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Effects of the COVID-19 Pandemic on Treatment Outcomes of Drug-Resistant Tuberculosis Patients in Twin Cities of Pakistan

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ABSTRACT

Pakistan is the world's fifth-highest Drug-Resistant Tuberculosis burden region. However, it is difficult to evaluate the setback of COVID-19 when concurrent tuberculosis is excluded in patients from Pakistan, where the national burden of tuberculosis and drug-resistant tuberculosis is substantial and rising despite management efforts. The COVID-19 pandemic is prevalent in countries where tuberculosis, notably drug-resistant tuberculosis is high. **Objectives:** To compare the pre and para-pandemic favourable and unfavorable outcomes of drug-resistant tuberculosis treatment in PMDT Units of Islamabad and Rawalpindi. **Methods:** A retrospective cross-sectional study was conducted.The study included Pre and Para-COVID-era drug-resistant tuberculosis patients (n=670) in three sites of Rawalpindi and Islamabad from 2016-2021. A non-probability consecutive sampling technique was applied. A validated structured questionnaire was administered to compare the treatment outcomes of drug-resistant tuberculosis patients. **Results:** Results show that pre-COVID n=240 (35.82%) and Para-Covid era drug-resistant tuberculosis patients n=226 (33.73%) had favourable treatment outcomes. Unfavorable outcomes before and during the pandemic were 128 (18.35%) and 82 (12.2%) respectively. COVID-19 has affected drug-resistant tuberculosis treatment outcomes, both favourable and unfavorable, which are far behind the treatment success targets set by WHO End-tuberculosis. **Conclusions:** It was concluded that this study compared drug-resistant tuberculosis treatment outcomes pre- and post-COVID-19, showing success rates surpassing WHO-End tuberculosis targets. Key factors included residential status, gender, and occupation.

INTRODUCTION

The COVID-19 pandemic threatens to undo recent gains in reducing the Tuberculosis (TB) disease burden and improving access to care around the world. The global treatment success rate for Multidrug-Resistant (MDR)/RR-TB remains poor, at 57% [1]. COVID-19, containment measures, and the dispersion of TB services have all conspired to cause delays in diagnosis or non-diagnosis and increased morbidity, mortality, transmission, and medication resistance arising from treatment interruption [2]. A 9-year setback in efforts to End TB has been caused by COVID-19, which had a detrimental influence on TB case notifications, which fell by 18% from 7.1 million in 2019 to 5.8 million in 2020. Over the next few years, there will probably be a significant increase in TB mortality due to decreased case-finding [3]. Multidrug-resistant tuberculosis (MDR-TB) remains a significant global health challenge, further exacerbated by the COVID-19 pandemic. Healthcare facilities have primarily concentrated on managing and

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preventing COVID-19, often neglecting other diseases like TB. Additionally, the pandemic has led to severe economic disruptions worldwide, causing high unemployment and loss of income, especially in low-income households in low- and middle-income countries (LMICs). This has resulted in nutritional deficiencies, delayed diagnoses, untreated illnesses, medication shortages, and treatment interruptions, all of which contribute to the rise of MDR-TB [4]. Various studies were performed to determine the association between TB and other pandemic situations. One of those studies indicates the relationship between TB and influenza. This showed that TB patients are more susceptible to influenza infection and immunosuppression. Moreover, influenza may hasten the progress of tuberculosis disease as both conditions impair the host's immune response [5]. Estimates indicate that DR-TB could claim around 75 million lives over the next 35 years, costing the global economy $16.7 trillion. A report from the Stop TB Partnership, developed in collaboration with Imperial College, Avenir Health, Johns Hopkins University, and the United States Agency for International Development. (USAID), warns that tuberculosis control efforts may further decline during the COVID-19 pandemic. This could result in an additional 6.3 million TB cases and 1.4 million TB-related deaths worldwide between 2020 and 2025, primarily due to resource shortages and forced lockdowns in TB-endemic regions [6]. Pakistan is the world's fifth-highest DR-TB burden region, a total of 3820 laboratory-confirmed confirmed RR-cases were enrolled of which 3004 cases were on DR treatment [7]. However, it is difficult to evaluate the setback of COVID-19 when concurrent TB is excluded in patients from Pakistan, where the national burden of TB and DR-TB is substantial and rising despite management efforts. Pakistan has one of the world's highest TB burdens, and COVID-19 control has limited people's ability to travel, forcing the TB program to decrease the need for in-person health facility visits and provide care closer to patients' homes. Remote treatment assistance via telemedicine, collaboration with private healthcare professionals, and the establishment of community medicine collecting sites are all strategies that might be beneficial in the future for delivering more convenient care to patients [8]. Drug-resistant tuberculosis needs prolonged and uninterrupted management to achieve successful outcomes among patients undergoing DR-TB therapy. This study aimed to summarize the effects of COVID-19 on DR-TB treatment outcomes in three PMDT sites of Rawalpindi and Islamabad by comparing the Pre pandemic and Para pandemic favourable and unfavorable outcomes of DR-TB treatment to understand how much the Pandemic has negatively influenced TB specifically drug-resistant TB control efforts. The lessons learned from the COVID-19 response would help us to improve the treatment outcomes of patients treated with Drug-resistant TB treatment. The worldwide TB eradication targets may be hampered by the coronavirus disease 2019 (COVID-19) pandemic. Tuberculosis registrations in Jiangsu Province, China, fell 52% in 2020 compared to 2015–2019. In 2020, treatment completion and drug-resistant tuberculosis screening decreased steadily. Efforts to prevent TB during and after the COVID-19 epidemic require immediate attention [9].

This study aims to compare the Pre and Para pandemic favourable and unfavorable outcomes of DR-TB treatment in PMDT Units of Islamabad and Rawalpindi.

METHODS

This was a retrospective cross-sectional study that included all Confirmed Pulmonary drug-resistant TB patients, enrolled and treated from 2016-2021. This study used National TB Control Program Pakistan ENRS (Electronic Nominal Registration System) data collected from its three Programmatic Management of Drug-Resistant TB (PMDT)-Sites, Pak-Emirates Military Hospital Rawalpindi, Rawalpindi Leprosy Hospital and Pakistan Institute of Medical Sciences Islamabad. A non-probability consecutive sampling method was employed in recruiting participants, during the study period and a total of 670 DR-TB patients (all types) were included (Figure 1).

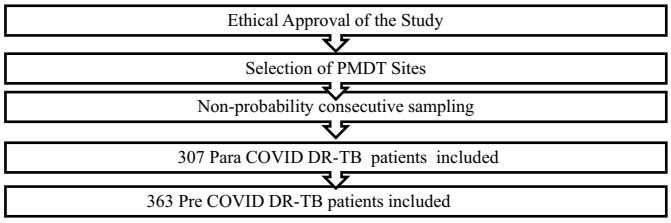

Figure 1: Sampling Strategy

Pre-Covid participants (n=363) were DR-TB patients who completed their treatment before COVID-19 while Para-Covid participants (n=307) completed treatment till 2021. The sample size was determined by taking the prevalence of rifampicin resistance of 0.05 from a previous study [10], a desired precision of 0.02, and a 95% confidence level. The sample size was calculated based on the sampling method recommended by WHO for drug resistance surveys in tuberculosis. n=Z2.p.(1-p)/e2. p=0.05, Z=1.96, q=(1-p) =0.95 and e=0.02. n= (1.96)2 x (0.05) x (0.95)/ (0.02)2. n= 670. Pre-pandemic cases (February 2016- June 2019). n=363. Para Pandemic cases (July 2019- December 2021). n=307. For clinical information, a structured questionnaire was adopted and modified according to local study settings from WHO guidelines for DR-TB surveillance [6]. The reliability of the questionnaire was determined using Cronbach's alpha (r=0.68). Ethical approval was obtained from the Armed Forces Postgraduate Medical Institute, National University of Medical Sciences (NUMS) Rawalpindi

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(IRB No.238-AAA-ERC-AFPGMI). A written informed consent was taken. Statistical analysis was carried out using SPSS version 26.0 and descriptive statistics like frequencies and percentages were calculated while a chi-square test of significance was applied to check associations between DR-TB treatment outcomes and the COVID-19 Pandemic.

RESULTS

Among 670 participants included in the study, more than half (n= 357, 53.3%) were males. The mean age of these participants was 38.02 ±18.46 years. The average duration of sickness before diagnosis with DR-TB for most of the participants was < 1 year (n= 556, 83.0%). The sociodemographic characteristics of participants are presented (Table 1).

Table 1: Frequencies and Percentages and Association of Pre and Para-COVID DR-TB Patients with Demographic Variables (n=670)

Variables	Category	Frequency (n=670)		p-Value
		Pre-COVID	Para-COVID	
Gender	Male	210 (31.34%)	147 (21.94%)	0.0006*
	Female	153 (22.83%)	160 (23.88%)	
Age	0-4 Years	4 (0.597%)	2 (0.298%)	0.304
	5-14 Years	17 (2.537%)	13 (1.940%)	
	15-24 Years	82 (12.23%)	87 (12.98%)	
	25-34 Years	71 (10.59%)	61 (9.104%)	
	35-44 Years	42 (6.268%)	41 (6.119%)	
	45-54 Years	68 (10.14%)	36 (5.373%)	
	55-64 Years	43 (6.417%)	37 (5.522%)	
	>=65 Years	36 (5.373%)	30 (4.477%)	
Marital Status	Unmarried	103 (15.37%)	104 (15.52%)	0.073
	Married	260 (8.80%)	203 (30.29%)	
Occupation	Housewife	87 (12.98%)	86 (12.83%)	0.001*
	Pvt/ Govt Job	133 (19.85%)	97 (14.47%)	
	Self Employed	22 (3.283%)	20 (2.985%)	
	Unemployed/ Retd	127(18.95%)	98 (14.62%)	
Province/ Region	AJK	57 (22.83%)	38 (22.83%)	0.022*
	FATA	0	1 (22.83%)	
	Federal	51 (22.83%)	33 (22.83%)	
	KPK	26 (22.83%)	11 (22.83%)	
	Punjab	226 (22.83%)	224 (22.83%)	
	Sindh	3 (22.83%)	0	

The chi-square test was applied for test significance. *p-value less than 0.05 was considered significant. SD: Standard Deviation. DR-TB: Drug-Resistant Tuberculosis

This represents that both favorable and unfavorable outcomes decreased in frequency during the COVID period. The frequency of favorable and unfavorable outcomes in the pre and para-COVID period is presented (Figure 2).

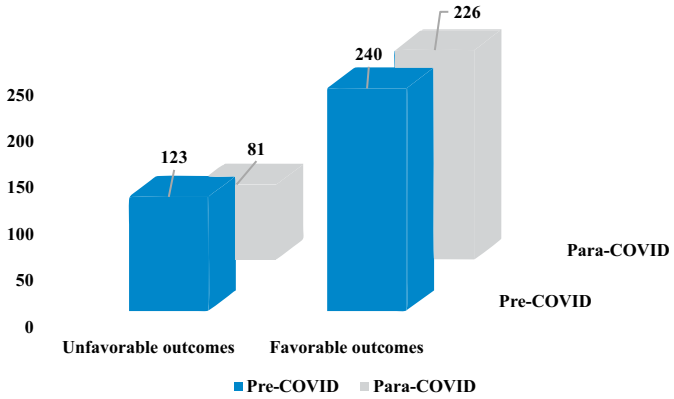

Figure 2: Frequency of Favorable and Unfavorable Outcomes in Pre-COVID and Para-COVID

Among the participants who had enrolled in PMDT-Sites during the COVID era were most affected. The association of Pre-COVID and Para-COVID Patients in each site including Pak Emirates Military Hospital (PEMH-Rawalpindi), Rawalpindi Leprosy Hospital (RLH), and Pakistan Institute of Medical Sciences (PIMS-Federal), with drug-resistant TB favourable and unfavorable treatment outcomes is presented in table 2 after applying chi-square test of significance. Both have a significant association ($p<0.05$) with the COVID-19 Pandemic (Table 2).

Table 2: Frequencies, Percentages and Association of Pre and Para-COVID Patients with DR-TB Treatment Outcomes and PMDT-Site (n=670)

Treatment Outcomes	n (%)		p-Value
	Pre-COVID	Para-COVID	
Un Favorable Outcomes	123 (18.3%)	81 (12.0%)	0.022*
Favorable Outcomes	24 0 (35.8%)	226 (33.7%)	0.0001*
PMDT- Sites			
PEMH Rawalpindi	115 (69.7%)	50 (30.3%)	0.0001*
RLH	82 (25.8%)	236 (74.2%)	
PIMS Islamabad	136 (72.7%)	51 (27.3%)	

*A p-value less than 0.05 was considered significant. PEMH: Pak Emirates Military Hospital Rawalpindi. PIMS: Pakistan Institute of Medical Sciences. RLH: Rawalpindi Leprosy Hospital. PMDT: Programmatic Management of Drug-Resistant Tuberculosis

In observing the months following the drug-resistant TB treatment majority of the study participants missed their follow-ups during the COVID-19 pandemic (Figure 3).

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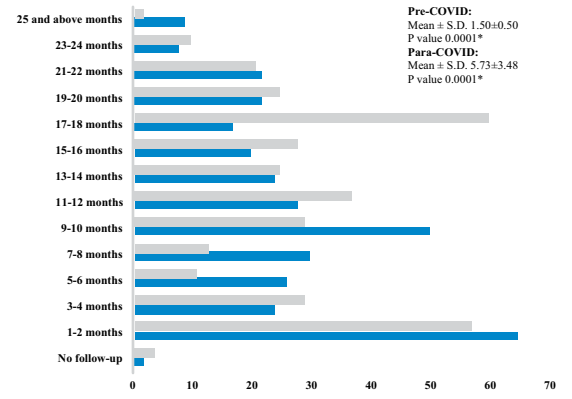

	No follow-up	1-2 months	3-4 months	5-6 months	7-8 months	9-10 months	11-12 months	13-14 months	15-16 months	17-18 months	19-20 months	21-22 months	23-24 months	25 and above months
Para-COVID DR-TB Patients' Follow-up2	3	56	28	10	12	28	36	24	27	59	24	20	9	1
Pre-COVID DR-TB Patients' Follow-up	1	64	23	25	29	49	27	23	19	16	21	21	7	8

Para-COVID DR-TB Patients' Follow-up2 Pre-COVID DR-TB Patients' Follow-up

Figure 3: Frequencies, Percentages and Association of Pre and Para COVID DR-TB Patients with Follow-Up Months (n=670)
The chi-square test was applied for test significance. *A p-value less than 0.05 was considered significant. DR-TB: Drug-Resistant Tuberculosis

The clinical characteristics were also assessed and the results showed that 99 (14.76%) of Para COVID patients had therapy in public facilities for susceptible TB. Moreover, 129 (19.25%) of the patients with drug-resistant tuberculosis had never had any treatment before being diagnosed. Among 307 DR-TB patients who were treated during the pandemic, only 4 (0.59%) had HIV, and 46 (6.84%) had a smoking history. Overall, the clinical characteristics had no significant association with the unfavorable treatment outcomes.

DISCUSSION

To the best of our knowledge, this is the first study to look at factors that can help or hinder general treatment results for drug-resistant TB patients in Rawalpindi and Islamabad PMDT-Units before and during the COVID-19 pandemic. The study's findings revealed that 18.35% (n=128) of pre-COVID participants had poor treatment outcomes, compared to 35.82% (n=240) of patients who had favorable treatment outcomes. Similar results were seen for Para-COVID participants: 33.73% (n=226) had favorable treatment outcomes, while 12.2% (n=82) had unfavorable ones. It is higher than the study which covered 10 PMDT-sites from Punjab- Pakistan [10], found an overall treatment success rate (favorable outcomes) of 32.1% and unfavorable treatment outcomes were 118 (64.1%) within 10 PMDT-Sites, showing that Pakistan is far behind the treatment success targets set by the WHO in the End TB strategy [7]. In terms of PMDT Sites, the results revealed that out of 187 DR-TB patients at PIMS Hospital Islamabad, 136 were enrolled and treated before the pandemic, and 51 were treated during the COVID-19 epidemic, having unfavourable treatment outcomes (7.6%), and out of 165 DR-TB patients at PEMH Rawalpindi, 115 were enrolled as pre-COVID, with 50 DR-TB patients having unfavourable treatment outcomes (Para-COVID participants) [8]. In Rawalpindi Leprosy Hospital, 82 Pre-COVID individuals received DR-TB treatment, while 35.2 % of 236 Para-COVID participants who received treatment during the COVID-19 Pandemic experienced unfavourable treatment outcomes [11]. Current findings showed that the highest enrolments of pulmonary drug-resistant tuberculosis occurred in the pre-COVID era at both PIMS Hospital Islamabad and PEMH Rawalpindi, but that enrolments of pulmonary drug-resistant tuberculosis increased at Leprosy Hospital during the pandemic. The highest enrolments of pulmonary drug-resistant tuberculosis occurred in the pre-COVID era at both PIMS Hospital Islamabad and PEMH Rawalpindi. The study examines a significant association between the COVID-19 effect and DR-TB patient enrolments as well as poor treatment results across all three PMDT sites(p=0.000). In ten high-burden nations, a study examined the DR-TB situation in 2018 and the United Nations High-Level Meeting (UNHLM) objective successes in high-burden countries (HBCs) [12]. According to the study's findings, there were severe limitations on travel within and between cities, which made it difficult for those with DR-TB to reach medical facilities. 56 patients (16.6%) had only a few months of follow-up. The average follow-up period for Para COVID patients was 5.73 (S.D. + 3.487) months. Due to travel limitations and concerns about catching COVID-19, TB patients have put off or skipped going to their follow-up visits. The COVID-19 Pandemic and the follow-up months of the DR-TB (Para-COVID) participants are significantly correlated (p=0.000). In terms of follow-up investigations, a study was carried out in China to see whether the COVID-19 Pandemic has had a sizable impact [13]. Healthcare professionals did their utmost to address the issue and get the drugs to patients in Rawalpindi and Islamabad PMDT sites, even though some countries during the epidemic faced a lack of anti-TB medications. After 6 months of treatment during the COVID period, there was a significant change (p=0.041) in the sputum conversion rate of smear-positive patients; out of 307 DR-TB patients, 210 (68.40%) had missing cultures. The treatment outcomes were impacted by missed culture findings, along with the cure rate, for 210 (31.3%) drug-resistant TB patients in the Para-COVID period. This is in line with earlier studies that demonstrate a decrease in recurrence rates with DOT [14]. The study looked at additional clinical aspects of the participants, including both Pre-COVID and Para-COVID DR-TB patients, to ascertain whether there is any relationship between these characteristics and the results of treatment. The study's conclusions are consistent with those of a Brazilian study, which discovered that there was no relationship between the clinical characteristics and

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the presence of comorbidities (p>0.05) [15]. Age shows a strong connection with failed treatment results among sociodemographic characteristics (p=0.000). It was clear that 132 unfavorable treatment outcomes between the ages of 15 and 54 which are economically active have been reported, with the majority occurring throughout the COVID duration, and display a worrying situation in terms of rolling back the improvements made in TB management over the past few decades. According to Namibian researchers' findings, only age groups were shown to be substantially linked with the failure to treat TB in the Oshana region [8, 16]. Current study demonstrates a statistically significant relationship between occupation and drug-resistant TB treatment failures during COVID-19 (p=0.027). Present findings support the study's findings that the 2019 and 2020 treatment outcomes will be comparable to be affected in light of the continuing COVID-19 pandemic [16, 17]. Gender and DR-TB may be related, according to several research. Multicenter case-control research carried out in Pakistan identified the male gender as a risk factor for MDR-TB [15], while some researchers have claimed that the prognosis of MDR TB is influenced by a woman's gender [18]. The results of current study indicate that gender is related to Pre-COVID and Para-COVID participants (p=0.006). In present study, a statistically significant link between DR-TB instances among Pre- and Para-COVID participants' employment and the residential region was found. More than half of the study participants were either housewives, retirees, or jobless. The majority of the study participants were from the Punjab province. Both the residential area and the occupation have a significant association with DR-TB patients (p=0.022 and 0.001), respectively. Among 670 participants, 249 were rural residents (43.88%) and 376 urban residents (56.12%) [19, 20].

CONCLUSIONS

It was concluded that this retrospective study compared treatment outcomes of DR-TB patients before and during the COVID-19 pandemic. Results showed treatment success rates exceeding WHO-End TB targets. Residential status, gender, and occupation were significant factors influencing outcomes in both periods.

Authors Contribution

Conceptualization: BRB
Methodology: FP, HM, RZ, NUI, YFK
Formal analysis: MZS
Writing review and editing: BRB

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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