Pak. J. Chest Med. 2024;30(03)

Original Article

journal homepage: https:/www.pjcm.net/

Pakistan Journal of Chest Medicine

Official journal of Pakistan Chest Society

Impact of Co-morbidities on Treatment Outcome of Multidrug-Resistant Tuberculosis in Khyber Pakhtunkhwa

Sajid Hayat[1], Anila Basit[1]✉, Itizaz Hayat[2], Sajjad Naseer[3], Maryam Hussain[4], Inayat Kashan[5], Zafar Iqbal[1]

[1]Department of Pulmonology, Medical Teaching Institute, Lady Reading Hospital, Peshawar – Pakistan [2]Department of Pulmonology, Medical Teaching Institute, Hayatabad Medical Complex, Peshawar – Pakistan [3]Department of Pulmonology, Fazaia Medical College, Islamabad – Pakistan [4]Department of Pulmonology, Combined Military Hospital, Peshawar – Pakistan [5]Al Zahra Polyclinic Hospital, Ministry of Health, Kuwait

Corresponding Author:
Anila Basit
Department of Pulmonology,
Medical Teaching Institute,
Lady Reading Hospital,
Peshawar – Pakistan
E-mail: anilalrh@gmail.com

Article History:

Received:	Jan 20, 2024
Revised:	Apr 25, 2024
Accepted:	July 27, 2024
Available Online:	Sep 02, 2024

Author Contributions:
AB conceived idea, SJ IH IK drafted the study, SJ ZI collected data, ZI MH did statistical analysis and interpretation data, AB SN did critical reviews manuscript. All approved final version to be published.

Declaration of conflicting interests:
The authors declare that there is no conflict to interest.

How to cite this article:
Hayat S, Basit A, Hayat I, Naseer S, Hussain M, Kashan I, Iqbal Z. Impact of Co-morbidities on Treatment Outcome of Multidrug-Resistant Tuberculosis in Khyber Pakhtunkhwa. Pak J Chest Med. 2024; 30(03):124-130

A B S T R A C T

Background: In the ongoing battle against both drug-susceptible and drug-resistant tuberculosis (DR-TB), multi-morbidity is becoming more and more acknowledged as a severe public health hazard. Co-morbidities should be adequately handled while treating MDR tuberculosis by enlisting the help of specialists from other fields.

Objective: To analyze various co-morbidities and its effect on final outcome of multi-drug-resistant tuberculosis patients.

Methodology: This prospective descriptive study was carried at department of pulmonology, Lady Reading Hospital, Peshawar, from 1st June 2021 till 30th May 2022. Sampling: A total of 157 participants with multi-drug resistant tuberculosis were registered which was confirmed based on PCR reporting resistance of the pathogen towards isoniazid and rifampicin. Co-morbidities were assessed in terms of diabetes mellitus, COPD, HIV and CKD. Analysis: Data analysis was performed using SPSS version 24.

Results: Male to female ratio was 1.7: 1. Age of the patients ranged from 20 to 60 years with mean age of 39. 37 ± 6.143 years. Mean BMI of the patients was 23.285 ± 2.5843 kg/m^2. Diabetes mellitus was the most frequent comorbidity observed in 48 patients (30.6%), followed by COPD in 33 patients (21.0%). This study showed that successful outcome of the study cases was 112 (71.4%) and unsuccessful outcome was 45 (28.6). Crosstabulation between comorbidities and final outcome showed that positive significant association was found among comorbidities and unsuccessful outcome (P-value <0.005).

Conclusion: Comorbidity is common among multidrug-resistant tuberculosis individuals in our local population. The most common concurrent illnesses is diabetes mellitus. Authorities must explore the involvement of additional professions, particularly endocrinologists.

Keywords: Multidrug Resistant Tuberculosis (MDR-TB); Co-morbidities; Diabetes Mellitus (DM)

Introduction

Tuberculosis (TB) is one of the deadly diseases which strike all efforts of health authorities throughout the world for control of TB and better health. Due to effective TB control program, TB is somewhat control in few parts of world but unfortunately its resurgence in the form Drug resistance TB (DR-TB). As there were using few decades old medicines for treatment of TB, resistance of its causative organisms to routine drugs showed high alerts for health authorities and DR-TB now become an important health crisis across the world.[1]

DR-TB is a manmade disease and there exist different factors responsible for its occurrence but the most prevalent and significant cause of drug resistance is inadequate adherence to or incorrect dose of anti-TB medication. Besides this another important factor is the presence of index case in the community which remain the main point of infection and this disease also spread from such case to other community members. So, it is very important for control of this disease to take special attention in treatment of TB/DR-TB to stop the spread of this disease and cut the chain the chain of this disease.

There are different types of DR-TB of which the most frequent and dangerous type is Multidrug resistant tuberculosis (MDR-TB). MDR-TB is a type of DR-TB, in which the causative organisms showed resistance to two most powerful anti-TB drugs i.e. Isoniazid (INH) and Rifampicin (RMP). Different treatment strategies used for treatment of MDR-TB. MDR-TB is a treatable disease, treated with second line drugs whereas drug susceptible TB is treated with first line ant-TB drugs.[2] As already stated that proper and adequate treatment is of much importance for achievement of successful treatment outcome. For accurate treatment strategies some important factors must know before starting the best suitable treatment and achieved successful outcome. Among these factors one important factor is presence of comorbidities. As different studies showed that different comorbidities such as human immunodeficiency virus (HIV) and Diabetic Mellitus (DM) play important rule in the final outcome of treatment and this affect significant negative association on final outcome. The impact of comorbidities on drug sensitive TB treatment is well-described, with conditions such as human immunodeficiency virus (HIV) infection, diabetes mellitus (DM), chronic kidney disease (CKD) and alcohol misuse all associated with worse treatment outcomes.[3,4] MDR/XDRTB treatment programs often report high proportions of these comorbidities, with the prevalence of HIV, and DM exceeding 10–20% in several large MDR/XDRTB cohort studies.[5-8]

Unfortunately, the relationship between comorbid conditions and MDR/XDRTB treatment outcomes remains poorly described in our region, where the rate of TB/MDR-TB is very high. The Asia-Pacific region bears the most significant brunt of MDR-TB due to a variety of causes such as a scarcity of availability of competent specialist advice, inadequate infrastructure, poverty, trouble getting prescriptions, a shortage of surveillance, and numerous others. Pakistan is also an impoverished nation that contributes significantly to the worldwide impact of MDR-TB and remain 5th on the basis of the presence of this disease.[7] So it is very important to conduct a study for find rate and any possible association of different comorbidities with final treatment outcome in MDR-TB patients.

Therefore, we aimed to examine the relationship between comorbidities and treatment outcomes of the enrolled MDR-TB. As a result, the present research project was designed to examine the co-morbidities and its effects on treatment of MDR-TB patient. This will provide us with a rough estimate of the prevalence of co-morbidities in our local population's response rates to MDR-TB treatment.

Objective

To analyze various co-morbidities and its effect on final outcome of multi-drug-resistant tuberculosis patients.

Methodology

This descriptive study was carried out at the Programmatic Management of Drug-Resistant TB Unit (PMDT), Department of Pulmonology, Lady Reading Hospital Peshawar. The study duration was from 1st June 2021 till 31st May 2022. Approval was taken from hospital ethical review committee.

Both male and female patients diagnosed with multidrug resistant tuberculosis in the age range 20 to 60 years were included. Multidrug resistant tuberculosis was defined as patients who were resistant to both rifampicin and isoniazid as detected by PCR based molecular drug sensitivity tests showing specific genetic mutations associated with mycobacterial resistance. The enrolled participants were screened for concurrent illness which included diabetes mellitus (overnight fasting glucose blood glucose level more than 126mg/dl), HIV (confirmed on ELISA), COPD (based on history and PFTs) and CKD (eGFR <60ml/min). Patients with extra-pulmonary tuberculosis, immunocompromised and non-compliant to medications were excluded.

Informed consent was taken from the study participants. Demographics were noted including age, gender, disease duration and BMI. Patients underwent detailed clinical evaluation with great emphasis on previous and current medical comorbid conditions during pretreatment evaluation. Patients were encouraged for self-reporting of any concurrent medical illness. Once the patient had given any history regarding comorbid medical conditions, the relevant documents and investigations were reviewed thoroughly. Medical comorbid conditions were extracted

Table 1. Baseline characteristics of study cases (n=157)

Characteristics	Frequency	Percentage (%)
Gender		
Male Female	117 40	74.0 26.0
Age Group (Years)		
20 – 40 41 – 60	87 70	55.41 44.59
Disease Duration		
Less than 15 months More than 15 months	82 75	54.67 45.33
Weight (Kg)		
<40 40 – 60 >60	57 91 09	36.3 57.9 05.7
Residence		
Urban Rural	59 98	37.6 62.3
Marital Status		
Unmarried Married Widow	111 45 1	70.7 28.6 0.6
Previous use of Second Line drugs		
Yes No	14 143	09.0 91.0

by relevant documents and appropriate investigations consistent with their diagnosis. Further, any other medical comorbid condition diagnosed during detailed pretreatment clinical evaluation and investigations at DR-TB center were also included in this study. Records maintained at DR-TB center were analyzed critically and data was extracted retrospectively.

The data was entered and saved in SPSS version 23. Descriptive statistics was used to analyze the data. Frequencies and percentages were calculated for categorical variables and mean ± standard deviation was calculated for the numerical variables. The co-morbidities were stratified according to different age groups, gender and duration of disease. Post-stratification chi square test at 5% level was applied and p-value of 0.05 or less was considered significant. All data will be displayed in the form of graphs and tables.

Results

A total of 157 enrolled MDR-TB patients were enrolled in this study. Age of the study cases ranged from 20 to 60 years. Mean age was 39.37 ± 6.143 years with mean BMI was 23.285 ± 2.5843 kg/m^2. Majority of the study cases were young and lower than 40 years of age. Ratio of male patients (74.0%) was greater as compared to female gender and majority 70.7% of the patients were unmarried. Previous disease duration before visiting the

Table 2. Frequencies and percentage of various comorbidities

Comorbidity	Frequency	Percentage (%)
Chronic Liver Disease	03	1.91
Depression	33	21.01
Diabetes Mellitis	48	30.6
Hepatitis	04	2.54
HIV	03	1.91
COPD	13	8.2
Total	104	66.2

present unit for treatment also varies and disease duration was 18.47 ± 1.171 month. Weight also varies among the study cases and 36.3% of the study cases having weight lower than 40Kg. Study cases also belongs from different areas of Khyber Pakhtunkhwa and adjacent tribal areas and 62.3% of the study cases belongs to rural areas. Among the study cases 14 (9.0%) also used second line drugs before starting of their present treatment (Table 1).

Out of the total study cases, 104 individuals (66.2%) experienced comorbidities along with MDR-TB. The most prevalent comorbidity was diabetes mellitus, which was present in 48 patients (30.6%). Additionally, depression was identified in 33 (21.0%) patients. Various other comorbidities, including CLD, Hepatitis, HIV, and COPD were also observed (Table 2).

The subgroup analysis revealed a higher prevalence of depression among patients under age of 40, particularly among males, and those with disease durations of less than 15 months. However, no statistically significant positive association were observed with any of the characteristics. Notably, a significant link between depression and gender was identified among the study cases (Table 3).

Comorbidities is one of the important factors in final treatment outcome. This study showed that successful outcome of the study cases was 112 (71.4%) and unsuccessful outcome was 45 (28.6). Crosstabulation between comorbidities and final outcome showed that positive significant association was found among comorbidities and unsuccessful outcome (P-value <0.005) Table 4.

Discussion

MDR-TB poses significant treatment challenges, because of longer duration of treatment duration and use of multiple types of second line drugs, often accompanied by severe side effects. Different types of treatment

Table 3. Cross tabulation of Depression and Diabetes Mellitus with different characteristics of study subjects

Disease		Age			Gender			Disease Duration		
		20-40 years	41-60 years	P-Value	Male	Female	P-Value	<15 Months	>15 Months	P-Value
Depression	yes	22	11	0.009	25	8		19	14	0.045
	no	65	49		62	62		68	56	
Diabetes Mellitus	yes	30 (34.5%)	18 (25.7%)	0.063	36 (30.0%)	12 (30.0%)	0.891	31	58	0.091
	no	57 (74.5%)	52 (74.3%)		81 (69.2%)	28 (70.0%)		51	51	

Table 4. Crosstabulation of comorbidities and final treatment outcome

Comorbidities	Treatment Outcome		P-Value
	Successful outcome	Unsuccessful Outcome	
Yes	67 (74.9)	38 (30.1)	< 0.005
No	45 (37.1)	07 (14.9)	
Total	112 (71.4)	45 (28.6)	157 (100.0)

strategies also exist to treat this disease but so far, no considerable choice was existed to treat patients with MDR-TB fully successfully. In accordance with WHO guidelines, a comprehensive and collaborative approach is recommended to ensure favorable patient outcomes and reduce disease burden. Nevertheless, the optimal management and treatment strategy for MDR-TB are subjects of ongoing research and have yet to be definitively established. Various factors contribute to the ultimate prognosis of patients with MDR-TB. Among these factors, comorbidities hold a crucial role in both the treatment process and the eventual outcome of MDR-TB cases.

The current study identified various co-morbidities among the stud cases, with 104 cases (66.2%) exhibiting such coexisting conditions. Notably, Diabetes mellitus emerged as the most prevalent comorbidity, affecting 48 individuals (30.6%) within the study cohort. This finding aligns with the outcomes of other investigations. Dhingra et al. reported a 37.0% prevalence of DM comorbidity,[9] while Yew et al. found 36.5% of patients with DM co-occurrence.[10] Similarly, Joseph et al. documented a comorbidity rate of 31.5% for Diabetes Mellitus.[11]

Within the present study, a positive correlation found between DM and the final treatment outcomes of the study cases. Patients with DM is a chance of likelihood of experiencing unfavorable final treatment outcome. Furthermore, circumstances exacerbated when diabetic patients did not adequately monitor their condition. These collective findings underscore the designation of DM comorbidity as a risk factor for diverse adverse treatment results. Therefore, the provision of specialized care becomes imperative for this patient subset. Notably, managing uncontrolled Diabetes, if detected early in the course of treatment, presents a feasible approach. Collectively, these observations underscore the significance of diligent monitoring, comprehensive education, and effective counseling when addressing medication adherence among TB-DM patients.

One of the primary challenges faced by MDR-TB patients with diabetes is the achievement of successful treatment outcomes. This dilemma can be attributed to inadequate glucose control, whereby chronic hyperglycemia undermines the effectiveness of antituberculosis treatment. Furthermore, it impairs the elimination of MTB by compromising the microvasculature and diminishing lung perfusion, thereby hindering optimal immune surveillance. Another contributing factor is the observed deficiency in plasma levels of antituberculous drugs among DM patients compared to non-DM counterparts. Consequently, the implementation of therapeutic drug monitoring interventions or the establishment of corrected dosages, especially for those with uncontrolled DM, becomes imperative to ensure efficacious treatment.

Ensuring the complete duration of DR-TB treatment assumes paramount importance, while concurrently addressing DM management through dietary adjustments, lifestyle modifications, metformin, insulin, or other drugs utilized for DR-TB-DM patients. Special care must be exercised to prevent potential interactions between TB drugs and DM treatment. Considering these specific details, it is imperative to direct meticulous attention to every aspect of the care cascade process. This involves actively involving TB–DM patients within the healthcare system, especially in the early phases of TB treatment, to offer vital counseling concerning lifestyle interventions. These interventions encompass essential areas, including nutrition, weight management, smoking cessation, and engagement in physical activity.

A comprehensive approach involves the assessment of these patients by interdisciplinary specialists, including endocrinologists, to validate the DM diagnosis and deliver comprehensive guidance on nutritional adjustments and lifestyle transformations.[12]

Another prevalent comorbidity found in the present study was depression. Two types of factors triggered level of depression. One is disease while other is stigma related depression. Previous studies have also reported a high proportion of people with MDR-TB suffering from depression.[12-16] These conditions were almost equally diagnosed at baseline and during treatment. Management of depression required pharmacological therapy along with psychological counselling. Diagnosis and management of all these comorbidities were possible due to the model of care with systematic counselling and the availability of a psychiatrist within the same health facility where MDR-TB care was provided.

Another comorbidity that effects the final outcome is HIV which also find in the present study. Frequency of HIV is 1.91%. This rate is lower as compared to other study like

in Indian research, 3 (4.40%) were HIV positive; similarly, 9 (14%) were HIV positive at the time of treatment beginning in a Tanzanian study.[17,18] A recent systematic analysis discovered an increased relative risk of poor treatment outcomes among HIV positive individuals.[19]

HIV infection stands as a prominent cause of both drug-susceptible and drug-resistant tuberculosis. This can be attributed to accelerated disease progression and impaired absorption of anti-TB drugs, potentially leading to drug resistance and unsuccessful treatment outcome. Moreover, these factors synergistically elevate mortality rates in individuals afflicted with both DR-TB and HIV, in stark contrast to DR-TB patients without HIV infection.

Pulmonary comorbidities also play role in the disease development. In the present study COPD also found in 8.2% of the study cases. Different studies showed that COPD can promote the development of TB by damaging innate lung defense, impairing lung function and changing lung structure.[20,21] Patients with TB with COPD were two times more likely to die and 2.5 times more likely to have MDR-TB than those without COPD.[22,23]

The current study aimed to explore the frequencies of various comorbidities among the selected patients and to elucidate their impact on the final outcomes of enrolled MDR-TB patients at the selected study center. This study demonstrated that enhanced reporting of outcomes linked to specific comorbidities could provide insights into the mechanisms that lead to unfavorable treatment results in diverse categories of DR-TB patients.

It's important to note that certain crucial information, such as Drug Susceptibility Testing for second-line anti-TB drugs, contact history, and prior therapeutic regimens, was not accessible within the scope of this study, potentially influencing the obtained results. Additionally, in this study, all comorbidities were collectively analyzed without explicitly delineating the individual effects of each comorbidity. Consequently, more comprehensive and insightful examinations, encompassing both epidemiological and cellular/molecular dimensions, are urgently warranted to delve deeper into the contribution of comorbidities to TB/DR-TB within the Khyber Pakhtunkhwa region.

Conclusion

Comorbidity was prevalent among MDR-TB patients at PMDT LRH. Among the observed co-morbidities, Diabetes Mellitus and Depression stood out as the most frequent conditions. Moreover, this study underscored the significant impact of comorbidities on the ultimate treatment outcomes for the study participants. Consequently, it becomes imperative to provide heightened attention and specialized care for individuals grappling with comorbid conditions.

References

1. Zignol M, Dean AS, Falzon D, van Gemert W, Wright A, van Deun A, et al. Twenty years of global surveillance of antituberculosis-drug resistance. N Engl J Med. 2016;375(11):1081-9.
2. Van Rie A, Warren RM. MDR tuberculosis control: time to change the dogma? Lancet Respir Med. 2015;3(12):907-9.
3. Baker MA, Harries AD, Jeon CY, Hart JE, Kapur A, Lönnroth K, et al. The impact of diabetes on tuberculosis treatment outcomes: a systematic review. BMC Med. 2011;9:81. DOI: 10.1186/1741-7015-9-81.
4. Kwak N, Kim HR, Yoo CG, Kim YW, Han SK, Yim JJ. Changes in treatment outcomes of multidrug-resistant tuberculosis. J Tuberc. 2015;19:525–530.
5. Seddon JA, Hesseling AC, Willemse M, Donald PR, Schaaf HS. Culture-confirmed multidrug-resistant tuberculosis in children: clinical features, treatment, and outcome. Clin Infect Dis. 2012;54:157–166. DOI: 10.1093/cid/cir772.
6. Duraisamy K, Mrithyunjayan S, Ghosh S, Nair SA, Balakrishnan S, Subramoniapillai J, et al. Does Alcohol consumption during multidrug-resistant tuberculosis treatment affect outcome?. A population-based study in Kerala, India. Ann Am Thorac Soc. 2014;11:712–718. DOI: 10.1513/AnnalsATS.201312-447OC.
7. Khan MA, Mehreen S, Basit A, Khan RA, Jan F, Ullah I, et al. Characteristics and treatment outcomes of patients with multi-drug resistant tuberculosis at a tertiary care hospital in Peshawar, Pakistan. Saudi Med J. 2015;36(12):1463.
8. Falzon D, Mirzayev F, Wares F, Baena IG, Zignol M, Linh N, et al. Multidrug-resistant tuberculosis around the world: what progress has been made? Eur Respir J. 2015;45(1):150-60.
9. Samuels JP, Sood A, Campbell JR, Khan FA, Johnston JC. Comorbidities and treatment outcomes in multidrug resistant tuberculosis: a systematic review and meta-analysis. Sci Reports. 2018;8(1):1-3.
10. Dhingra VK, Rajpal S, Mittal A, Hanif M. Outcome of multi-drug resistant tuberculosis cases treated by individualized regimens at a tertiary level clinic. Indian J Tuberc. 2008;55:15-
11. Pawar KS, Dixit R. Prevalence of Co morbidities among patients having Multi Drug Resistant Tuberculosis: A Retrospective Analysis. JMSCR. 2018;6: 1029-1032.
12. Alene KA, Clements ACA, McBryde ES, Jaramillo E, Lönnroth K, Shaweno D, et al. Mental health disorders, social stressors, and health-related quality of life in patients with multidrug-resistant tuberculosis: A systematic review and meta-analysis. J Infect. 2018;77:357-67.

13. Vega P, Sweetland A, Acha J, Castillo H, Guerra D, Smith Fawzi MC, et al. Psychiatric issues in the management of patients with multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2004;8: 749-59.
14. Das M, Isaakidis P, Bergh R, Van Den, Kumar AM V, Nagaraja SB, Valikayath A, et al. HIV, multidrug-resistant TB and depressive symptoms: when three conditions collide. Glob Health Action. 2014;1: 1–5.
15. Deribew A, Tesfaye M, Hailmichael Y, Apers L, Abebe G, Duchateau L, et al. Common mental disorders in TB/HIV co-infected patients in Ethiopia. BMC Infect Dis. 2010;10: 201. pmid:20618942.
16. Ambaw F, Mayston R, Hanlon C, Alem A. Burden and presentation of depression among newly diagnosed individuals with TB in primary care settings in Ethiopia. BMC Psychiatry. 2017;17: 1–10. pmid: 28049496.
17. Orenstein EW, et al. Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. Lancet Infect Dis. 2009;9:153–161. DOI: 10.1016/S1473-3099(09) 70041-6.
18. Moher D, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1.
19. Weiss P, Chen W, Cook VJ, Johnston JC. Treatment outcomes from community-based drug resistant tuberculosis treatment programs: a systematic review and meta-analysis. BMC Infect Dis. 2014;14:333.
20. Sethi S, Murphy TF. Infection in the pathogenesis and course of chronic obstructive pulmonary disease. N Engl J Med. 2008;359:2355–65.
21. Inghammar M, Löfdahl CG, Winqvist N, Ljungberg B, Egesten A, Engström G. Impaired pulmonary function and the risk of tuberculosis: a population-based cohort study. Eur Respir J. 2011;37:1285–7
22. Inghammar M, Ekbom A, Engström G, Ljungberg B, Romanus V, Löfdahl CG, Egesten A. COPD and the risk of tuberculosis-a population-based cohort study. PloS One. 2010;5(4):e10138.
23. Pradipta IS, Forsman LD, Bruchfeld J, Hak E, Alffenaar JW. Risk factors of multi drug resistant tuberculosis: a global systematic review and meta-analysis. J Infect. 2018;77:469–78.