Medical conditions associated with Multi-Drug Resistance Tuberculosis and their effect on outcome

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Date Received: Feb 11, 2020
Date Revised: April 10, 2020
Date Accepted: May 13, 2020

Author Contributions

MSM UU conceived idea, MSM drafted the study, UU collected data, MSM did statistics analysis and interpretation, Both critical review manuscript and approved final version to be published.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

Abstract

Background: Tuberculosis is the second leading infectious cause of death worldwide. MDR TB is a form of tuberculosis in which MTB is resistant to two or more first line agents, usually INH and rifampicin. Despite new treatment modalities, MDR-TB still has high mortality. Many comorbidities are either responsible for development of MDR-TB or they delay the response to treatment.

Objective: The primary aim of this study was to see medical conditions associated with multi drug resistance tuberculosis and their effect on outcome.

Methodology: This was cross sectional study that was carried out from June 2015 to July 2019.545patients were included in the study. Patients were checked for comorbidities and data was recorded d on Performa. Patients outcome was determined at the end of treatment in terms of treatment completed, cured died failure to treatment, lost to follow up, still undertreatment and transfer out.

Results: The mean age in our study was 38.80+ 17.05 years. Most of the patients were in age range of 15-24 years 22.9% (N= 125), followed by 25-34 years 21.5% (N= 117). There were 52.1% (N= 284) male and 47.9% (N= 261) female. Majority of patients were non-smoker non addict 95.4% (N= 520). Only 2.6% (N= 14) of patients were smoker. The prevalence of various diseases was diabetes mellitus 22.4% (N= 122), Hepatitis C 4.6% (N= 25), diabetes with other complications 3.9% (N=21) and HIV 0.6% (N=3).DM was found as strongest risk factor for mortality in our study.Fifteen patients died because of DM alone.

Discussion: There are many comorbidities which effect the outcome of MDR TB. In our study diabetes was the strongest risk factor for mortality.

Key Words: Tuberculosis; Multidrug-Resistant TB; HIV; Diabetes Mellitus; Patient Outcome Assessment

This article may be cited as: Musharaf MS, Usman U. Medical conditions associated with Multi Drug Resistance Tuberculosis and their effect on outcome. Pak J Chest Med 2020; 26 (2):63-67

Introduction

Johann Schonlein was the first one to use the term "tuberculosis" in the 1834. It is estimated that, Mycobacterium tuberculosis the causative organism,may have been around three million years ago.[1] The name and terminology before the discovery of organism changed with passage of time. "Phthisis" in ancient Greece, "tabes" in ancient Rome, and "schachepheth" in ancient Hebrew. In the 1700s, it was called "the white plague" and "consumption" in the 1800s. During eighteenth century, it was also called the "Captain of all these men of death".[2]

By the discovery of streptomycin, it was shown that the number of deaths by tuberculosis were reduced by 51% over a period of twenty-three years, a great relief in early twentieth century. The further relief from the horror of TB came with the discovery of rifampicin, that change the game both in terms of cure rate and duration of treatment.[3]

But the enjoyment was short lived. In 1956 resistant strains of TB were first identified in Great Britain.[2] These strains were resistant to streptomycin, para-aminosalicylic acid (PAS), and isoniazid (INH). In late 80s, there was again resurgence of tuberculosis. This time it was entirely different strain that had gained the

resistance to core line drugs i.e. isoniazid and rifampicin. It was then named as multi drug resistance tuberculosis or MDR-TB (MDR). In response to this resurgence, the WHO issued a declaration of a global health emergency in 1993. Every year, nearly half a million new cases of MDR-TB are diagnosed worldwide.[4]

There are many factors that are involve in emergence of MDR-TB. First mycobacterium itself has a property of developing resistance. The mechanism behind this process is called "Random Mutation and Natural Selection." The process is done through vertical and horizontal gene transfer.[2] Among patient's factors, compliance is the biggest issue for acquiring resistance.[5] Other factors include poor absorption, in adequate dosage according to weight, early stoppage of drug, contact with MDR-TB patient.[6] HIV is also a contributory factor in resurgence of Tb and especially MDR-TB.[7]

Worldwide in 2016, there were an estimated 4.1% of new cases and 19% of previously treated cases with MDR-TB. Drug resistance surveillance data show that an estimated 240,000 people died from MDR-TB in 2016 alone.[8]

Unfortunately, the situation in Pakistan is not very promising. Pakistan estimated to have the fourth highest prevalence of MDR-TB globally. We have estimated 510,000 new TB cases each year. Out of those approximately 15000 developing drug resistant TB cases every year. Our country accounts for 61% of the MDR-TB burden in the WHO Eastern Mediterranean Region.[10] The risk factors for MDR-TB pertaining to our population are delays in diagnosis, unsupervised, inappropriate and inadequate drug regimens, poor follow-up and lack of a social support program for high-risk populations.[10]

Many comorbidities are either responsible for MDR-TB or they delay the response to treatment.[11] One of the most important disease is human immune-deficiency virus(HIV). Similarly smoking is associated with more extensive lung disease, lung cavitation and positive sputum smear and culture at the baseline.[12] Diabetes mellitus (DM) not only prone the patient to MDR-TB, they also have atypical presentation radiologically and clinically. Present study tries to find out such association in our population.

Objective:

To determine the association and frequencies of common diseases in our multi drug resistance tuberculosis (MDR-TB) patient presenting to a Faisalabad MDR treatment facility which is district level treatment facility.

Methodology

This was cross sectional study that was carried out from June 2015 to July 2019.

Samples and Data collection procedure:

Both genders, male and female were included in study. Patients were adults with age more than 14 years. The patients enrolled were either diagnosed at MDR-DOTS facility or they were referred for MDR-TB treatment. Diagnosis of MDR-TB was either PCR for MTB with rifampicin resistance (commonly called GeneXpert) or culture based. Written permission was taken from all enrolled participants/patients that their clinical and laboratory findings may be published scientifically without disclosing their identity.

Table 1. Demographic characteristics of the study cases

Demographic Data of Patients		
Sex		
	Frequency	Percent
Male	261	47.9
Female	261	47.9
Age in years with Standard Deviation		
38.80± 17.05 years		
Age Groups		
15-24	125	22.9
25-34	117	21.5
35-44	93	17.1
45-54	86	15.8
5-14	10	1.8
54-64	65	11.9
65+	49	9.0

Table 2. Smoking and HIV status of the study cases

Smoking, IV Drugs & HIV status of Patients		
Smoking & I.V Drug Abuse Habits		
	Frequency	**Percent**
IV drug Abuse	1	0.2
Huqa Smoking	2	0.4
Tobacco Chewing	2	0.4
Naswar Chewing	6	1.1
Cigarette Smoking	14	2.6
Non-Smoker	520	95.4
HIV Status of Patients		
Negative	534	98
Positive	3	0.6
Refused for testing	8	1.5

Procedure:

Once the patient agreed to be included in study they were asked about status of smoking, diabetes mellitus, HIV status, Hepatitis B and C, Acid peptic disease, Chronic liver disease, Chronic kidney disease, Systemic hypertension, Cataract, Valvular heart disease, Ischemic heart disease and Epilepsy. If patient do not know their current status, blood samples were sent for HIV by ELISA, blood sugar fasting with HbA1C, renal function test, liver function test, HBsAg and anti-HCV by ELISA, eye examination by ophthalmologist for cataract, blood pressure monitoring for two weeks, if symptoms related to heart, ECG with echocardiography, and if symptoms suggestive of epilepsy then EEG. Later results were recorded in performa.

Statistical Analysis:

Descriptive statistics of all continuous variables were calculated as means and standard deviation, whereas categoric data were expressed as percentages. All analyses were done with SPSS version 20.0 for Windows.

Results

545patientspresented during above time period. The mean age in our study was 38.80+ 17.05 years. Most of the patients were in age range of 15-24 years 22.9% (N= 125), followed by 25-34 years 21.5% (N= 117).There were 52.1% (N= 284) male and 47.9% (N= 261) female. Majority of patients were non-smoker non addict 95.4% (N= 520). Only 2.6% (N= 14) of patients were smoker. The prevalence of various diseases was diabetes mellitus 22.4% (N= 122), Hepatitis C 4.6% (N= 25), diabetes with other complications 3.9% (N=21) and HIV 0.6% (N=3). Eight patients in our study refused for HIV testing. DM is the predicator and significantly associated with the final outcome as compared to other medical conditions.

Discussion

Despite new treatment modalities, MDR-TB still has high mortality. According to WHO, in 2014, the patients who enrolled 16% of patient died while during the treatment.[14] Lower educational level, greater number of previous TB treatment episodes and co-morbidities e.g. diabetes mellitus were independently associated with increased mortality among MDR-TB cases.[15] Abdul Majeed et al, in their showed few factors that were pertaining to our population mainly lower baseline body weight, sputum and/or culture positive result, adverse reaction of the treatment and no or partially under DOTs.[9]

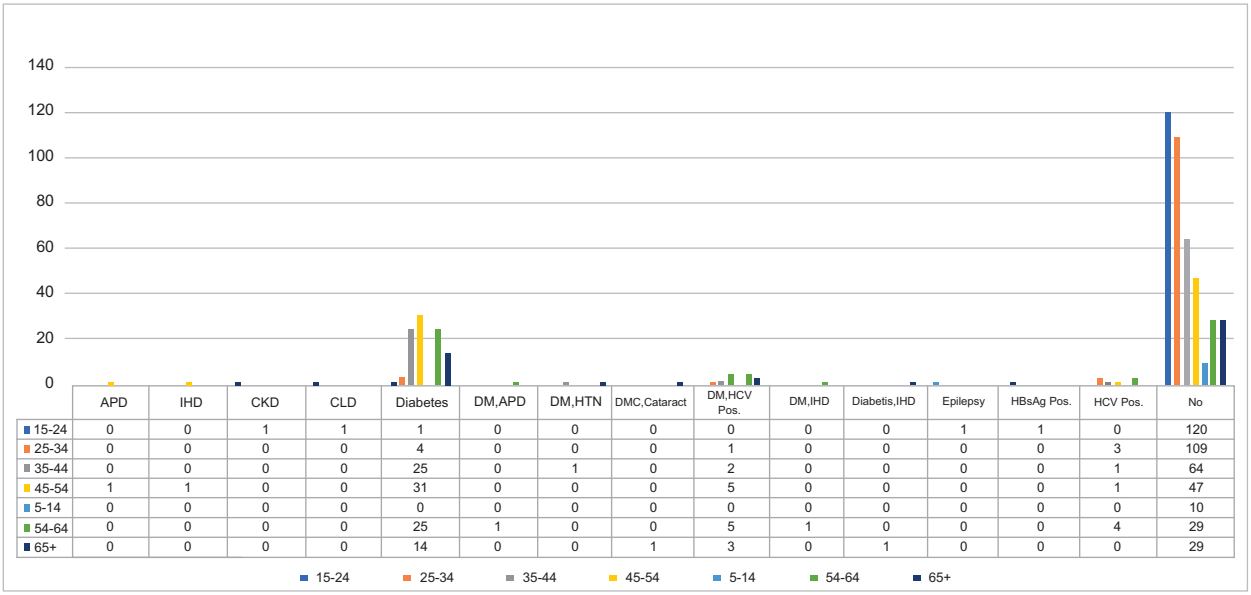
The mean age in our patients was 38.80 years which is usual age of diagnosis globally.[9,15] Out of them most of our patients were young with 22.9% of patient in 15 to 24 year age group. This age is usually most reproductive age group for working. However, between 45-54 years age group, most common suffering from medical conditions. Diabetes mellitus is the most common disease in this age group.

Majority of patients are non- smoker 95.4% (N=520).

Medical Conditions and Effect on Outcome

Medical Conditions	Outcome							Total
	Complete	Cured	Died	Failed	Lost to follow up	Still under Tx	Transfer out	
APD	0	0	1	0	0	0	0	1
IHD	0	1	0	0	0	0	0	1
CKD	0	0	0	0	0	1	0	1
CLD	0	0	1	0	0	0	0	1
DM	2	32	15	0	6	42	3	100
DM, APD	0	0	1	0	0	0	0	1
DM, HTN	0	1	1	0	0	0	0	2
DM, Cataract	0	0	1	0	0	0	0	1
DM, HCV Pos.	0	7	3	0	0	6	0	16
DM, Valvular Heart Dis.	0	0	0	0	0	1	0	1
DM, IHD	0	0	0	0	0	1	0	1
Epilepsy	0	0	0	0	0	1	0	1
HBsAg Pos.	0	1	0	0	0	0	0	1
HCV Pos.	1	3	0	0	0	5	0	9
No Ailment	**12**	**134**	**69**	**9**	**24**	**156**	**4**	**408**

DM= diabetes mellitus, CKD= chronic kidney disease, APD= acid peptic disease, CLD= chronic liver disease(non HBV and HCV), HTN= systemic hypertension, IHD= ischemic heart disease.



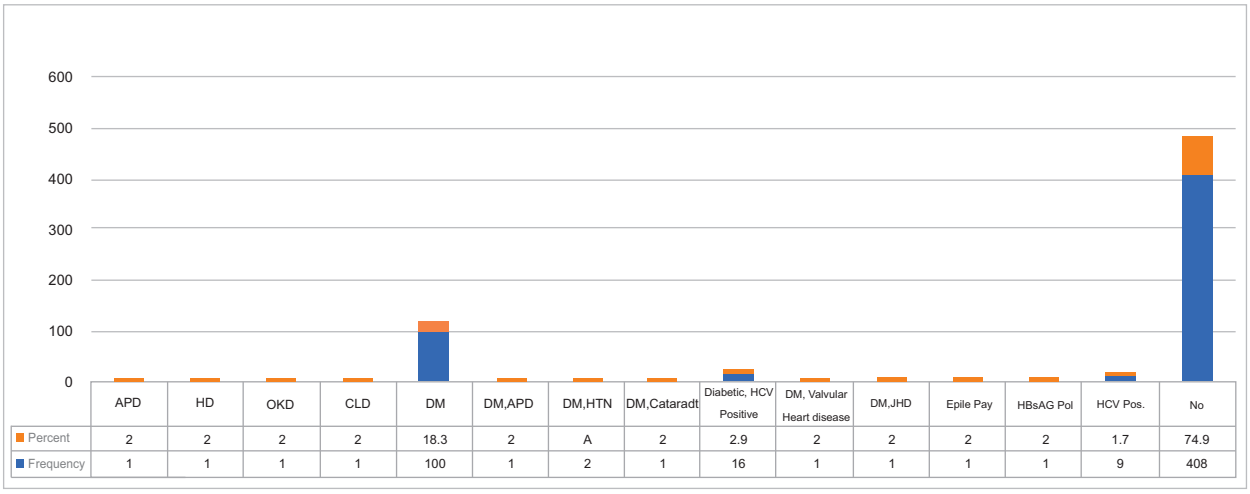
	APD	IHD	CKD	CLD	Diabetes	DM,APD	DM,HTN	DMC,Cataract	DM,HCV Pos.	DM,IHD	Diabetis,IHD	Epilepsy	HBsAg Pos.	HCV Pos.	No
15-24	0	0	1	1	1	0	0	0	0	0	0	1	1	0	120
25-34	0	0	0	0	4	0	0	0	1	0	0	0	0	3	109
35-44	0	0	0	0	25	0	1	0	2	0	0	0	0	1	64
45-54	1	1	0	0	31	0	0	0	5	0	0	0	0	1	47
5-14	0	0	0	0	0	0	0	0	0	0	0	0	0	0	10
54-64	0	0	0	0	25	1	0	0	5	1	0	0	0	4	29
65+	0	0	0	0	14	0	0	1	3	0	1	0	0	0	29

Figure 1. Relationship of medical condition with age

Chi C.Leung, Wing W.et al. in their study showed that smokers have more extensive disease and have poor response to trettment1.[12] Similar results were shown by Wang JY etal, that smoking produces poor outcome. But in our study analysis showed that smoking did not affect the outcome. 89 patients died in non-smoker group versus 2 patients in smoker group. Similarly, outcomes of cure and completed are not affected by smoking status (p <0.01). 170 patients in smoker group versus 3 patients in non-smoker got cured.

HIV strongly effects the outcome in MDR-TB. It is the strongest risk factor for the development of active TB either drug-susceptible or drug-resistant TB.[17] MDR-TB is the leading cause of death among HIV-infected persons and may accelerate the course of HIV infection.van der Walt M et al, in their study showed there is significant impact of mortality in MDR-TB with HIV. In fact, they label HIV as a strongest risk factor to predict mortality.[18] In our study, only three patients were HIV positive owing to low level of prevalence of HIV in Pkistan.[19] In outcome analysis, three patients died in "patient refused to testing group" versus one patient who was HIV positive.

Diabetes mellitus was the most common medical condition. The prevalence of diabetes in our study was 22.4% (N=122). In a study by Marina Kikvidze et al, the prevalence of diabetes mellitus was 5% in Georgian population USA. The effect of diabetes in their study did not differ significantly on outcome13. In our study DM is the strongest predictor of mortality (p 0.001) when compared to mortality to non-diabetic



	APD	HD	OKD	CLD	DM	DM,APD	DM,HTN	DM,Cataradt	Diabetic, HCV Positive	DM, Valvular Heart disease	DM,JHD	Epile Pay	HBsAG Pol	HCV Pos.	No
Percent	2	2	2	2	18.3	2	A	2	2.9	2	2	2	2	1.7	74.9
Frequency	1	1	1	1	100	1	2	1	16	1	1	1	1	9	408

Figure 2. Correlation of medical conditions with age of the study cases

group. Fifteen patients died because of DM alone. Three patients died with DM and hepatitis C. In three patients, DM was also contributory factor. So screening and meticulous management of DM is imperative for successful treatment of MDR-TB.

This study is probably first in Faisalabad district region to evaluate the effect of various diseases on outcome. But the study has limitation also. More information regarding the DM control during the treatment time should be available, as this would give more precise information regarding the cause of death. Similarly, the patients should be counselled more thoroughly regarding the HIV status as three out of eight patients in "patient refused for testing" died.

Conclusion

This study high lights the importance of proper evaluation of various medical conditions at the start of treatment. The mortality and treatment outcome differ significantly, if associated medical conditions are known before the start of treatment. The current study finds DM as a strongest factor for mortality and these patients should be carefully monitor and observe for poor outcome.

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