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Study of Pattern and Occurrence of Multiple Co-morbidities in Patients with Drug Resistant Tuberculosis

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Abstract

Background and Objectives: India has the highest burden of tuberculosis (TB) in the world. Drug resistance and the co-morbidities associated with TB, acting as factors affecting both, the incidence and treatment outcome, further complicate the situation. Hence, there is a need to analyse the occurrence and pattern of comorbidities associated with DR-TB.

Methods: This is a cross-sectional study, based on record review; studying people diagnosed with DR-TB between January 2018 and March 2020. Data was recorded from their treatment cards; which included parameters such as age, weight, height, gender, HIV status, liver, renal, and thyroid functions, blood haemoglobin level, RBS, and an audiogram.

Results: It was found that most of the patients in the study (71.07%) had at least one comorbidity, which is considerably higher as compared to previous studies. The most common comorbidity found in the study population overall was altered renal function, followed by hearing loss and moderate anaemia. Also, it was found that patients had clusters of comorbidities. The most common pattern of comorbidities in patients with two comorbidities was anaemia with altered renal function (15.23%). Whereas the pattern in patients with three comorbidities was anaemia with altered renal function and hearing loss (27.27%). An altered thyroid function and diabetes were also found in considerable numbers of patients.

Conclusions: The prevalence of comorbidities in patients with DR-TB was found to be high. Also, certain patterns of comorbidities were found to be associated with the disease. Thus, with further study, we may be able to define new high-risk populations based on their comorbidities as well as predict their responsiveness to treatment, which may prove useful in achieving our goal of eradicating TB in India by 2025.

Keywords: Anaemia, Comorbidity, Drug-Resistant Tuberculosis, Pattern; Renal Function.

Introduction

Tuberculosis (TB) is an infectious disease caused by bacteria of the Mycobacterium complex. [1] The most common bacterium in that complex is *Mycobacterium tuberculosis*. This is responsible for majority of the cases of tuberculosis in humans. Tuberculosis generally affects the lungs (known as pulmonary tuberculosis); but sometimes it can occur in other parts of the body as well (extra-pulmonary tuberculosis). It is one of the oldest diseases known to affect humans and the leading cause of infectious deaths worldwide. [1]

Tuberculosis can be classified based on the sensitivity of the causative organisms to the anti-tubercular drugs. Multi-drug-resistant tuberculosis (MDR-TB) is a variant of TB in which the bacilli are resistant to (at least) Isoniazid and Rifampicin.[2]

Despite 90 years of vaccination and 60 years of chemotherapy, tuberculosis (TB) remains the world's leading cause of death from an infectious agent. [3] India has an ambitious goal of eradicating TB before 2025. But India is the country with the highest TB burden in the world. [4] Also, drug-resistant tuberculosis (DR-TB) is a significant problem, and India now has the highest number of cases of multidrug-resistant tuberculosis (MDR-TB) in the world, contributing one-fourth of the global burden. [5] 2.69 million new cases of TB were reported in India in 2019, out of which 90% were incident TB cases (new & relapse/recurrent) and 94% were initiated on TB treatment. [4] In 2019, out of the TB cases notified, 66,255 were diagnosed as MDR-TB.

MDR-TB is also more difficult to treat than normal drug sensitive TB. [2] And studies have shown that comorbidities can further complicate the situation and become an obstacle to solving the problem of TB. [6]

Comorbidity is defined as the co-occurrence of two chronic conditions in an individual. Comorbidity and multimorbidity are increasingly being recognized as serious public health concerns and obstacles to the control of both drug-sensitive TB (DS-TB) and drug-resistant TB (DR-TB) globally. [6]

Various comorbidities like diabetes mellitus, HIV infection, and impaired liver or renal function may be associated with tuberculosis; both as factors aiding the disease's contraction as well as factors determining the response to treatment. The effect of certain comorbidities, such as diabetes mellitus and HIV, on the treatment outcome of drug sensitive tuberculosis has been studied and documented. [7] But the same is not true in the case of DR-TB. Although such comorbidities may be associated with the infection, and even act as determinants in the treatment outcome of the patients, their association with DR-TB is not well documented. [7]

Apart from HIV and diabetes mellitus, there is sufficient evidence to suggest that comorbidities such as chronic kidney disease, cigarette smoking, and alcohol abuse are associated with the risk of developing DS-TB and DR-TB and affecting their treatment outcomes. [6]

Hence, there is a need to find and analyze the pattern of comorbidities associated with TB. There have been some extensive studies in settings outside India on this topic, but for Indian settings, there is still a lot of scope in this direction.

The purpose of this study is to find the prevalence of comorbidities like HIV, diabetes, altered renal, liver, and thyroid functions, and hearing loss in patients with DR-TB at the time of detection of TB in an Indian setting. Additionally, this study aims to analyze the pattern of comorbidities found in the patients at the time of diagnosis.

Objectives

1. To find the prevalence of different conditions like diabetes, anaemia, liver dysfunction, renal dysfunction, hearing loss, thyroid functioning, HIV status, and BMI in patients with drug-resistant tuberculosis at the time of diagnosis.
2. To study the pattern or cluster of multiple comorbidities in these patients if multiple conditions are present in them.

Material and Methods

This was a cross-sectional study based on record review (January 2018–March 2020). The sample population for the study was, the patients diagnosed with DR-TB at Sir Sayajirao General Hospital, Vadodara, Gujarat; between January 2018 & March 2020 and receiving treatment at the city TB center.

The study was commenced after receiving proper approval from the Institutional Ethics Committee for Biomedical and Health Research (IECBHR) [Approval No. IECBHR/139-2021, dated November 27, 2021] and the state TB officer (STO) under NTEP.

A total of 197 patients were included in the study. All patients included in the study were adults diagnosed with drug resistant tuberculosis and had undergone a pre-treatment evaluation. Patients below 18 years of age and patients with incomplete pre-treatment evaluations were excluded from the study.

Patients diagnosed with DR-TB are treated after a pre-treatment evaluation. This includes HIV status, liver function tests, renal function tests, serum TSH levels, serum electrolyte levels, CBC, blood haemoglobin levels, assessment of hearing loss, random blood sugar, and chest x-ray. This data was collected from the treatment cards of patients, which were accessed at the City TB Centre after taking permission from the District TB Officer (DTO).

Overall following parameters were analysed in this study:

1. Age when the patient was diagnosed with DR-TB
2. Gender of the patient
3. Height and weight at the time of diagnosis
4. Site of TB (pulmonary or extrapulmonary)
5. HIV status
6. Liver Function (S. bilirubin, SGPT levels)
7. Renal Function (S. creatinine, S. urea levels)
8. Thyroid Function (S. TSH levels)
9. Blood Haemoglobin level
10. Random Blood Sugar
11. Total WBC count
12. Platelet count
13. Audiogram result

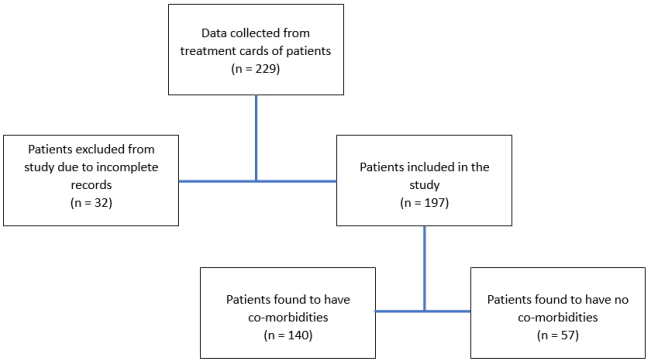

Figure 1: Patient recruitment and analysis flow chart

The names of the techniques used for various tests included in the pre-treatment evaluation and their normal range used for analysis are mentioned in Table 1.

Table 1: Baseline Investigation as a pre-treatment evaluation in patients with Tuberculosis

Test	Technique used	Normal Range
S. Bilirubin (Direct)	Cliniquant-FSR, DCA method	0 – 0.4 mg/dl
S. Bilirubin (Indirect)	Cliniquant-FSR, DCA method	0.1 – 0.8 mg/dl
SGPT	Modified IFCC method	< 40 U/L
S. TSH	Microwell ELISA Immunoassay	0.4 – 5.5 mIU/L
S. Creatinine	Modified Jaffe's method	Males: 0.7 – 1.4 mg/dl Females: 0.6 – 1.2 mg/dl
S. Urea	GLDH test [GLDH-DST]	13 – 45 mg/dl
RBS	GOD-POD	Normal = < 140 mg/dl Pre-Diabetic = 140 – 190 mg/dl Diabetic = > 190 mg/dl
CBC (WBC & Platelets)	Horiba XLR (Horiba es60)	WBC: 4000 – 10000 / mm^3 Platelets: 1.5 – 5 lakhs / mm^3
Blood Hemoglobin	Horiba XLR (Coulter Principle)	Normal = > 13 g/dl Mild Anemia = 10.1 – 13 g/dl Moderate Anemia = 7.1 – 10 g/dl Severe Anemia = < 7 g/dl
HIV	1] Comb Aids – RS (immune-dot assay) 2] Voxpress rapid test kit (immuno-chromatography) 3] Tredo Tri-dot test (immuno-flow through assay)	-
Audiogram	Pure Tone Audiometry (Maico MA 53)	-10 – 25 dB
BMI[10]	Formula: BMI = Weight (kg) / Height (m^2)	Normal = < 18.0 – 22.9 kg/m^2 Overweight = 23.0 – 24.9 kg/m^2 Obese = > 25.0 kg/m^2

The prevalence of anaemia in India is considerably high.[11] So only moderate and severe anaemia are considered comorbidities.

The data was collected in MS Excel 2007, and the analysis was done in Epi Info version 7.[12] The quantitative variables (age, BMI) are expressed as mean (± standard deviation) and are also grouped and represented in percentage with a 95% confidence interval (table 2). The qualitative variables (liver function, renal function, anaemia, HIV, site of TB, diabetes mellitus, and hearing loss) are expressed as percentages with a 95% confidence interval (table 4). The patterns of comorbidities are expressed in percentages with a 95% confidence interval (table 6). Also, the individual comorbidities are expressed in a bar graph (Figure 2). And the number of comorbidities is expressed in percentage with a 95% confidence interval (table 5) and as a pie chart (Figure 3).

Table 2: General demographic profile in patients with Tuberculosis

Parameter	Number of Patients (Total = 197)	Percentage (%)	With 95% CI (In percentages)
Age			
0 – 10	0	0	0
11 – 20	20	10.15	6.10 – 14.19
21 – 30	60	30.46	24.29 – 36.62
31 – 40	47	23.86	18.14 – 29.57
41 – 50	35	17.77	12.64 – 22.89
51 – 60	22	11.17	6.94 – 15.39
61 – 70	10	5.08	2.13 – 8.02
71 – 80	2	1.01	-0.32 – 2.34
81 – 90	1	0.50	-0.44 – 1.44
91 – 100	0	0	0
Gender			
Male	134	68	61.74 – 74.25
+Female	6	32	25.74 – 38.25
BMI			
< 18.0	115	58.38	51.77 – 64.98
18.1 – 24.9	63	31.98	25.73 – 38.22
> 25	19	9.64	5.68 – 13.59

Table 3: Pattern of Patients with Tuberculosis

Site of TB	Number of Patients (Total = 197)	Percentage (%)	With 95% CI (in percentages)
Pulmonary	185	93.9	90.69 – 97.10
Extra-pulmonary	12	6.1	2.89 – 9.30

Table 4: Prevalence of various comorbidities in patients with Tuberculosis

Comorbidity	Number of Patients with DR TB (Total = 197)	Percentage (%)	With 95% CI (in percentages)
HIV			
Reactive	13	6.6	3.13 – 8.37
Non-reactive	184	93.4	89.93 – 95.17
Liver Function			
Altered	31	15.73	10.65 – 18.33
Normal	166	84.27	79.18 – 86.86
Renal Function			
Altered	50	25.38	19.30 – 28.48
Normal	147	74.62	68.54 – 77.72
Audiogram			
Hearing Loss Present	49	24.87	18.84 – 27.95
Normal	148	75.13	69.09 – 78.21
Blood Sugar			
Pre-Diabetic	11	5.59	2.38 – 7.22
Diabetic	11	5.59	2.38 – 7.22
Normal	175	88.82	84.43 – 91.08
Blood Hemoglobin			
Mild Anemia	102	51.77	44.80 – 55.34
Moderate Anemia	49	24.87	18.84 – 27.95
Severe Anemia	3	1.53	0.19 – 2.40
Normal	43	21.83	16.60 – 24.77

Total WBC Count	87	44.16	37.23 – 47.70
Increased	2	1.02	0.38 – 1.73
Decreased	108	54.82	47.78 – 58.37
Normal			
Platelet Count	20	10.15	5.93 – 12.30
Increased	2	1.02	0.38 – 1.73
Decreased	175	88.83	84.43 – 91.08
Normal			

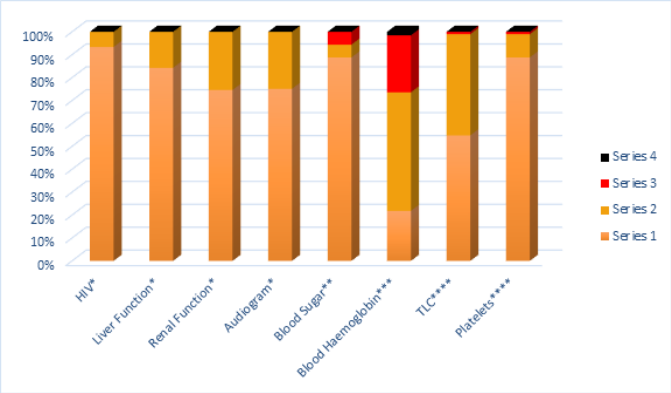

Figure 2: Prevalence of various co-morbidities in patients with Tuberculosis

*for HIV, Liver function, Renal function, Audiogram; series 1 = Normal & series 2 = Altered.

**for Blood sugar; series 1 = normal, series 2 = Pre-diabetic, series 3 = Diabetic.

***for Blood haemoglobin; series 1 = normal, series 2 = mild anaemia, series 3 = moderate anaemia, series 4 = severe anaemia.

****for TLC and Platelet count; series 1 = normal, series 2 = increased, series 3 = decreased.

Results

A total of 229 patients were enrolled in the study. But due to dropouts or the loss of follow-up cases of patients, only 197 patients could be utilized for analysis. The flowchart for the selection of data and analysis is shown in Figure 1.

The gender and age distribution patterns are shown in Table II. More males (68%) than females (32%) were diagnosed with DR-TB. The mean age of the patients considered for the study is 37.20 (+ 14.22) years, and the most common age groups for detection of TB were found to be 21 to 30 years (30.46%), followed by 31 to 40 years (23.86%).

Out of the 197 patients diagnosed with DR-TB during the period considered for the study, most of the patients (93.90%) were found to have pulmonary TB, with only a few (6.10%) having extra-pulmonary TB, as shown in Table 3.

The distribution of BMI among the patients at the time of diagnosis is shown in Table 2. According to it, the majority of the patients (53.38%) were underweighted at the time of diagnosis. The number of comorbidities detected in patients as per the pre-treatment evaluation is shown in Table IV. Out of the 197 patients, most (71.07%) had at least one comorbidity, while only a few (28.93%) had no comorbidities at the time of detection of DR-TB.

The prevalence of various comorbidities considered in the study is shown in Table IV. And the most common comorbidities found in the study population are altered renal function (25.38%), followed by hearing loss (24.87%), and moderate anaemia (24.87%).

The most common comorbidities seen in patients with only one comorbidity, two comorbidities, and three comorbidities, respectively, are shown in Table 6.

The most common comorbidity in patients with only one comorbidity was found to be hearing loss (22.48%). And the most common pattern of comorbidities found in patients with two comorbidities was anaemia with altered renal function (15.23%). Whereas the most common pattern in patients with three comorbidities was anaemia with altered renal function and hearing loss (27.27%).

Table 5 : Number of comorbidities in patients with Tuberculosis

Number of Comorbidities	Number of Patients (Total = 197)	Percentage (%)	With 95% CI (in percentages)
0	57	28.93	22.85 – 35.00
1	76	38.58	32.05 – 45.10
2	41	20.81	15.37 – 26.24
3	19	9.65	5.69 – 13.60
4	4	2.03	0.14 – 3.91

Table 6: Most common patterns of comorbidities in patients with Tuberculosis

Most Common Patterns of Comorbidities	Number of Patients	Percentage (%)	With 95% CI (in percentages)
1 Comorbidity			
Hearing loss	20	22.48	16.88 – 28.07
Altered Renal Function	17	19.10	13.83 – 24.36
Anemia	15	16.85	11.83 – 21.86
2 Comorbidities			
Anemia + altered Renal Function	7	15.23	10.41 – 20.04
Anemia + Hearing loss	4	8.69	4.91 – 12.46
Anemia + Pre-diabetes	4	8.69	4.91 – 12.46
3 Comorbidities			
Anemia + altered renal function + hearing loss	6	27.27	21.30 – 33.23
Anemia + hearing loss + altered liver function	3	13.64	9.04 – 18.23

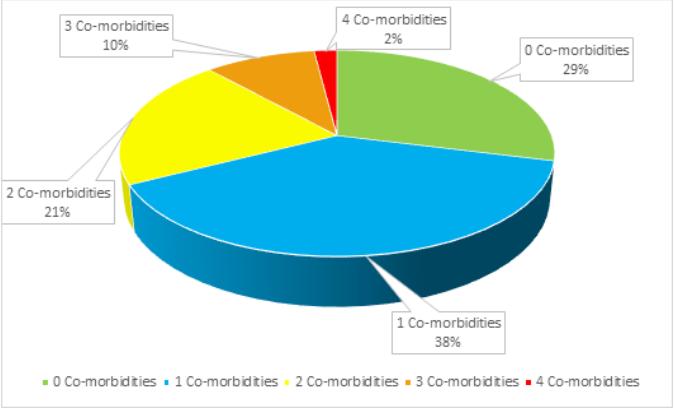

Figure 3: Number of co-morbidities in a patient with Tuberculosis

Discussion

Tuberculosis is still the leading cause of death from an infectious agent in the world, even after about a century of vaccination and 60 years of chemotherapy.[1] And India, with the world's highest burden of the disease, has an ambitious goal of eliminating TB by 2025.[4]

Out of the study population, a majority of the patients (68%) diagnosed with DR-TB were males, while 32% were females. Thus, males are found to be affected more by DR-TB than females. The male-to-female ratio is 2.125. This is close to the gender ratio found in an earlier Indian study (2.73) done by Jain S. et al. [13]

The patients considered in the study range in age from 18 years to 88 years, with the mean age being 37.20 (± 14.22) years. This is higher than that in a previously conducted Indian study by Giri OP et al., in which the mean age was found to be 20.52 years. [14] The most common age groups among the patients were found to be 21–30 years (30.46%), 31–40 years (23.86%), and 41–50 years (17.77%). Whereas the least common age groups were 81–90 (0.50%), 71–80 years (1.01%), and 61–70 years (5.08%). This pattern of age of patients diagnosed with DR-TB indicates that the prevalence of TB is higher in the initial age groups and then starts declining gradually after the age group of 21–30 years.

Out of the patients diagnosed with DR-TB, a majority of them (58.38%) were found to have a BMI less than 18.0, and a few (9.64%) had a BMI greater than 25, while 31.98% had a normal BMI (18.1 – 24.9).[10] Patients with low BMI (<18.0) are fewer in this study as compared to an earlier Indian study done by Jain S et al., which reported 88.6% of patients having low BMI. [13] This may be pointing towards the role of nourishment and general wellbeing in preventing the contraction of diseases like TB. This is important because it has been found that a low BMI (<18.5) is associated with poor treatment outcomes. [15] Also, BMI is known to be an indicator of treatment for DR-TB. [16] Hence, it is important to focus on the different profiles of BMI in DR-TB patients.

71.07% of patients in the study had at least one comorbidity at the time of diagnosis. This prevalence is close to the results documented in a study by Olusola A. Adejumo et al., done in Nigeria (70.3%). [6] But it is considerably higher as compared to previously done Indian studies by Dr. Kamendra Singh Pawar et al. and Dhingra VKet al., which reported prevalence of 37% and 40.1%, respectively. [8] [17]

A study done by Olusola A. Adejumo et al. in Nigeria and a South African study by Sogebi OA et al. in South Africa reported an association between hearing loss and TB of 13.8% and 78.8%, respectively. [6] [19] But an Indian study by Nizamuddin S. et al. reported it to be 22.7%. [18] This study found the prevalence of hearing loss in the study population to be 24.87%, which is close to the findings of the study done in India but quite higher than that reported in the Nigerian study. [18] [6]

One of the greatest risk factors for the development of TB is HIV. [6] According to the India TB Report 2020, the HIV co-infection rate in incident TB cases is

estimated to be 3.4%. [4] Also, the mortality rate in this group is very high. Among the TB-HIV co-infected patients, 9700 die every year. [4] The prevalence of HIV in the study population was 6.6%, which is slightly higher than a figure of 4.4% from a study done by Deivanayagam CN et al. [20] But it is lower than the prevalence of HIV in TB seen in African countries like Nigeria (10.4), as reported in a study by Olusola A. Adejumo et al. [6]

In the study population, 26.4% of patients were found to have moderate-to-severe anaemia at the time of diagnosis. The prevalence of anaemia overall (mild, moderate, and severe) was 78.17%. But as the prevalence of anaemia in India is considerably high, only moderate and severe anaemia were taken as comorbidities. [11]

Due to urbanization and socio-economic development, the prevalence of diabetes mellitus (DM) has increased to about 7.8%. [4] Studies show that around 20% of TB cases in India also have diabetes. [4] Studies also indicate that diabetes can worsen the clinical course of TB. [4] It was found in this study that the prevalence of diabetic comorbidity with MDR-TB was 11.18%, with diabetes and pre-diabetic conditions being 5.59% each. This is comparable to the findings of another Indian study done in Madhya Pradesh by Anil Kumar Agawalet et al., where the prevalence was found to be 15.5%. [9] This association with diabetes also indicates the high prevalence of DM in the Indian general population, as per a study by Saharia GK et al. [22] Also, diabetes has been found to be a significant comorbidity and a factor having an impact on the treatment outcome. [13] This association between these two, which are some of the greatest health problems in India, suggests that we should emphasize screening for TB in areas with a high prevalence of DM and vice versa.

An altered thyroid function was seen in 9.12% of patients in the study population. This is lower than the prevalence reported in a study done in a Nigerian setting (13.8%) by Olusola A. Adejumo et al. [6] Also, a study done in Meghalaya by Saharia GK et al revealed a significant association between altered TSH levels (both hyperthyroidism and subclinical hypothyroidism) and TB, suggesting the need for mandatory TSH level screening at baseline and 6 months into the treatment. [22]

The most common pattern of comorbidities in patients with two comorbidities was found to be anaemia with altered renal function (15.23%), while the most common pattern found in patients with three comorbidities was anaemia with altered renal function and hearing loss (27.27%). Such a prevalence of clusters or combinations of comorbidities points towards a need for further study in this direction to highlight the high-risk populations for contracting TB or patients most likely to have an affected treatment outcome. This may prove helpful in achieving our goal of eliminating TB by 2025.

Conclusion

The prevalence of co-morbidities in patients with DR-TB was found to be high. There were certain comorbidities seen repeatedly, indicating their greater association with the disease. Also, certain common patterns of comorbidities were found to be associated with the disease. Thus, with further study, we may be able to define new high-risk populations based on their comorbidities as well as predict their responsiveness to treatment. Hence, it is imperative to move forward in this direction, as it may be extremely useful in achieving our goal of eliminating tuberculosis by 2025.

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Ethical Permission: The study was commenced after receiving proper approval from the Institutional Ethics Committee for Biomedical and Health Research (IECBHR) [Approval No. IECBHR/139-2021, dated November 27, 2021]. and the state TB officer (STO) under NTEP.

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