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Treatment Outcomes Of Drug Resistant Tuberculosis Patients: A Retrospective Analysis Of Data From 2012 To 2022

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Abstract

Tuberculosis remains a formidable global health challenge, with drug-resistant strains posing significant hurdles in its eradication efforts. Addressing the challenge of drug-resistant and multidrug-resistant tuberculosis requires a multifaceted approach encompassing enhanced diagnostics, novel therapeutics, and patient-centered care models. This study aims to find the treatment outcomes of DR-TB patients registered at tertiary care settings along estimation of impact of associated adverse events.

This retrospective study was undertaken at a tertiary care setting of Lahore Punjab Pakistan during the year 2023. Using a predefined scheme of variables data was collected Regression analysis was applied by taking death and treatment failure as adverse outcomes excluding the treatment defaulter patients as their final fate was not known.

A total of 1438 drug resistant TB patients comprising of 49.4% males and 50.6 females with mean age of patients at the time of registration as 35.08±15.91 years were included in final analysis. A high number of 17.4% patients were died, 56.2% patients were cured and 10.4% successfully completed their treatment. Rate of loss to follow up was noted to be 11.1% and treatment failure were 4.9% in this study. Regression model showed that patients aged ≥34 years, patients having previous history of treatment and treatment strategy other than LTR are at greater risk of adverse events.

Overall success rate of treatment remained to be 66.6% remained far below of the target laid down by the WHO. A high mortality rate was found to be associated with drug resistant tuberculosis patients. Age ≥34 years, prior history of TB treatment and treatment strategy are risk factors for death of DR TB patients.

Keywords: Drug resistant, Tuberculosis, Multidrug resistant, extensively resistant, Poly resistant.

Introduction

Tuberculosis (TB) remains a formidable global health challenge, with drug-resistant strains posing significant hurdles in its eradication efforts. (Iqbal et al.) Among these, drug-resistant tuberculosis (DR-TB) and multidrug-resistant tuberculosis (MDR-TB) represent critical subsets characterized by resistance to conventional anti-TB medications. Despite advancements in medical science, the management of DR-TB and MDR-TB patients remains complex, necessitating tailored therapeutic approaches and vigilant monitoring to achieve favorable treatment outcomes. (Munir et al., 2024)

The emergence of drug resistance in TB is primarily attributed to various factors, including inappropriate treatment regimens, inadequate drug supply, patient non-adherence, and compromised immune systems. DR-TB refers to strains resistant to at least one first-line anti-TB medication, while MDR-TB denotes resistance to two frontline drugs, namely isoniazid and rifampicin. These resistant strains significantly complicate treatment, requiring prolonged therapy with second-line drugs that are often less effective, more toxic, and costly. (Iqbal et al., 2018) Understanding treatment outcomes in DR-TB and MDR-TB patients is crucial for optimizing therapeutic strategies and improving patient prognosis. Treatment success is typically assessed based on predefined criteria established by global health organizations, including the World Health Organization (WHO). These criteria consider factors such as sputum culture conversion, treatment completion, and absence of treatment failure or relapse. (Falzon et al., 2017)

One of the primary challenges in managing DR-TB and MDR-TB is achieving and sustaining culture conversion, which denotes the sputum samples from positive to negative for TB bacilli. Additionally, treatment adherence plays a pivotal role in determining outcomes, with non-adherence contributing to treatment failure and the development of further drug resistance. (Ajema et al., 2020) Despite many efforts, challenges persist in achieving optimal treatment outcomes in DR-TB and MDR-TB patients. Access to appropriate diagnostic tools and second-line medications remains limited in many resource-limited settings, exacerbating treatment delays and compromising patient care. Furthermore, the high pill burden, prolonged treatment duration, and adverse drug reactions associated with second-line regimens pose significant barriers to treatment adherence and patient retention in care. (Lan et al., 2020) In addition to pharmacological innovations, efforts to enhance treatment outcomes in DR-TB and MDR-TB patients have emphasized the importance of patient-centered care, community engagement, and innovative delivery models. Collaborative initiatives between governments, non-governmental organizations, and international stakeholders have facilitated the scale-up of comprehensive TB care programs, aimed at improving treatment access, quality, and outcomes. (Rosu, 2023)

In conclusion, addressing the challenge of drug-resistant and multidrug-resistant tuberculosis requires a multifaceted approach encompassing enhanced diagnostics, novel therapeutics, and patient-centered care models. For better understanding of DR-TB treatment it is necessary to understand the prior outcomes therefore this study aims to find the treatment outcomes of DR-TB patients registered at tertiary care settings along estimation of impact of associated adverse events.

Material and Methods

This retrospective study was undertaken at a tertiary care setting of Lahore Punjab Pakistan during the year 2023. Ethical approval from institutional review board was obtained through letter no. 719/RC/KEMU dated August 29, 2022 before analysis. A census based data of all patients registered at programmed management of DR TB (PMDT) site was obtained for the patients registered from 2012 to 2022.

Using a predefined scheme of variables data was entered in the statistical package of social sciences (SPSS) software version 20.0. This scheme considered gender, age, age groups and occupation of DR TB patients. Further characteristics included previous history of TB treatment, presence of any other comorbidity and history of addiction. New patients were those who directly infected with DR strain of TB having no prior history of TB treatment and known as primary DR TB patients. Category I (Cat I) patients having history of treatment with four first line drugs including isoniazid, rifampicin, pyrazinamide and ethambutol. Category II (Cat II) patients having history of treatment with all five first line drugs including streptomycin as fifth chemotherapeutic agent. Private are those patients who had a history of TB treatment from private entities who used non standardized combination of drugs for treatment of TB.

Patients are labelled as rifampicin resistant, MDR, extensively drug resistant (XDR), pre-XDR and poly drug resistant at PMDT site according to standard definitions of WHO. Patients are then enrolled for various schemes of treatment by MDR physician using assessment and standardized criterion laid down by WHO. (Falzon et al., 2017) Scheme implies long treatment regimen (LTR), short treatment regimen (STR), modified LTR and

modified STR. Patients not showing the response may be shifted to LTR from STR. Some patients may also require to place in individualized treatment groups in accordance of suitability and drug resistant pattern. Treatment outcomes were measured as cured; having three months consecutive culture negative reports, treatment completed; having three consecutive months smear negative reports and clinically evaluated as recovered, treatment failure, died during treatment and defaulted from treatment.
Continuous variable like age was reported in mean and standard deviation by gender-wise segregation. Qualitative variables like gender, histories, comorbidities, patient labelling, treatment schemes and outcomes were reported in frequencies and percentages. Regression analysis was applied by taking death and treatment failure as adverse outcomes excluding the treatment defaulter patients as their final fate was not known.

Results

A retrospective data of total 1438 drug resistant TB patients was analyzed comprising of 710 (49.4%) males and 728 (50.6%) females. Mean age of patients at the time of registration was remained to be 35.08±15.91 years, where mean age of males was 38.40±15.51 years remained high as compared to mean age of females as 31.83±15.63 years with a significant difference (p-value <0.0001). Patients were segregated in various age groups and it was revealed that most of the drug resistant patients registered in the age of 15 – 46 years as depicted in Figure 1.

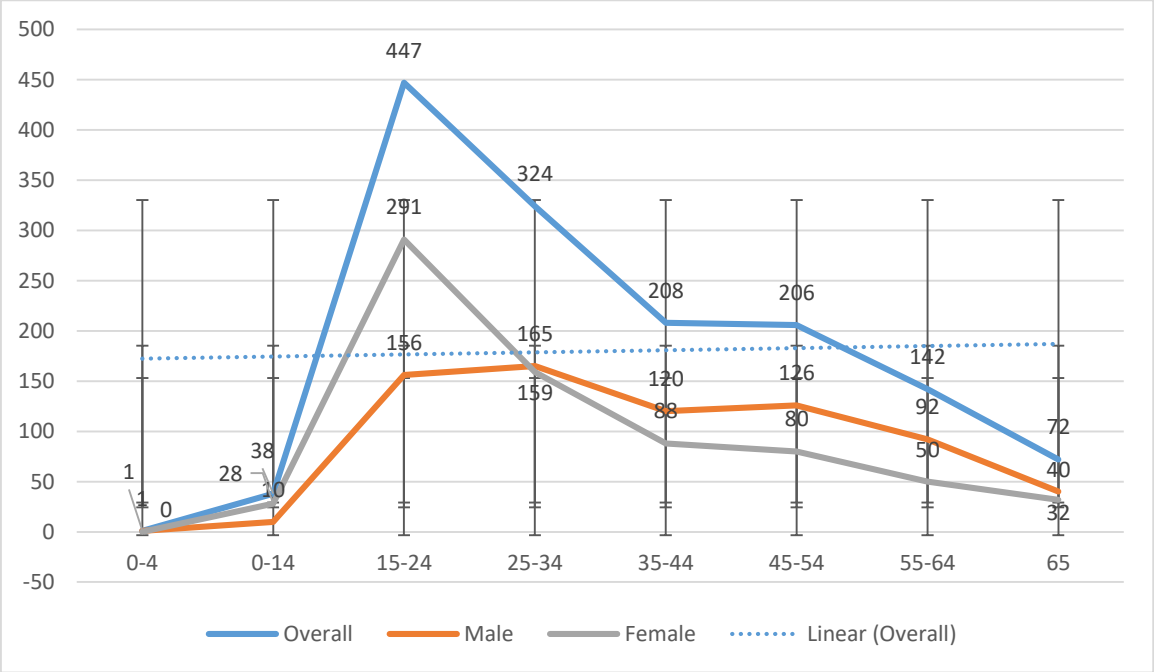

Figure 1: Gender-wise distribution of age groups among registered drug resistant TB patients

Most of the 30.8% patients belong to the labor class while 415/728 (57.0%) females were house wives. A good numbers of 19.4% patients were students of which female gender had a bigger contribution of 28.6% (208/728) while only 10.0% (71/710) males were student. A minute number of 0.7% healthcare workers were also registered for drug resistant TB. Overall distribution of occupation of drug resistant TB patients is presented in figure 2.
Various characteristics of the patients were also analyzed which showed that only 17.4% were new patients and had primary drug resistant TB while rest had varied previous history of TB treatment. Similarly most prevalent comorbidity was diabetes as at least 16.5% had this disease whereas 5.9% patient had history of addiction. Most of the 67.2% patients were labelled as MDR TB patients, 25.9% rifampicin resistant while 1.7% were found to be XDR TB patients. Treatment strategy for most of 75.2% drug resistant TB patients remained to be LTR. Distribution of baseline characteristics with reference to gender are presented in Table 1.

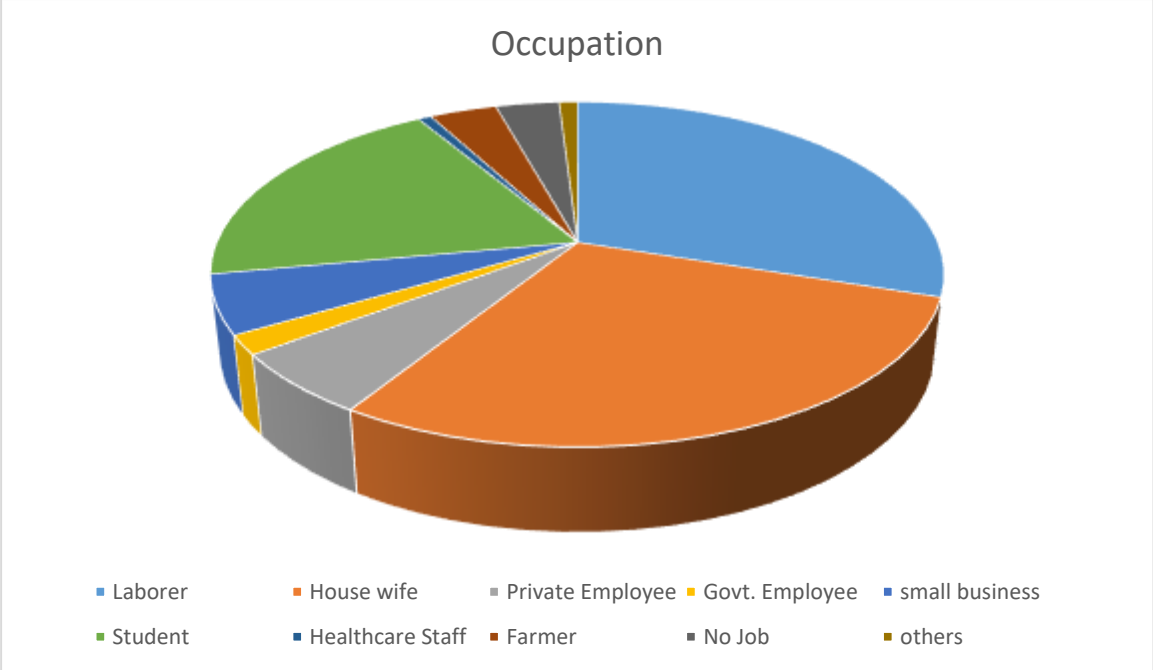

Figure 2: Occupation of drug resistant TB patients.

Table 1: Characteristics of drug resistant TB patients

Characteristics		Gender				Total	
		Male		Female			
		n	%	n	%	n	%
Previous History of treatment	New	135	19.0	115	15.8	250	17.4
	Cat I	447	63.0	474	65.1	921	64.0
	Cat II	84	11.8	84	11.5	168	11.7
	Private	44	6.2	55	7.6	99	6.9
Comorbidity	Diabetes	127	17.9	110	15.1	237	16.5
	[a]CVD	2	0.3	3	0.4	5	0.3
	Hepatitis	9	1.3	6	0.8	15	1.0
	AIDS	1	0.1	0	0.0	1	0.1
	[b]Hep & Diab	2	0.3	2	0.3	4	0.3
	[c]Diab & CVD	3	0.4	2	0.3	5	0.3
	[d]Diab & AIDS	0	0.0	3	0.4	3	0.2
	Others	8	1.1	3	0.4	11	0.8
	None	558	78.6	599	82.3	1157	80.5
Addiction	Smoking	67	9.4	0	0.0	67	4.7
	Alcohol	0	0.0	0	0.0	0	0.0
	Smoking and Alcohol	8	1.1	0	0.0	8	0.6
	Others	8	1.1	2	0.3	10	0.7
	None	627	88.3	726	99.7	1353	94.1
Patient Label	Rifampicin Resistant	194	27.3	178	24.5	372	25.9
	Multidrug Resistant	464	65.4	503	69.1	967	67.2
	Pre-XDR	38	5.4	30	4.1	68	4.7
	XDR	11	1.5	14	1.9	25	1.7
	Poly Drug Resistant	3	0.4	3	0.4	6	0.4
Treatment Strategy	LTR	530	74.6	551	75.7	1081	75.2
	STR	106	14.9	109	15.0	215	15.0
	LTR- Modified	16	2.3	17	2.3	33	2.3
	STR-Modified	19	2.7	21	2.9	40	2.8
	*Shifted to LTR	38	5.4	25	3.4	63	4.4
	Individualized	1	0.1	5	0.7	6	0.4

[a]Cardiovascular Disease, [b]Hepatitis and Diabetes, [d]Diabetes and CVD, [d]Diabetes and AIDS, *Initially started treatment with STR then Shifted to LTR

Treatment outcomes of drug resistant TB patients are shown in Table 2. A high number of 17.4% patients were died during the treatment. A total of 56.2% patients were cured and 10.4% successfully completed their treatment to make an overall good effect of 66.6%. Rate of loss to follow up was noted to be 11.1% in this study.

Table 2: Treatment outcomes of drug resistant TB patients

Treatment Outcome	Gender				Total	
	Male		Female			
	n	%	n	%	n	%
Cured	383	53.9	425	58.4	808	56.2
Treatment Completed	80	11.3	70	9.6	150	10.4
Died	118	16.6	132	18.1	250	17.4
Treatment Failed	38	5.4	33	4.5	71	4.9
Loss to follow Up	91	12.8	68	9.3	159	11.1

Table 3: Computation of adverse events by regression model

Variables		Outcomes				Adj. Odds ratio (95 %CI) Full model	Adj. Odds ratio (95% CI) Reduced model
		Adverse		Cured & Completed			
		n	%	n	%		
Age (Years)	≤ 33	215	27.3	573	72.7	Ref	Ref
	≥34	265	40.8	385	59.2	1.97 (1.52 – 2.56)	1.85 (1.48 – 2.32)
Gender	Male	247	34.8	463	65.2	Ref	
	Female	233	32.0	495	68.0	0.93 (0.74 – 1.18)	
Previous History of treatment	New	69	27.6	181	72.4	Ref	Ref
	Cat I	322	35.0	599	65.0	0.71 (0.40 – 1.25)	0.74 (0.54 – 1.02)
	Cat II	63	37.5	105	62.5	0.66 (0.34 – 1.29)	0.7 (0.46 – 1.08)
	Private	26	26.3	73	73.7	1.15 (0.57 – 2.32)	1.21 (0.71 – 2.09)
Comorbidity	Diabetes	88	37.1	149	62.9	Ref	
	[a]CVD	4	80.0	1	20.0	0.12 (0.02 – 1.15)	
	Hepatitis	4	26.7	11	73.3	1.56 (0.49 – 5.19)	
	AIDS	1	100.0	0	0.0	0.0 (0.0)	
	[b]Hep & Diab	2	50.0	2	50.0	0.93 (0.09 – 8.98)	
	[c]Diab & CVD	1	20.0	4	80.0	2.31 (0.25 – 21.46)	
	[d]Diab & AIDS	2	66.7	1	33.3	0.38 (0.04 – 4.27)	
	Others	6	54.5	5	45.5	0.35 (0.09 – 1.35)	
	None	372	32.2	785	67.8	0.89 (0.64 – 1.25)	
Treatment Strategy	LTR	381	35.2	700	64.8	Ref	Ref
	STR	49	22.8	166	77.2	1.86 (1.03 – 3.40)	1.92 (1.35 – 2.72)
	LTR- Modified	11	33.3	22	66.7	1.04 (0.49 – 2.24)	1.04 (0.50 – 2.21)
	STR-Modified	8	20.0	32	80.0	2.20 (0.99 – 4.89)	2.13 (0.96 – 4.72)
	*Shifted to LTR	26	41.3	37	58.7	0.69 (0.41 – 1.19)	0.75 (0.44 – 1.26)
	Individualized	5	83.3	1	16.7	0.13 (0.02 – 1.15)	0.11 (0.12 – 0.96)

Regression model was applied for adverse events where death and treatment failure were taken as adverse events while loss to follow up was excluded. Binary age was calculated to be 33 years and regression model showed that patients aged ≥34 years are at greater risk of adverse events. Similarly patients having previous history of treatment and treatment strategy other than LTR are also at greater risk of adverse events. Gender and comorbidities were not proven risk of adverse events among drug resistant TB patients as presented Table 3.

Discussion

The death rate among DR-TB patients is a critical aspect of understanding the severity and impact of this disease. Despite advancements in TB treatment, DR-TB remains associated with high mortality rates, posing significant challenges to healthcare systems worldwide. A high mortality rate of 17.4% in present study remained higher from an Ethiopian study that reported a mortality rate of 11.3%. (Bofe, 2022) However, findings are in agreement with another American study which collected the samples from high TB burden

countries and reported a mortality rate starting from 6% among drug susceptible TB cases which ranged up to 39% among pre-XDR and XDR TB cases [OR:4.92, CL: 95%, CI: 2.47 – 9.78]. (Zürcher et al., 2021) Another study has reported a global mortality rate of 20% among DR TB patients hence in accordance to present findings. (Kizito et al., 2021)

Another study from Southern Punjab of Pakistan evaluated the records of 184 XDR TB patients in various treatment centers and presented a mortality rate of 45.1% very high as compared to present study, a higher rate of treatment failure 13% and lower rate of loss to follow up as 6%. (Atif et al., 2022) These variable findings may be due to the inclusion of only XDR-cases while all DR TB cases were included in present study. Another study from Pakistan also reported promising findings (Massud et al., 2023) with present study reported a success rate of around 69% alike 66.6% in present study, a mortality rate of 17.7% versus 17.4% in present study and loss to follow up as 12.5% versus 11.1% in this study. A study from Province Baluchistan of Pakistan also reported a mortality rate of 19.9%, an overall treatment success of 71.6%, loss to follow up as 7.5% and failure rate of 1.1%. (Khan et al., 2019) Findings thus may be comparable with present outcomes.

In multivariate regression analysis age ≥34 years, patients having history of previous TB treatment and treatment strategy other than LTR are at greater risk of adverse events which includes death and treatment failure. Age greater than 40 years has also reported as a risk factor by other recent study. (Khan et al., 2019) Studies have also reported a baseline weight of <40 years as a risk factor of death and failure (Javaid et al., 2017); (Ahmad et al., 2015) but this remained a limitation at present due to high number of missing values in the data. However history of previous treatment and LTR treatment strategy needs to be explored further by cohort analyses.

Conclusion

Overall success rate of treatment including cure and treatment completed remained to be 66.6% remained far below of the target of cure rate of ≥75% laid down by the WHO form better management of DR TB at PMDT sites. A high mortality rate was found to be associated with DR TB. Rate of treatment failure is also of great concern but high numbers of defaulters must be focused as they remain more infectious being non-adherent to treatment. Age ≥34 years, prior history of TB treatment and treatment strategy are risk factors for death of DR TB patients.

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CRediT authorship contribution statement

Muhammad Kashif Munir: Conceptualization, Data curation, Writing original draft, Investigation, Formal Analysis, Methodology, Software. **Sana Rehman, Faiz Ahmad Raza, Asif Hanif & Muhammad Amer Nazir:** Data collection, Data management, Data curation, Writing-review and editing, Visualization, Validation, Resources, Project administration. **Muhammad Aasim:** Data processing, Data Analysis, Data Acquisition on SPSS.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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