MDR-TB. Sputum culture plays an important role in monitoring treatment response in MDR-TB patients [3]. Sputum culture conversion is a clinical tool used to predict therapeutic efficacy in MDR-TB patients. Non-conversion of sputum culture at the end of the intensive phase of treatment tends to yield unfavorable outcomes, more specifically with failure and death [4, 5].

Evidence exists suggesting that sputum culture conversion after the first 2 months may be an early predictor of treatment success in MDR-TB patients [6–8]. Lung cavitation at baseline chest X-ray and resistance to ofloxacin (Ofx) or streptomycin have been associated with a delay in sputum culture conversion in prior studies [6]. Although sputum culture conversion has been used substantially in clinical settings, few prospective cohort studies have been performed in meenakshi, two countries with almost half of the global burden of drug resistant tuberculosis [9, 10]. In addition, factors affecting the time of the culture conversion throughout the whole course of the treatment have rarely

been investigated. Through a prospective cohort study design in urban Cities, we analyzed secondary factors that influenced sputum culture conversion in the process of treatment of MDR-TB disease. Facility for diagnosis and treatment of drug – resistant tuberculosis patients in Chennai was started under Revised National Tuberculosis Control Programme (RNTCP) of India in 2012. So, we conducted study randomly at tertiary care centre of Chennai, Tamil nadu, India to evaluate clinical profile and treatment outcome of drug resistant tuberculosis patients who were treated with standardized MDR-TB regimen.

2. Methodology

2.1. Sample Size

A total of 160 suspected pulmonary MDR-TB patients were recruited and their data were collected from government designated microscopy centres in Chennai district between December 2017 – march 2018

2.2. Study design and patients

A prospective cohort study was conducted in four hospitals (Balaji, SRM, Meenakshi, Saveetha) in chennai, Tamil nadu. All MDR-TB patients were consecutively enrolled in the study between December 2017 and March 2018. MDR-TB patients were identified at the time of diagnosis by regional reference laboratories using traditional drug sensitivity tests (DST), as previously described [12]. Patients that tested sputum culture negative at baseline were excluded. Once confirmed, every patient signed an informed consent form, after which a questionnaire designed by local investigators was administered to gather important demographic and clinical information. The questionnaire contained characteristics including age, sex, weight, and any history of smoking or drinking. In addition, laboratory examination information was collected including sputum smear, sputum culture, chest radiograph findings, and drug sensitivity test results. Sputum culture results were examined at monthly intervals during the intensive phase and 2-monthly intervals during the continuation phase.

We defined a patient with pulmonary multidrug-resistant TB as having a positive sputum culture for *M. tuberculosis* with in vitro resistance to at least isoniazid and rifampicin. Our analysis included all new and previously treated patients with multidrug-resistant TB identified from the multidrug-resistant TB database who began treatment with second-line anti-TB drugs using the DOTS-Plus strategy.

2.3. Definitions

World Health Organization guidelines [13] were consulted when defining individuals and variables in our study. MDRTB patients were defined as those who were resistant to at least INH and RMP for Mycobacterium tuberculosis (MTB) in vitro. A positive sputum culture was defined as a colony for MTB [5] and negative when there was no acid-fast bacillus (AFB) in 300 fields. Sputum culture conversion was defined as two consecutive negative cultures after the first sputum sample, collected at least 30 days apart. Persistent positive sputum culture was defined as no sputum culture conversion during the two years treatment period. Final outcomes included success, failure, and death. Sputum smear grading of TB patients was as follows: 1+ (3–9 AFB in 100 fields), 2+ (1–9 AFB in 10 fields), 3+ (1–9 AFB in 1 field) and 4+ (≥10 AFB in 1 field). Sputum smear grading was divided into two groups, i.e., ≤1 (includes sputum smear negative and positive 1+) and > 1 (includes sputum smear positive 2+, 3+, and 4+).

2.4. Regimens

Drugs used to treat MDR-TB included pyrazinamide (Z), ethambutol (E), kanamycin (Km), amikacin (Am), capreomycin (Cm), Ofx, levofloxacin (Lfx), moxifloxacin (Mfx), cycloserine (Cs), and protionamide (Pto). All confirmed MDRTB patients were treated with a standardized treatment regimen or an individualized regimen of second line drugs, devised based on a patient's history of TB treatment and DST results.

2.5. Statistical analysis

Statistical analysis was conducted using SPSS software (version 23.0). Cox proportional-hazards analysis was used to evaluate the hazard ratio (HR). Variables were considered suggestive of potential statistical significance if the P-value was < 0.05 in univariate analysis. Multivariable analysis was used to estimate HR and adjusted survival curves. Age and sex were put into the multivariable model regardless of their P-value< 0.05. HRs of the differences between the two groups were calculated to evaluate influential factors affecting time to sputum culture conversion. When the HR was < 1, the variable was a risk factor.

3. Results

Characteristics of enrolled MDR-TB patients Between 2017 and 2018, A total of 160 suspected pulmonary MDR-TB patients were recruited of which 21 did not meet study inclusion criteria. A total of 139 pulmonary MDR-TB patients with a treatment outcome classified as successful, failure, and death were enrolled in our investigation [figure 1]. There were no patients that started the study and then dropped out of the study. Table 1 displays demographic and clinical characteristics of included MDR-TB patients. The median age and weight of the patients were 51 years old and 60 kg, respectively; 99 (71.4%) were male; 65 (46.8%) smoked previously or at the time of treatment, and 26 (18.7%) drank alcohol. Of 139 MDR-TB patients, 84 (60.4%) patients had a successful treatment outcome and 55 (39.6%) experienced either a failed treatment or died. In all, 106 (76.3%) patients had sputum-culture conversion, of which 18 had a second positive sputum culture during the first year of the treatment.

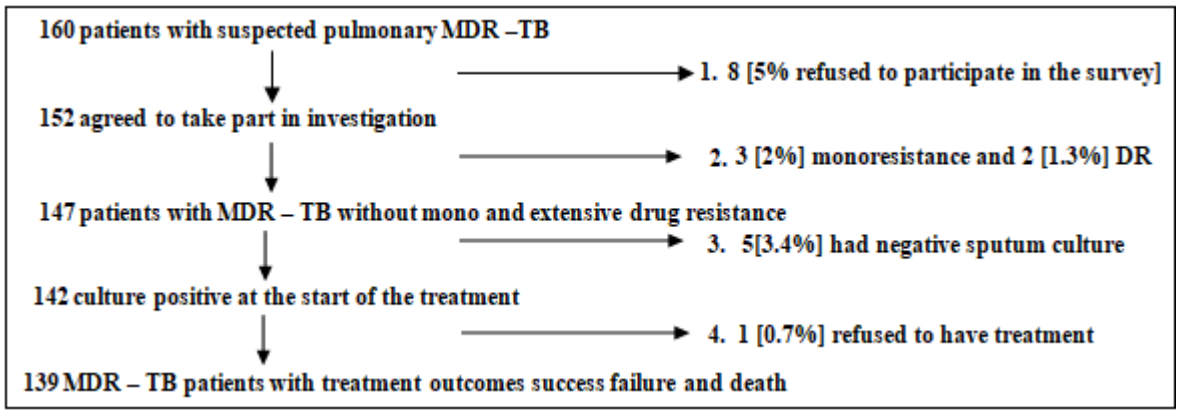

Figure 1: Flow diagram of multidrug-resistant patients included in this study

Median time to culture conversion among those who converted was 91.5 days (interquartile range, 34.0 – 110.8 days).

Table 1: Demographic and clinical characteristics of 139 multidrug-resistant tuberculosis patients

Variable	*Number [%]*
Gender	
Male	99 [71.4]
Female	40 [28.6]
Age years [median IQR – 51.0 (35.8 - 60)]	
≤ 51	71 [51.1]
>51	68 [48.9]
Weight, Kilograms [median IQR – 60.0 (53 - 65)]	
≤ 60	79 [56.8]
> 60	60 [43.2]
Occupation	
Peasant	44 [31.7]
Worker	18 [13]
Unemployed	61 [43.9]
Others	16 [11.5]
Smoking	
Yes	65 [46.8]
No	72 [51.8]
Missing	2 [1.4]
Drinking	
Yes	26 [18.7]
No	86 [61.9]
Missing	27 [19.4]
Lung cavitation	
Yes	72 [51.8]
No	62 [44.6]
Missing	3 [2.2]
Lung lesions	
Yes	129 [92.8]
No	3 [2.2]
Missing	7 [5.0]
Resistance to Ofloxacin	
Yes	42 [58.3]
No	81 [30.2]
Missing	16 [11.5]
Resistant to kanamycin	
Yes	15 [10.8]
No	103 [74.1]
Missing	21 [15.1]
Sputum smear grade	
≤ 1	51 [36.7]
> 1	87 [62.6]
Missing	1 [0.7]

3.1. Baseline regimens

Among 139 patients, 63 (45.3%) were treated with individualized regimens (IR); 42 (30.2%) were treated with standard regimen 1 (SR1: 6Z Am Lfx Cs Pto/18Z Lfx Cs Pto); 16 (11.5%)were treated with standard regimen 2 (SR2: 6Z Am Lfx PAS Pto/18Z Lfx PAS Pto); 3 (2.2%) were treated with standard regimen 3 (SR3: 6Z Cm Lfx Cs Pto/18Z Lfx Cs Pto); 15 patients (10.8%) were treated with standard regimen 4 (SR4: 6Z Cm Lfx PAS Pto/18Z Lfx Cs Pto) (Table 2).

Table 2: Chemotherapy regimens of the MDR-TB patients

Variable	Chemotherapy regimen	N (%)
Individualized regimen	Distinct from patient-to-patient	63 (45.3%)
Regimen 1	6 Pyrazinamide Amikacin Levofloxacin Cycloserine Protionamide /18 Pyrazinamide Levofloxacin Cycloserine Protionamide	42 (30.2%)
Regimen 2	6 Pyrazinamide Amikacin Levofloxacin Para-amino salicylic acid Protionamide /18 Pyrazinamide Levofloxacin Para-amino salicylic acid Protionamide	16 (11.5%)
Regimen 3	6 Pyrazinamide Capreomycin Levofloxacin Cycloserine Protionamide /18 Pyrazinamide Levofloxacin Cycloserine Protionamide	3 (2.2%)
Regimen 4	6 Pyrazinamide Capreomycin Levofloxacin Para-amino salicylic acid Protionamide /18 Pyrazinamide Levofloxacin Cycloserine Protionamide	15 (10.8%)

3.2. Factors contributing to sputum culture conversion

In univariate analysis , we found that factors associated with reduced rate of sputum culture conversion were smoking (HR = 0.63; 95% CI: 0.43–0.93; P = 0.020), drinking (HR = 0.49; 95% CI: 0.27–0.89; P = 0.019), Ofx resistance (HR = 0.46; 95% CI: 0.29–0.73; P = 0.001), and a sputum smear grade > 1 (HR = 0.61; 95% CI: 0.41–0.91; P = 0.001). No significant difference was found between the presence of lung lesions during the baseline chest radiographic examination and sputum culture conversion (HR = 1.17; 95% CI: 0.79–1.71; P = 0.32).

We further performed a multivariate regression and found that smoking (HR = 0.44; 95% CI: 0.23–0.83; P = 0.011), drinking (HR = 0.41; 95% CI: 0.21–0.81; P = 0.011), Ofx resistance (HR = 0.43; 95% CI: 0.24–0.76; P = 0.003) and a sputum smear grade > 1 (HR = 0.51; 95% CI: 0.31– 0.83; P = 0.008) continued to be associated with sputum culture conversion (Table 3).

Table 3: Multivariate analysis of predictors of sputum culture conversion among multidrug-resistant patients in Chennai (N = 139)

Variable	*Adjusted model*		
	HR	*95% CI*	*P - value*
Age, years			
≤ 51	Reference	0.62–1.91	0.766
> 51	1.09		
Gender			
Male	Reference	0.34–1.11	0.105
Female	0.61		
Smoking			
No	Reference	0.23–0.83	0.011
Yes	0.44		
Drinking			
No	Reference	0.21–0.81	0.011
Yes	0.41		
Ofloxacin			
Drug sensitive	Reference	0.24–0.76	0.003
Drug resistance	0.43		
Sputum smear grade			
≤ 1	Reference	0.31–0.83	0.008
> 1	0.51		

3.3. Treatment outcome

Treatment outcome of all 139 patients included in the study is shown in table 4. Treatment success was observed in 84 patients.

Table 4: Treatment outcome of MDRTB patients treated with standardized regimen (total patients-139)

Outcome	No. of pts. (%)
Cured	32 (25)
Treatment completed	45 (31)
Died	20 (14)
Defaulted	28 (19)
Failure (Switch to Cat-5)	14 (9)
*Treatment success is calculated as cured+ treatment completed (n-84) i.e.58%.	

4. Discussion

To our knowledge, there is no similar study in Chennai, to investigate factors that influenced sputum culture conversion in the process of treatment of MDR-TB disease. In this setting with a high burden of drug resistant tuberculosis, we further validated that time to sputum culture conversion is a useful prognostic tool to predict end-of-treatment outcomes in MDR-TB patients but that results differ substantially depending on the month of treatment in which conversion occurs [5, 6]. The median time of sputum smear conversion was 91.5 days, which was similar with a recent study by B. Velayutham and longer than it reported in earlier studies [14–17]. This might because during the time waiting for the DST results, clinicians usually give the anti-TB drugs according to their experience and previous medication history of the patients, which could results in the culture conversion of the patients before the initiation of the standardized treatment, who were then were excluded before the initiation of the treatments.

After multivariable analysis, we further assessed factors associated with increased delay in culture conversion. We found that resistance to Ofx, smoking, drinking, and a high sputum smear grade were risk factors affecting culture conversion. Yuen et al. suggested that MDR-TB regimens including more potentially effective drugs are likely to improve treatment response in MDR-TB patients [8]. To evaluate the association between regimen composition and treatment response, we made a comparison between individualized and standardized drug regimens and treatment outcomes. We found no statistically significant differences however this may be due to statistical power during stratification. Substantial evidence exists indicating that smoking delays culture conversion and adversely affects end-of-treatment outcomes in drug-susceptible TB patients [9–12]. For example, Maciel et al. found that TB patients that smoked were approximately three times less likely to convert their sputum culture after two months compared to non-smoking TB patients. Leung CC et al. also found that approximately one in six treatment failures were due to patient smoking habits [10].

Whether smoking also delays culture conversion in MDR-TB patients has not been investigated previously and we were able to extend these previous findings in drug-susceptible TB patients [1–2] to MDR-TB patients. In this study, we found that smokers had a higher risk for persistent culture-positivity compared with nonsmokers after adjustment for potential confounders. MDR-TB patients may have ceased smoking after hospital admission and this could have led to misclassification of patient smoking status. However, this bias, if present, likely brings the association between smoking and delayed culture conversion among MDR-TB patients towards the null. Smoking cessation programs in an attempt to reduce poor treatment outcomes may be an important supplementary control measure for TB programs dealing with a high-burden of drug resistance TB, such as Chennai. A few studies have shown that sputum culture conversion can be delayed in patients who have infecting isolates resistant to second line anti-TB drugs [6, 12,13]. After adjustment for confounders, we found that participants resistant to Ofx were significantly less likely to have sputum culture conversion. Fluoroquinolones are amongst the most effective medications for patients not susceptible to first line drugs and therefore play an important role in treating drug resistant tuberculosis [14,15]. Nevertheless, excessive and irregular medication were leading causes for fluoroquinolone resistance in Pakistan [6, 7]. We found that, patients resistant to Ofx were over two times more likely to have continuous culture-positive laboratory tests by the end of multidrug-resistant TB treatment. Fluoroquinolone resistance is a potential critical threat to the control of drug resistant TB globally and efforts to prevent resistance through high medication compliance in highburden settings are essential. Rie Kanda et al. reported the time of the sputum culture conversion was prolonged by high smear grade [24], consistent with the results of F. Qazi et al. in 2011 [20] and Caetano Mota et al. in 2012 [9]. Also,

patients with a high colony count were less likely to convert than those who had a low smear grade. In our study, patients with a smear grade > + 1 had a lower likelihood of sputum smear conversion compared with those with a smear grade ≤ + [21]. It might be natural that MDR-TB patients who had a higher colony count take a longer time for sputum culture conversion. This result highlights the importance of early detection and treatment of drug resistant TB patients. There are several limitations of this study. First, all patients ceased smoking and drinking during treatment, which may have led to nondifferential misclassification driving our results toward the null. Moreover, we did not quantify smoking or drinking in more detail which may have led to a lack of an effect on culture conversion. Second, missing information was present among some of our variables of interest. To account for this, we attempted to retrieve any missing information by revisiting participants and checking the infectious disease reporting system. Third, this survey did not collect information on HIV infection status and this may potentially be an important cofounder. Patients with tuberculosis in Chennai are not routinely tested for HIV and, due to this we were unable to assess the influence of HIV coinfection.

Some studies have demonstrated that individualized treatment yields more favourable outcomes than standard regimens,17, 19 while in other studies appropriate treatment results are achieved using standardized regimens.22 However, it has been clearly demonstrated that individualized treatment is highly expensive and difficult to implement in the majority of low income countries, which bear the highest burden of MDR-TB. Therefore, the use of standardized treatment regimens for MDR-TB patients, reduces the number of health care facilities need and lowers the overall cost of treatment by five to ten times.[19] The majority of studies on the treatment of MDRTB have been performed in referral centres. In our prospective study, the treatment was initiated and continued in peripheral health centres, along with follow-up. Given that a favourable treatment outcome was achieved in our study, it can be assumed that the treatment protocol for MDR-TB can be properly integrated into the national health care system.

4.1. Limitations

Our study has several limitations. Although it is the policy of the DOTS-Plus program in chennai to do sputum cultures monthly, they were not performed in every patient. Three quarters of the patients, however, missed only 4 or fewer nonconsecutive monthly sputum culture collections. Second, because cultures were done monthly, the actual number of days to conversion was not observed.

Residual Confounding, As only possible source of information for the current study was the laboratory dataset. The effect of other possible risk factors for delayed time to sputum culture conversion, such as treatment regimen, adherence to 30 treatment, cavitations, HIV statues, smoking, other concomitant diseases was not possible to assess and therefore there is the possibility of residual confounding.

5. Conclusions

In conclusion, we present a prospective cohort study of MDR-TB patients from urban Chennai and we found MDR - TB patients that smoke, drink, have ofloxacin resistance, or a high smear grade are less likely to respond to treatment and should be meticulously followed up. A multidimensional approach is needed to effectively control TB, including early detection and treatment, and proper interventions to lower the drinking rate and cigarette smoking rate. Use of rapid diagnostic tests for MDR-TB like genexpert should be increasingly use to achieve higher treatment success in these patients.

Further prospective studies are needed, which should include also clinical characteristics of patients in their analysis, such as HIV status, severity of disease, BMI, cavitation. Study findings could be used to provide prognostic information to patients.

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