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To Study the Relationship of Different Resistant Patterns among MDR/PRE XDR (MDR +FQ/SLI)/XDR Patients with Early Treatment Response at NITRD

Udvass Kumar Kotokey and Rupak Singla

Department of Pulmonologist, National Institute of Tuberculosis and Respiratory Diseases, New Delhi, Delhi 110030, India

ABSTRACT

Tuberculosis is one among the major health problems worldwide including our country, caused by Mycobacterium tuberculosis. There are many numbers of deaths occurring globally due to tuberculosis. According to Global TB report 2019, 10 million people were affected with TB, of these 7 million people were detected and officially notified. 1.6 million deaths were attributed to TB in 2018. To study the relationship of different resistant patterns among DR-TB patients with early treatment response i.e., proportion of culture conversion by the end of six months of treatment in terms of number of people converted and time taken for conversion in National Institute Of TB and Respiratory Diseases (NITRD) and factors affecting early culture conversion in MDR/PRE XDR/XDR TB patients. The present study was a Prospective Cross-sectional Observational study. This Study was conducted from January 2019 to October 2019 at Department of TB and Respiratory Diseases, National Institute of Tuberculosis and Respiratory Diseases, New Delhi. In our study, majority of the DR TB patients were undernourished (BMI <18.5 kg m^{-2}). In the MDR group, the association between BMI and culture conversion in terms of time taken (<3 months) was not statistically significant (p>0.05). In our study 23/74 (31.1%) patients were smokers. Smokers were 9/25 (36%) among MDR, MDR FQ resistant cases 10/36 (26.4), none among MDR SLI resistant cases and 4/10 (44.4%) among XDR. There are very few studies on early culture conversion of MDR TB patients and even fewer in case of PRE XDR and XDR. Correlation of various factors with early culture conversion was made in MDR as well as PRE XDR and XDR patients in the sane study. Several reversible factors that influenced early treatment outcome were identified like BMI, anemia, hypoalbuminemia and correlated resistance pattern of ATT drugs with early culture conversion.

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Key Words

Tuberculosis NITRD, MDR/PRE XDR/XDR, TB

Corresponding Author

Rupak Singla,
Department of Pulmonologist, National Institute of Tuberculosis and Respiratory Diseases, New Delhi, Delhi 110030, India

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INTRODUCTION

Tuberculosis is one among the major health problems worldwide including our country, caused by Mycobacterium tuberculosis. There are many numbers of deaths occurring globally due to tuberculosis. According to Global TB report 2019, 10 million people were affected with TB, of these 7 million people were detected and officially notified. 1.6 million deaths were attributed to TB in 2018.

Drug-resistant TB continues to be a growing public health threat. There were 0.5 million new cases of drug resistant TB in 2018. Only 1 in 3 of the estimated multidrug-resistant TB or rifampicin-resistant TB (MDR/RR TB) cases were enrolled in treatment in 2018.The incidence of Drug resistance TB being 484,000 worldwide in 2018. The three countries with the largest share of the global burden were India (27%), China (14%) and the Russian Federation (9%). Globally, 3.4% of new TB cases and 18% of previously treated cases had multidrug-resistant TB or rifampicin-resistant TB (MDR/RR-TB).The lab confirmed XDR TB cases were 13100 in 2018.The treatment outcome and success rate among MDR/RR-TB cases were only 56% globally in 2018.

India is the highest TB burden country in the world having an estimated incidence of 26.9 lakh cases in 2019 (WHO). According to global TB report 2019, incidence of MDR TB in India is 10 per 100,000 population.

In India, detection of DR TB through RNTCP has been progressively rising with increased access to various forms of DST. According to India TB Report 2020 during 2019, 66,255 MDR/RR TB cases were diagnosed and 56,569 (85%) of them were put on treatment, of which, 40,397 (71%) patients were initiated on shorter MDR TB regimen at the time of diagnosis of MDR or RR. National TB Elimination Programme has seen improvement over 2018 (79% were put on treatment and only 35% were initiated on shorter MDR TB regimen).

The determination of different resistance patterns among various Anti Tuberculosis Treatment (ATT) drugs is of paramount importance in treatment and evaluation of DR TB patients. With this view the first ever National Anti TB Drug resistance survey was done. It was the largest drug resistance survey conducted in India. The key findings of this survey are as follows.

Among all TB patients tested, MDR-TB rate was 6.19% with 2.84% among new and 11.60% among previously treated TB patients. Among MDR-TB patients, additional resistance to any fluoroquinolone was 21% and any second line drug resistance was 3.84%. Among MDR-TB patients, XDR-TB rate was 1.3%.

Drug resistance is defined as a reduction in effectiveness of a medication such as an antimicrobial in treating a disease or a condition to which it was previously sensitive. Rapid identification of DR TB is achieved by using a combination of NAAT (CBNAAT/TruNAAT), first- and second-line LPA and Liquid culture DST for specific drugs[1].

MATERIALS AND METHODS

Study site: The study was conducted at the National Institute of Tuberculosis and Respiratory Diseases. This Institute serves as the Nodal DRTB Centre for 4 districts covering a population of 4 million. There are 4 chest clinics under NITRD for management of drug-resistant TB under PMDT. The chest clinics are NITRD, Brijwasan, Malviya Nagar and RTRM. All diagnosed drug-resistant TB patients from these clinics are referred to NITRD for management of DR-TB:

- **Study design:** It was a Prospective Cross-sectional Observational study
- **Period of study:** January 2019 to October 2019

Selection criteria:

- **inclusion criteria:** Pulmonary MDR/MDR-FQ-R, MDR-SLI-R/XDR patients enrolled under PMDT
- **Exclusion Criteria:**
  - Not willing to participate in the study
  - Pregnant and breast feeding patients
  - Patients with Extra pulmonary diseases or both extra pulmonary and pulmonary

RESULT AND DISCUSSION

The emergence of drug resistance among TB patients has become a significant public health problem in several countries and an obstacle to effective TB control.

In a country like India, where TB is endemic and FQs and SLIs are used commonly even in non-tubercular infections, the need was felt to evaluate the occurrence of different drug resistance patterns among DR-TB patients. Identification of the factors affecting early culture conversion in these groups is necessary to improve the outcome of the patients.

The present study was planned to study the correlation between different DR TB resistance patterns such as MDR, PRE XDR (MDR+FQ/MDR+SLI) and XDR with early culture conversion in the terms of time taken and number of people converted. Various factors affecting the early culture conversion and drug-resistance profile were evaluated.

MDR and early culture conversion: Out of 25 patients, 24 had culture conversion in our study. More than half of the MDR TB patients had culture conversion by less than 3 months. This was comparable to the findings of a retrospective cohort conducted by Piubello *et al*.[1]

conducted a study a study where 65 MDR patients were initiated on shorter regime where 58 patients (89%) achieved culture conversion by 3 months.

When correlation was done with drug resistance, neither in low level or high level had any statistically significant impact on early culture conversion.

Achieving early culture conversion in MDR TB patients in our study could be due to the use of Bedaquiline, better management of co-morbidities, better DST facilities, better follow up and tertiary care center.

MDR with second line drugs resistance (Pre XDR and XDR): In this group 45 out of 49 patients had culture conversion by 6 months. Majority of the patients had early culture conversion by 2 months. Almost all patients in this group received Bedaquiline containing regime.

In our study by univariate analysis culture conversion at 2 months was found to be statistically significant in this group.

Similar treatment outcomes have recently been reported for patients with multi/extensively drug-resistant tuberculosis (PRE/XDR-TB) in settings where optimal resources for individualized therapy are available. Heyckendorf *et al*.[2] conducted a study in Germany where 2-month smear conversion rate was 78%; and time to culture conversion was 39 days in drug-resistant tuberculosis (PRE/XDR-TB).

The resistance to second line drugs did not have a statistically significant impact on early culture conversion in PRE XDR and XDR patients.

Evaluation of early treatment outcome in terms of time taken and the factors affecting time to culture conversion.

Using unilabiate analysis co relation of various factors with culture conversion was done with time intervals of less than 1 month and greater than 1 month, less than 2 months greater than 2 months, less than 3 greater than 3 months.

Age distribution and early culture conversion: In our study, majority of the enrolled DR TB patients were young having the age of $\leq$40 years. Even though a high proportion of patients in our study belonged to the age of $\leq$40 years, the association between younger age and culture conversion in terms of time taken in both study groups was not statistically significant (p>0.05).

Another retrospective follow up study age was not associated with early culture conversion in DR TB patients[3].

Younger population having better immunity which leads to increased bacillary clearance could be the reason of early culture conversion in the young. These results highlight the greater occurrence of DR TB among economically productive age group leading to a greater risk of transmission at the workplace, greater loss of work hours and greater economic burden to the country. Therefore, much attention should be paid to younger people during their first-line TB treatment and screening for drug resistance should be prioritized among this population.

Gender distribution and early culture conversion: In our study, among all the DR TB patients males were predominant gender.

In the MDR group, the association between gender and early culture conversion in terms of time taken (<3 months) was not statistically significant (p>0.05).

In MDR with resistance to second line drugs, female gender and early culture conversion in terms of time taken was statistically significant (p = 0.04). Females had a better 2 month conversion rate than the males.

In our study males were the predominant sex and various DR TB patterns were also more common in males as can be observed in the above data. In studies conducted by and Liu *et al*.[4] prevalence of FQ resistance and SLI resistance was lower among females and more among males.

The reasons could be low awareness level and delay in diagnosis at various respective centers. An Indian study found that males were less likely to be diagnosed early with TB and further suggested that delayed sputum conversion in males could be attributed to alcohol consumption and smoking habits and less adherence to treatment.

BMI and early culture conversion: In our study, majority of the DR TB patients were undernourished (BMI <18.5 kg m^{-2}). In the MDR group, the association between BMI and culture conversion in terms of time taken (<3 months) was not statistically significant (p>0.05).

In MDR with resistance to second line drugs, the association between BMI and early culture conversion (<2 months) was statistically significant (p = 0.025). People with lower BMI had culture conversion later than 2 months.

Park *et al*.[5] retrospectively evaluated 218 patients with MDR-TB and analyzed the association between BMI sputum culture conversion within 3 months, failure to achieve sputum culture conversion within 3 months was independently associated with having a low BMI.

Assemie *et al*.[6] conducted a study to evaluate factors affecting 2 month culture conversion in MDR TB patients. The independent factor for delayed sputum culture conversion was body mass index below 18.5 kg m^{-1}.

Nutritional status of a patient plays a key role in early culture conversion in DR TB patients. Low BMI

indicates malnutrition, which leads to decreased levels of immunoglobulin and macrophage activation and this leads to defective bacterial killing. This in turn leads to delayed culture conversion. Studies 27-29 had reinforced the association between malnutrition and TB, the probable bidirectional influence of one on the other, in which malnutrition predisposes to TB infection and TB causes wasting.

Low BMI patients are more prone to develop tuberculosis and chances of recurrent infections are high in such patients.

Smoking and early culture conversion: In our study 23/74 (31.1%) patients were smokers. Smokers were 9/25 (36%) among MDR, MDR FQ resistant cases 10/36 (26.4), none among MDR SLI resistant cases and 4/10 (44.4%) among XDR.

In the MDR group, the association between smoking and early culture conversion in terms of time taken (<3 months) was statistically significant (p = 0.03). Non smokers had earlier 3 month conversion.

In MDR with resistance to second line drugs, the association between smoking and early culture conversion (<2 months) was statistically significant (p = 0.04). Non smokers had earlier 2 month culture conversion than smokers.

Magee *et al*.[7] conducted a study to evaluate the impact of smoking on culture conversion in DR TB patients. Of patients included in the study (N = 1,852), smoking was present in (47.7%) of the study group. Correlation of smoking with delayed culture conversion was statistically significant.

Diabetes mellitus and early culture conversion: In this study, we studied affect Diabetes Mellitus on culture conversion. Among enrolled patients, 12/74 (11.7%) patients had DM type II. Patients with diabetes mellitus were 5/25 (20%) among MDR, 6/36 (15.8%) among MDR FQ resistant cases, none among SLI resistant cases and 1/10 (10%) among XDR cases. No significant association was observed between DM with early treatment outcome in DR TB patients (p>0.05).

Chest x-ray involvement and early culture conversion: In this study, it was observed that 38/74 (48.6%) patients had bilateral CXR involvement and 58/74 (78.3%) patients had Cavity in CXR. 16/74 (54.01%) of the study participants had far advanced disease on chest X-ray and 27/74 (36.5%) had moderately advanced disease.

In the MDR group, the association between chest x ray and early culture conversion (<3 months) was statistically significant (p = 0.01). Patients without cavities in chest x-rays had earlier 3 month culture conversions.

In MDR with resistance to second line drugs , the association between chest x ray and early culture conversion (<2 months) was statistically significant (p = 0.04). Patients with non cavitatory chest x-ray profiles had earlier 2 month culture conversion.

Socio-economic status and early culture conversion: In our study, it was observed that 37/74 (50%) patients belonged to lower socioeconomic class and 35/74 (47.3%) patients were from lower middle socioeconomic class. In the MDR group, the association between socioeconomic status and early culture conversion (<3 months) in terms of time taken was statistically significant (p = 0.02). Patients belonging to the middle class had earlier 3 month culture conversions. In the another group of MDR with resistance to second line drugs, the association between socioeconomic status and early culture conversion in terms of time taken (<2 months) was statistically not significant (p>0.05). It has been observed that patients living in the lower socioeconomic status have low monthly income, poor housing and living conditions, lack of employment; and residency in a rural area. These factors increases the risk of MDR TB around six folds and leads to poor adherence to treatment. In a study conducted by Kulkarni *et al*., 64% MDR patients belonged to lower socioeconomic class and 17.1% belonged to middle socioeconomic class.

Anemia and early culture conversion: In our study, 36 (48.7%) patients had anemia. In the MDR group, the association between anemia and early culture conversion in terms of time taken (<3 months) was not statistically significant (p>0.05). In MDR with resistance to second line drugs, the association between anemia and early culture conversion in terms of time taken (<2 months) was statistically significant (p = 0.008). Therefore, MDR with second line drug resistance patients without anemia had early culture conversion. Irbah *et al*.[8] conducted a retrospective cohort to know the impact of anemia on the culture conversion in the DR TB patients. 83 of 201 MDR-TB patients (41.3%) had anemia with the average of Hemoglobin level 11.4±1.2. Anemia was not found to be statistically significant with culture conversion. Similarly in an Ethiopian study on MDR TB, that anemia was associated with delayed culture conversion (>6 months) 64. TB infection causes inflammation and causes an increase circulating hepcidin and thereby impairs dietary iron absorption and systemic utilization of iron, resulting in iron sequestration and anemia 63. Another reason for increase occurrence of anemia in DR TB subjects could be the cause of various drugs used in DR TB that causes anemia. Therefore, anemia should be managed among the MDR TB patients to improve the time to culture conversion.

Hypoalbuminemia and early culture conversion: In our study, majority of study population had hypoalbuminemia.

In the MDR group, the association between hypoalbuminemia and early culture conversion in terms of time taken (<3 months) was not statistically significant (p>0.05).

In MDR with resistance to second line drugs, the association between hypoalbuminemia and early culture conversion in terms of time taken (<2 months) was statistically significant (p = 0.025). Patient without hypoalbuminemia had a faster 2 month conversion rate.

Pattern of Drug Resistance among study participants and co relation with early culture conversion: Correlation between drug resistance patterns of various ATT drugs such as isoniazid (high and low level), pyrazinamide, FQ (ofloxacin, levofloxacin, moxifloxacin, moxifloxacinh) and SLI (kanamycin, capreomycin, amikacin) with early culture conversion were made. No statistically significant association was seen between drug resistance pattern and early culture conversion in both the groups (p>0.05).

Study conducted by Click *et al*.[9] observed correlation between isoniazid low level and high level (inh A and katG) resistance with time to culture conversion.It was seen that mutation to both low and high level isoniazid(inh A and katG) was associated with delay in culture conversion (>3 months).

In our study we did not find statistically significant correlation between ATT drugs and early culture conversion. The reason could be our small sample size.

CONCLUSION

This study was a cross sectional study. About 74 DR TB patients were enrolled who visited NITRD opd. We assessed MDR PRE XDR and XDR patients with various factors and correlation was made between them with early culture conversion. Among 74 enrolled patients 57/74 (77%) patients had age of ≤40 years and 17/74 (23%) were aged more than 40 years. Of the 74 patients included in the study, 46 (62.2%) were male and 28 (37.8%) were female. Male to female ratio was 1.6:1. 37 (50%) were upper lower, 35 (47.3%) were lower middle and 1 (2.7%) was upper middle. Of the study population 19 (25.7%) were smokers, 4 (5.4%), 51 (68.9%) were nonsmokers. The data shows that in the study population only 8 (10.8%) had alcohol intake history and 66 (89.2%) had no history of alcohol intake. The number of people enrolled in the study 12 (16.2%) had DM and 62 (83.8%) did not have the disease. In the study group 56 (75.7%) patients were underweight, 17 (23%) were normal and 1 (1.4%) was overweight. Among the study population 36 (48.6%) patients had anemia and 38 (51.4%) had no anemia. Among the study population 56 (75.7) had hypoalbuminemia and 18 (24.3%) had normal serum albumin. Among the study population 64 (86.5%) had fasting blood sugar below 126 mg dL^{-1} and 10 (13.5%) had above 126 mg dL^{-1}. Among the study population 58 (78.4%) have cavity on x-ray while 16 (21.0%) have no cavity. In the MDR group middle socioeconomic status, nonsmoker and no cavity on chest x-ray had statistically significant co relation with early culture conversion (<3 months). In the MDR with second line resistance (PRE XDR and XDR) normal BMI, no anemia, no hypoalbuminemia, no cavity on chest x-ray and female gender had statistically significant co relation with early culture conversion (<2 months). This study is unique in a way in the following ways:

- There are very few studies on early culture conversion of MDR TB patients and even fewer in case of PRE XDR and XDR
- Correlation of various factors with early culture conversion was made in MDR as well as PRE XDR and XDR patients in the sane study
- Several reversible factors that influenced early treatment outcome were identified like BMI, anemia, hypoalbuminemia
- This study also correlated resistance pattern of ATT drugs with early culture conversion

REFERENCES

1. Piubello, A., S.H. Harouna, M.B. Souleymane, I. Boukary and S. Morou *et al* 2014. High cure rate with standardised short-course multidrug-resistant tuberculosis treatment in Niger: No relapses. Int .J .Tuberc Lung Dis., . 18: 1188-1194.
2. Heyckendorf, J., F. van Leth, K. Avsar, G. Glattki and G. Günther *et al*., 2018. Treatment responses in multidrug-resistant tuberculosis in germany. Int. J. Tuberculosis Lung Dis., 22: 399-406.
3. Akalu, T.Y., K.F. Muchie and K.A. Gelaye, 2018. 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, Vol. 13, No. 6. 10.1371/journal.pone.0199320
4. Liu, C.H., N. Yang, Q. Wang, Y.L. Hu, L. Li, G.Y. Zhang and B. Zhu, 2011. Risk factors associated with fluoroquinolone-resistant tuberculosis in a Beijing tuberculosis referral hospital. Respirology, 16: 918-925.
5. Park, H.O., S.H. Kim, S.H. Moon, J.H. Byun and J.W. Kim *et al*., 2016. Association between body mass index and sputum culture conversion among South Korean patients with multidrug resistant tuberculosis in a tuberculosis referral hospital. Infec. and Chemother., 48: 317-323.

6. Assemie, M.A., M. Alene, P. Petrucka, C.T. Leshargie and D.B. Ketema, 2020. Time to sputum culture conversion and its associated factors among multidrug-resistant tuberculosis patients in eastern Africa: A systematic review and meta-analysis. Int. J. Infect. Dis., 98: 230-236.
7. Magee, M.J., R.R. Kempker, M. Kipiani, N. Tukvadze, P.P. Howards, K.M.V. Narayan and H.M. Blumberg, 2014. Diabetes mellitus, smoking status and rate of sputum culture conversion in patients with multidrug-resistant tuberculosis: A cohort study from the country of georgia. PLoS ONE, Vol. 9. 10.1371/journal.pone.0094890.
8. Irbah, S.N., A.P. Pratiwi, F. Vidiast and D. Handayani, 2019. The impact of anemia in prolong culture conversion amongs MDR-TB patients in persahabatan hospital Indonesia. Int. J. Infect. Dis., 79: 1-150.
9. Click, E.S., E.V. Kurbatova, H. Alexander, T.L. Dalton and M.P. Chen *et al*., 2020. Isoniazid and rifampin-resistance mutations associated with resistance to second-line drugs and with sputum culture conversion. J. Infect. Dis., 221: 2072-2082.