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Treatment outcomes and risk factors associated with unsuccessful treatment outcomes among extra pulmonary tuberculosis patients

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Abstract

Background The World Health Organization report 2021 states that about 10.6 million people got tuberculosis, and 17.0% of them had extra-pulmonary tuberculosis. There is not much published research on extra-pulmonary tuberculosis in Pakistan. The objective of this study was to find out the success rate and the predictors for unsuccessful treatment outcomes of EPTB patients.

Methods This study was retrospective cohort study, the study included 320 EPTB patients who were registered and treated at BMCH Quetta, Balochistan, from January 1, 2021 to June 30, 2021. SPSS version 21 was used to analyze the data, and a p-value 0.05 was used to determine statistical significance.

Results The treatment had a success rate of 74.4% overall, with 12.4% of the patients LTFU, 5.6% died, and 2.4% failed the treatment. Age older than 60 years (OR = 10.440, p = 0.000) and having meningeal tuberculosis (OR = 3.506, p = 0.008) were found to be predictors for unsuccessful treatment outcomes.

Conclusion The success rate of EPTB did not meet the End TB Strategy's goal of >90%, as set by the World Health Organization. Therefore, elderly patients and those with meningeal tuberculosis need special attention to improve treatment outcomes.

Key words extra pulmonary TB, TB-high burden country, risk factors, Pakistan

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Introduction

Tuberculosis (TB) is a bacterial infection caused by Mycobacterium tuberculosis (MTB). This bacterium primarily affects the lungs, leading to a condition referred to as pulmonary tuberculosis (PTB). However, it can also spread to other organs, giving rise to various forms of the disease such as abdominal, cutaneous, genitourinary, lymph node, meningeal, musculoskeletal, miliary, ocular, oral, pleural, and pericardial TB. These forms are collectively known as extra-pulmonary TB (EPTB) [1].

In 2021, TB had a significant global impact, affecting approximately 10.6 million individuals and causing 1.6 million deaths. Among these cases, 6.4 million were either new or recurring instances, with about 17% of them classified as EPTB, where the infection spreads to other organs. The prevalence of EPTB varies across different regions. In Africa, it is 13%, in the Americas 14%, in South-East Asia 21%, in Europe 16%, in the Eastern Mediterranean 23%, and in the Western Pacific, it was 8% [1].

Pakistan holds the fifth position among high burden TB nations, contributing to 5.8% of the global TB cases [2]. Additionally, Pakistan bears a significant load of EPTB cases, constituting 20% of the entire reported TB cases form the country [3, 4]. The diagnosis and treatment of EPTB can present challenges owing to the non-specific symptoms like fever, night sweats weight loss, and malaise as well as organ-specific manifestations [5]. Despite these challenges, both PTB and EPTB are treated with the same standard regimen. The treatment regimen contains four drugs isoniazid, ethambutol, rifampicin, and pyrazinamide for the initial two months, and treated with isoniazid and rifampicin for the next four months [6, 7]. To combat TB effectively, the WHO aims for a treatment success rate of over 90% for EPTB as part of its end TB strategy. However, different countries have reported varying treatment outcomes, ranging from low rates of 52.3- 80.5% [4, 8-12] to higher rates of 90.0-90.5% [13, 14].

Different factors have been associated with PTB, such as male gender, younger age, immunosuppressant, and HIV infection [15-17]. While some other studies have reported female gender and older age to EPTB [18-20]. Diabetes has also been reported as a risk factor associated with unsuccessful treatment outcomes in

Table 1. Base line Sociodemographic and clinical characteristics of EPTB patients.

Characteristics		Patients (N)	Percentages (%)
Gender	Male	122	48.8
	Female	128	51.2
Age groups (Years)	≤14	90	36.0
	15-30	68	27.2
	31-44	28	11.2
	45-60	35	14.0
	>60	29	11.6
Site of TB	Meningeal	121	48.4
	Abdominal	59	23.6
	Pleural	25	10.0
	Spinal	18	7.2
	Lymphatic	13	5.2
	Bone/ Joints	10	4.0
	Other	4	1.6
Registration	New	193	77.2
	Failure	12	4.8
	Relapse	18	7.2
	Unknown Previous History	27	10.8
Weight Category (Kgs)	<30	85	34.0
	31-60	119	47.6
	>60	46	18.4

Table 2. Treatment outcomes of EPTB patients.

Site of TB	Completed No. (%)	LTFU No. (%)	Death No. (%)	Failure No. (%)	Not evaluated No. (%)
Meningeal	84 (69.4)	21 (17.4)	10 (8.3)	3 (2.5)	3 (2.5)
Abdominal	48 (81.4)	5 (8.5)	0 (0.0)	2 (3.4)	4 (6.8)
Pleural	15 (60.0)	1 (4.0)	3 (12.0)	1 (4.0)	5 (20.0)
Spinal	16 (88.9)	1 (5.6)	1 (5.6)	0 (0.0)	0 (0.0)
Lymphatic	11 (84.6)	2 (15.4)	0 (0.0)	0 (0.0)	0 (0.0)
Bone/ Joints	9 (90.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)
Other	3 (75.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total (N=250)	186 (74.4)	31 (12.4)	14 (5.6)	6 (2.4)	13 (5.2)

PTB and EPTB cases [13, 21].

Pakistan has reported an impressive 93% treatment success rate for all types of TB [1]. However, when it comes to EPTB, there is limited research on treatment outcomes and associated risk factors in Pakistan. Some studies conducted in the country have revealed varying EPTB treatment success rates, ranging from 60-90% [3, 4, 11, 22, 23]. The current study aims to investigate the clinical types of EPTB, treatment outcomes, and find out the risk factors associated with unsuccessful treatment among EPTB patients registered at Bolan Medical Complex Hospital (BMCH) in Quetta, Balochistan, Pakistan. The current study can help to enhance the understanding and management of EPTB in the region.

Methods and Materials

Study Design and Settings

The current study was a record based observational study. This study was conducted at BMCH Quetta, which is a leading tertiary care hospital serving a large population in the city and the entire province, as well as patients from Afghanistan and Iran. The study included all the records of EPTB patients who were registered at BMCH from January 1, 2021, to June 30, 2021. The treatment outcomes of these patients were known until December 31, 2021.

Data Collection

The data was collected by using data collection form which was purposely designed for this study was used. The socio-demographic, clinical and microbiological data was collected from the TB patient files. The data had different important factors including patients' age, gender, place of residence, district, presenting signs and symptoms, co-morbidities, site of TB infection, previous TB history, treatment category, body weight, and treatment outcomes. Unsuccessful treatment outcomes were assessed based on the standard guidelines defined by the World Health Organization (WHO) and the National Tuberculosis Program (NTP). These outcomes were considered unsuccessful if patients experienced death, treatment failure, or loss of follow-up during the treatment period. Following these guidelines, the study aimed to gain insights into the clinical manifestations of EPTB, treatment outcomes, and associated risk factors for unsuccessful treatment among EPTB patients at Bolan Medical Complex Hospital (BMCH) in Quetta, Balochistan, Pakistan.

Statistical Analysis

We used the Statistical Package for the Social Sciences (SPSS) version 21 to analyze the data. We presented categorical variables as frequencies and percentages, and for continuous variables, we reported the mean and standard deviations, where applicable.

We conducted multivariate binary logistic regression (MVBLR) to identify the risk factors associated with unsuccessful treatment outcomes. This statistical technique helped us assess the relationship between multiple independent variables and the binary outcome variable of treatment success or failure for patients with EPTB.

All the independent variables that showed a p-value of 0.2 or less in the univariate analysis were included in the MVBLR. Univariate analysis involved examining each independent variable separately against the outcome variable without considering the effects of other variables. By using a threshold of $p \leq 0.2$, we made sure that potentially relevant variables were considered for further investigation in the multivariate analysis. If the p-value for an independent variable in the MVBLR was less than 0.05, it was considered to have a statistically significant association with unsuccessful treatment outcomes of EPTB patients.

Results

In the current study a total of 320 EPTB patients were registered and treated at the study site. However, 70 patients' medical records were excluded in the final analysis due to missing data for various reasons and finally 250 patients were included and analyzed.

Socio-demographic and clinical characteristics

The baseline socio-demographic and clinical characteristics of the patients are presented in table 1. In the current study 51.2% were female, 77.2% of the patients were classified as new cases, and 48.4% accounted for meningeal TB, indicating that this form of EPTB was prevalent among the patients (**Table 1**).

Treatment Outcomes

Table 3. Univariate and multivariate analysis of EPTB patients.

Variable		Unsuccessful outcome		Multivariate analysis		Multivariate analysis	
		No, No.(%)	Yes, No.(%)	OR (95%CI)	p-value	OR (95%CI)	p-value
Gender	Female	96 (82.1)	21 (17.9)	1	-	1	-
	Male	90 (75.0)	30 (25.0)	1.524 (0.814-2.854)	0.188	1.177 (0.590-2.347)	0.644
Age groups (Years)	≤14	73 (82.0)	16 (18.0)	1	-	1	-
	15-30	50 (78.1)	14 (21.9)	1.278 (0.573-2.850)	0.550	1.229 (0.528-2.858)	0.633
	31-44	26 (92.9)	2 (7.1)	0.351 (0.075-1.632)	0.182	0.386 (0.079-1.877)	0.238
	45-60	26 (83.9)	5 (16.1)	0.877 (0.292-2.634)	0.816	1.169 (0.370-3.692)	0.790
	>60	11 (44.0)	14 (56.0)	5.807 (2.230-15.124)	0.000	10.440 (3.511-31.047)	0.000
Site of TB	Meningeal (NO)	102 (85.7)	17 (14.3)	1	-	1	-
	Meningeal (YES)	84 (71.2)	34 (28.8)	2.429 (1.268-4.651)	0.007	3.506 (1.378-8.924)	0.008
	Abdominal (NO)	138 (75.8)	44 (24.2)	1	-	1	-
	Abdominal (YES)	48 (87.3)	7 (12.7)	0.457 (0.193-1.084)	0.075	1.073 (0.335-3.440)	0.906
	Pleural (NO)	171 (78.8)	465 (21.2)	1	-	-	-
	Pleural (YES)	15 (75.0)	5 (25.0)	1.239 (0.428-3.588)	0.693	-	-
	Spinal (NO)	170 (77.6)	49 (22.4)	1	-	-	-
	Spinal (YES)	16 (88.9)	2 (11.1)	0.434 (0.096-1.951)	0.276	-	-
	Lymphatic (NO)	175 (78.1)	49 (21.9)	1	-	-	-
	Lymphatic (YES)	11 (84.6)	2 (15.4)	0.649 (0.139-3.028)	0.583	-	-
	Bone/ Joints (NO)	177 (77.6)	51 (22.4)	1	-	-	-
	Bone/ Joints (YES)	9 (100.0)	0 (0.0)	0.0 (0.000)	0.999	-	-
	Other (NO)	183 (78.5)	50 (21.5)	1	-	-	-
	Other (YES)	3 (75.0)	1 (25.0)	1.220 (0.124-11.984)	0.865	-	-

Table 3. Univariate and multivariate analysis of EPTB patients (Continued).

Variable		Unsuccessful outcome		Multivariate analysis		Multivariate analysis	
		No, No.(%)	Yes,No.(%)	OR (95%CI)	p-value	OR (95%CI)	p-value
Registration	New	140 (76.9)	42 (23.1)	1	-	-	-
	Failure	9 (81.8)	2 (18.2)	0.741 (0.154-3.562)	0.708	-	-
	Relapse	15 (83.3)	3 (16.7)	0.667 (0.184-2.414)	0.537	-	-
	Unknown	22 (84.6)	4 (15.4)	0.606 (0.198-1.857)	0.381	-	-
Weight Category (Kgs)	<30	67 (80.7)	16 (19.3)	1	-	-	-
	31-60	84 (77.1)	25 (22.9)	1.246 (0.616-2.522)	0.540	-	-
	>60	35 (77.8)	10 (22.2)	1.196 (0.492-2.912)	0.693	-	-

CI: Confidence interval, EPTB: Extra pulmonary tuberculosis, Kgs: Kilo grams, OR: Odds Ratio.

The treatment outcomes of the 250 patients were evaluated, Out of these, 186 patients (74.4%) completed the treatment and were categorized as successful treatment outcome. However, 12.4% of patients were lost to follow-up, 5.6% died, and 2.4% were treatment failure. LTFU, death and treatment failure were collectively termed as unsuccessful treatment outcomes. While 5.2% of patients were not evaluated during the course of treatment (**Table 2**).

Risk factors associated with unsuccessful treatment outcomes

To find the risk factors univariate and multivariate binary logistic regression analysis was performed, patients aged >60 years (OR=5.807, p-value=0.000), patients diagnosed with meningeal TB (OR=2.429, p-value=0.007), had statistically significant association. Furthermore all those variable which had a p-value less than 0.2 were entered to MVBLR analysis. The results from the MVBLR analysis confirmed that patients >60 years (OR=10.440, p-value=0.000) and patients diagnosed with meningeal TB (OR=3.506, p-value=0.008) continued to show a statistically significant association with unsuccessful treatment outcomes as shown in **Table 3**. The model fit was based on a Hosmer-Lemeshow test that was not significant (p-value=0.530) and an overall classification table percentage of 74.4%.

Discussion

This study found that most EPTB patients were female (51.2%) and aged <14 years (36.0%), with meningeal TB as the predominant type (48.4%). The treatment success rate found in the study was only 74.4%, which fell short of the WHO's target of >90% to end TB and another study in Baluchistan (81.0%) [11, 24]. Other studies in Pakistan also reported similar results (40.7-71.1%) [4, 25]. Factors such as poor adherence to treatment, inadequate knowledge, possible side effects of medications, and a high percentage of pediatric patients in the study population could explain the lower success rate.

The study found that the rate of LTFU among EPTB patients was concerning, standing at 12.4%. This finding aligns with the results of similar studies conducted elsewhere [26-29]. The high rate of LTFU could be attributed to various reasons, including treatment failure, drug resistance, and unfortunately, deaths of some patients. Additionally, several reasons may contribute to this issue, such as the long duration of treatment, boredom or fatigue with taking medications over an extended period, a false sense of improvement after a certain time, a lack of knowledge about the disease, and poor communication between patients and healthcare workers [28, 30].

Identifying and addressing these risk factors are essential steps towards improving the success rate of treatment among TB patients, especially for those with EPTB. By tackling these underlying challenges, healthcare providers can enhance patient adherence to treatment protocols and reduce the occurrence of LTFU.

In the current study it was found that meningeal TB as the most prevalent type of EPTB, 48.4%, Abdominal TB 23.6%, and pleural TB at 10.0%. These findings align with similar studies conducted elsewhere [31-33].

In multivariate analysis those patients who were aged >60 were more prone to develop unsuccessful treatment outcomes incompliance to our study some other studies have also found older age as risk factor for unsuccessful treatment outcomes [12, 34]. Patients aged >60 may have more chance to develop unsuccessful treatment outcomes due to many factors. These include weakened immunity associated with aging, the presence of concurrent co-morbidities, complexities in managing multiple medications,

and difficulties in regularly visiting treatment facilities [35, 36]. Additionally, older patients might face challenges in adhering to treatment regimens due to factors such as mobility limitations, cognitive impairments, or social support constraints.

By acknowledging and understanding the factors that influence treatment outcomes, healthcare systems can develop specific strategies to improve the care and management of EPTB patients, particularly in high-risk groups such as the elderly.

Furthermore, among the different types of EPTB, meningeal TB was likely to develop unsuccessful treatment outcomes. This could be because of the longer treatment duration required for meningeal TB. The penetration of ethambutol and rifampicin into the cerebrospinal fluid is poor, which might lead to patients discontinuing treatment prematurely or being unaware of the importance of completing the treatment [37-39]. The mortality rate among patients with meningeal TB in this study was 17.4%, and the loss to follow-up rate was 8.3%, which was higher than other types of EPTB. Other studies from the United States, Iran, and Pakistan have also reported meningeal TB as a significant risk factor for unfavorable treatment outcomes [4, 40, 41].

The current findings cannot be generalized to the entire province or country. However some medical records of patients were incomplete so it was not feasible to capture a number of crucial variables that could have influenced the treatment outcome. The study revealed that the rate of treatment success among EPTB patients fell short of the TB End Treatment Strategy's goal, requiring immediate attention. In addition, future research should highlight the causes of LTFU.

Conclusion

The current study found a higher percentage of meningeal TB cases and a lower success rate of treatment for EPTB patients than the WHO target. LTFU and death were the main causes of unsuccessful treatment outcomes. Meningeal TB patients and those who aged >60 years had a higher chance of developing unsuccessful treatment outcomes. The success rate and overall management of EPTB can be improved by addressing these risk factors and enhancing treatment adherence.

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Ethics approval

The study followed ethical guidelines and obtained proper approval before conducting the research. The ethical approval was granted by the Research and Ethics Committee of the Faculty of Pharmacy and Health Sciences at the University of Balochistan, Quetta. Additionally, the study was authorized by the Medical Superintendent BMC hospital.

Data availability

The Data will be available upon request.

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Authors' contribution

Abdul Wahid conceptualized and supervised the study, while Rehana Salam, Urosa Bashir, Nighat Nawaz, and Fareeha Iqbal collected and entered the data. Asad Khan and Ghulam Mustafa Shahwani analyzed the data, and Abdul Ghafar and Wajeeha Sadique critically reviewed it.

Competing interests

The authors have reported no conflicts of interest.

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