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RESEARCH ARTICLE

Pre-treatment loss to follow-up among patients with rifampicin-resistant tuberculosis in Baluchistan, Pakistan, 2012-17: a retrospective cohort study [version 1; peer review: 1 approved with reservations, 1 not approved]

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Abstract

Background: Patients with rifampicin-resistant TB (RR-TB) pretreatment loss to follow-up continue to be a global health challenge. Although the accuracy of diagnosis significantly increased with the implementation of Xpert MTB/RIF assay, which is a rapid molecular based test and more sensitive than conventional microscopy which detects MTB even present in small limit of 136 MTB/ml of sputum, but still data suggest a wide treatment initiation gap among diagnosed. This study was done to assess the proportion of patients with RR-TB pretreatment lost to follow-up and the socio-demographic factors associated with this in Balochistan, Pakistan.
Methods: This was a retrospective cohort study based on review of the routinely managed program records. The data included all patients with RR-TB detected at Fatima Jinnah Chest & General Hospital Quetta and District Head Quarter Hospital Loralai, Xpert sites and enrolled at programmatic management of drug resistant TB (PMDT) sites during 2012-2017. Data collected was double-entered, validated and analyzed using EpiData.
Results: Of the 396 patients with RR-TB detected during 2012-17, 78 (19.8%) underwent pre-treatment lost to follow-up. The mean age of those detected with RR-TB was 37 years (SD ±16.98); 189 (48%) were of age group 15-34, while 60% were female. Among 84 individuals referred out to other facilities, only 6 started treatment. Almost half of the 'pretreatment lost to follow-up' patients were from age group 15-34, while 43 were from within the Quetta and Loralai districts.
Conclusions: The high proportion of patients with RR-TB that were pre-treatment lost to follow-up in Balochistan needs immediate strategies to establish linkages between Xpert and PMDT sites for the timely management of patients to prevent the spread of RR-TB infection.

Keywords

Rifampicin Resistant, tuberculosis, Pre-treatment loss to follow-up.

This article is included in the TDR gateway.

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How to cite this article: Kurd SA, Wali A, Fatima R *et al.* **Pre-treatment loss to follow-up among patients with rifampicin-resistant tuberculosis in Baluchistan, Pakistan, 2012-17: a retrospective cohort study [version 1; peer review: 1 approved with reservations, 1 not approved]** F1000Research 2018, **7**:1905 (https://doi.org/10.12688/f1000research.17057.1)

First published: 07 Dec 2018, **7**:1905 (https://doi.org/10.12688/f1000research.17057.1)

Introduction

Rifampicin resistant tuberculosis (RR-TB) continued to be a global health challenge. In 2017, the estimated incidence of RR-TB cases was 0.5 million, but only 0.13 million were notified to National TB Control Programs (NTPs), meaning 0.37 million RR-TB were not identified and notified. About 87% of these notified cases were enrolled for treatment, resulting in attrition of about 13% cases of RR-TB from system and high burden countries like India and China alone contribution was 40%. In 2017, the estimated RR-TB incidence in Pakistan was 15,000. The number of laboratory-confirmed cases was 3475, of which 3016 were enrolled for treatment[1].

An estimated 13% of RR-TB patients are missed from care in Pakistan in 2017[1]. There could be many reasons for missing cases of RR-TB, such as a lack of patient accessibility to health care facilities, patients reaching hospital but not being properly diagnosed, patients being diagnosed but not enrolled, and patients being privately diagnosed and treated, but not notified to the NTP. We defined patients as pre-treatment loss to follow-up, as "any RR-TB patient detected by Xpert MTB/RIF assay but not initiated on RR-TB treatment with a TB control program's setup (programmatic management of drug resistant TB (PMDT) site)[2]. Such patients, if untreated, are likely to die and/or continue to transmit the RR-TB infection in the community[3].

The World Health Organization (WHO) recommend that the Xpert MTB/RIF assay should be used rather than conventional microscopy as the initial diagnostic test in presumptive TB cases (PTC), which is endorsed in the majority of laboratories worldwide for rapid and improved diagnosis[4]. Only one in five people with RR-TB gain access to treatment[5]. Data from PMDT sites suggest that RR-TB cases are regularly being detected by Xpert testing, but not all are being enrolled for management at PMDT sites. In 2014; about 3243 cases of RR-TB were detected in Pakistan, while 2662 were enrolled for treatment[6].

Studies from neighboring countries like Bangladesh and India reported pretreatment lost to follow-up rates of 8–21 %[7–9]. Another study from Vietnam showed that only 18.7% (948/5065) of RR-TB cases were enrolled for treatment[10]. Studies from Zimbabwe and South Africa reported 44% and 53% RR-TB patients started treatment, respectively[11]. However; in Pakistan we find limited data regarding enrollment of RR-TB patients, which are a potential source for the spread of DR-TB in the community[3]. Hence; this important issue needs to be addressed from both a patient and public health perspective. Therefore this study was done to assess the magnitude of pre-treatment loss to follow-up of RR-TB patients detected and enrolled for treatment and factors associated, that could be investigated thoroughly.

Methods

Study design

This is a retrospective cohort study based on review of the routinely managed program data and records.

Study settings

Balochistan is one of the five provinces of Pakistan, and is situated on the southwest part of the country. It is the largest province and covers an area of 347,190 km²[12]. It constitutes approximately 44% of the total land area of the country and is comprised of 33 districts[13]. In 2017, the population was estimated at 1.2 million[14], which is scattered across difficult-to-reach terrain. The capital of the province is Quetta, the ninth largest city of Pakistan, which located in the northwest of the province near the Pakistan-Afghanistan border and is densely populated (with a population of 2 million).

TB care facilities established by the Provincial TB Control Program (PTP) through an integrated approach at the existing primary, secondary and tertiary health care facilities are providing free-of-cost diagnosis and treatment services to TB patients. There were three Xpert sites in the province during the study period, where Xpert MTB/RIF assay services were available for diagnosis of RR-TB patients. The PTP had also the PMDT sites for the management of the diagnosed DR-TB patients namely; Fatima Jinnah Chest and General Hospital Quetta, District Head Quarter Hospital Loralai and District Head Quarter Hospital Turbat.

Study site

The data from Fatima Jinnah Chest and General Hospital (Quetta) and DHQ Hospital (Loralai) sites was included in study. The PMDT site in Turbat was excluded from the study because it was not functional during the study period.

Study population

The study population included all RR-TB patients detected at Xpert sites and enrolled at PMDT sites from 2012–17. All RR-TB patients referred out for enrollment at other than the study PMDT sites were also included. Patients detected at Xpert site that died before enrollment at PMDT site were excluded from pretreatment lost to follow-up.

Sources of data and data collection

Data were extracted from the RR-TB registers of the Xpert site's program database and was validated with the Electronic Nominal Registration System (ENRS) at PMDT sites. Data was entered on a structured data collection form. Socio-demographic variables, including age, sex, address of patient (within and out of district) and distance from PMDT site, were collected to find out any association with outcome variable pre-treatment loss to follow-up.

Data confidentiality

Data of patients was collected on a designed data collection form and was kept confidential in password protected computer in soft and lockable cabinet in hard. The demographic characteristics of patients was not revealed in study except address, as it was requirement of study to find out association with enrollment of patient. This data is only be accessible to principle investigator and will be maintained securely for five years after completion of study.

Ethical approval

The data being utilized for the research projects is program data routinely collected, validated and processed by the principal investigator, and an ethical clearance request letter from program manager TB control program was obtained, which stated that a

specific local ethical clearance was not required in utilizing this data. There was no direct contact with the patient, so requirement for patient consent were waived.

Statistical analysis
Data collected was double- entered, validated and analyzed using EpiData version 3.1 for entry and version 2.2.2.183 for statistical analysis. Descriptive analysis was used for the proportion of patients with RR-TB. The association of socio-demographic factors with pre-treatment loss to follow-up was assessed using a chi-square test. The level of significance was set at $P<0.05$.

Results
Patients with RR-TB
A total of 78 (18.9%) out of 396 detected patients with RR-TB were pre-treatment loss to follow-up. Of the detected RR-TB patients, 98% were from the Xpert site at Fatima Jinnah Chest and General Hospital (Quetta) and 60% were females. The mean age was 37 years (SD-16.98) and 189 were of age group 15–34. About 55% were from outside the district, with 10 patients from out of the country. The median distance of the patient's residence from PMDT sites was 78 km (range, 2–782 km) and only 6 patients started treatment among 84 individuals referred out to other facilities. A significant association was found between address and distance of patient's residence with pre-treatment lost to follow-up (P<0.05) (Table 2). Raw data for this study are available on OSF[15].

Pretreatment lost to follow-up patients
Out of 78 pretreatment lost to follow up patients, 55% belonged to the 15–24 age group and females were almost 58%. About 51% patients were from within the district while 13% from outside of the country and 43 patients (55 %) were within 50 km of PMDT sites. A significant association was found between address and distance of patient's residence with pre-treatment lost to follow-up (P<0.05); (Table 2).

Discussion
The study reported that 19.8% of RR-TB patients were pretreatment loss to follow-up among RR detected patients at selected PMDT sites of Balochistan. The possible reasons for pretreatment loss to follow-up may be due to poor coordination among Xpert and PMDT sites[3], lack of awareness about disease and treatment; however, studies in other settings show enough knowledge among individuals about RR-TB as a disease[16–18], indicating the need to assess the knowledge and attitude of individuals about TB in Pakistan. Also observed has been treatment refusal from the patient's side due to the stigma surrounding TB in society[19,20].

We found an association between pretreatment loss to follow-up with address and patient's residence distance from PMDT sites. It is evident that the majority of patients those who were lost to follow up were from Quetta district and areas which were within 50 km of PMDT sites, which indicated that patients might give the wrong address at time of registration for their convenience and requirement for enrollment. Patients lost from outside the country were from Afghanistan, and were

Table 1. Socio-demographic characteristics of Rifampicin Resistant patients diagnosed at Xpert sites, Balochistan, 2012–17.

Variables	Total, n	%
Participants	396	100
PMDT Site		
PMDT Quetta	389	98.2
PMDT Loralai	07	1.8
Age, years		
<15	10	2.5
15–34	189	47.7
35–54	117	29.5
≥55	80	20.2
Sex		
Male	159	40.2
Female	237	59.8
Address		
Within district	155	39.1
Outside district	220	55.6
Outside province	10	2.5
Outside country	11	2.8
Residence		
Urban	189	47.7
Rural	207	52.3
Patient residence distance from PMDT site in KMS		
00–50	153	38.6
51–300	137	34.6
>300	106	26.8
Xpert results (RR +VE)	396	100
Treatment started at same facility		
Yes	312	78.8
No	84	21.2
Referred out for treatment	30	7.6
Treatment started among referred out patients	06	20
Initial loss to follow up	78	19.7

RR+ve, rifampicin-resistance positive.

considered pretreatment loss to follow-up because we couldn't find any documented proof of their treatment initiation at PMDT sites in the country of residence.

A large proportion of RR-TB patients and pretreatment loss to follow-up belong to the younger age group (15–35 years). One reason seems to be that young patients are more exposed to the outside world and are in contact with individuals. Secondly, due to Islamic and Pakistani culture, young individuals facilitate activities for their old family members in many aspects of life

Table 2. Factors associated with pre-treatment loss-to-follow-up among Rifampicin Resistant patients at PMDT sites, Balochistan, 2012–17.

Variable	PTLF		P-value
	n	%	
Total	78	100	
Age, years			
<15	00	0.0	0.24
15–34	43	55.1	0.24
35–54	20	25.6	0.24
=>55	15	20.4	0.24
Sex			
Male	33	42.3	0.66
Female	45	57.7	0.66
Address			
Within district	43	51.1	<0.05*
Outside district	24	30.8	
Outside province	01	1.3	
Outside country	10	12.8	
Residence			
Urban	33	42.3	0.28
Rural	45	57.7	0.28
Distance, km			
00–50	43	55.1	<0.05*
51–300	09	11.5	
>300	26	33.3	

PMDT, programmatic management of drug resistant TB; PTLF, Pre-treatment lost to follow-up.
*Significant association

without any precautions, which might be a potential source of disease transfer to young age groups, which means that screening of these patients should be strongly suggested.

This study has multiple strengths. First, that data was routinely maintained program data, recorded in both hard and soft forms at PMDT sites. Second, data was double-entered and validated to ensure quality[21]. Third, all RR-TB patients included in study to obtain the precise results. Lastly, the study was conducted in accordance to guidelines of Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[22].

The limitations of this study was that we couldn't access patients directly as the data were collected from previous routinely recorded data; most of those patients who were referred out for treatment, particularly those from outside Pakistan, were reported as pretreatment loss to follow-up because we couldn't find any record of their treatment. However, they might be undergoing treatment.

The results of this study indicate important implications for policy makers. A strong strategy is needed to strengthen the out-of-country referral system. A strong channel should be made between Xpert sites and PMDT sites for registration of patients and coordination training should be given to persons involved in this process. I.D cards should be made mandatory to fill patient fields in the Xpert register at time of registration to provide accurate details for tracing purpose. Data from both PMDT and Xpert sites should be routinely reviewed to ascertain patient registration status and the timely tracing of patients. Patient proper education and awareness at the time of referral and enrollment for MTB/RIF assay at Xpert site. Community awareness interventions should be initiated to improve knowledge about TB, in particular RR-TB, and to counter stigma against this disease in society.

Conclusion
The high proportion of pre-treatment loss to follow-up among detected patients with RR-TB in Baluchistan needs immediate strategies for establishment of linkages between Xpert and PMDT sites for the timely management of patients to prevent the spread of DR-TB infection.

Data availability
Raw data associated with this study are available on OSF. Also included is a description of abbreviations used in the dataset. DOI: https://doi.org/10.17605/OSF.IO/9UP87[15].

Data are available under the terms of the Creative Commons Zero "No rights reserved" data waiver (CC0 1.0 Public domain dedication).

References

1. **Global TB Report**. 2018.
   Reference Source

2. MacPherson P, Houben RM, Glynn JR, *et al.*: **Pre-treatment loss to follow-up in tuberculosis patients in low- and lower-middle-income countries and high-burden countries: a systematic review and meta-analysis.** *Bull World Health Organ.* 2014; **92**(2): 126–38.
   PubMed Abstract | **Publisher Full Text** | **Free Full Text**

3. Wali A, Kumar AMV, Hinderaker SG, *et al.*: **Pre-treatment loss to follow-up among smear-positive TB patients in tertiary hospitals, Quetta, Pakistan.** *Public Health Action.* 2017; **7**(1): 21–5.
   PubMed Abstract | **Publisher Full Text** | **Free Full Text**

4. Acosta CD, Rusovich V, Harries AD, *et al.*: **Selection of a moxifloxacin dose that suppresses drug resistance in Mycobacterium tuberculosis, by use of an *in vitro.* pharmacodynamic infection model and mathematical modeling.** *International Journal of Tuberculosis and Lung Disease.* 2014; **2**.

5. **At first global ministerial meeting on TB, MSF and Stop TB Partnership give governments deadline to dramatically increase access to testing and treatment - World ReliefWeb**. [cited 2018 Mar 30].
   Reference Source

6. **Usaid: Mdr-Tb Country Profile**. 2016; 1.
   Reference Source

7. Hossain ST, Isaakidis P, Sagili KD, *et al.*: **The Multi-Drug Resistant Tuberculosis Diagnosis and Treatment Cascade in Bangladesh.** *PLoS One.* 2015; **10**(6): e0129155.
   PubMed Abstract | **Publisher Full Text** | **Free Full Text**

8. Shewade HD, Kokane AM, Singh AR, *et al.*: **Treatment Initiation among Patients with Multidrug Resistant Tuberculosis in Bhopal District, India.** *J Tuberc Res.* 2017; **5**: 237–42.
   Publisher Full Text

9. Shewade HD, Shringarpure KS, Parmar M, *et al.*: **Delay and attrition before treatment initiation among MDR-TB patients in five districts of Gujarat, India.** *Public Health Action.* 2018; **8**(2): 59–65.
   PubMed Abstract | **Free Full Text**

10. Hoang TT, Nguyen NV, Dinh SN, *et al.*: **Challenges in detection and treatment of multidrug resistant tuberculosis patients in Vietnam.** *BMC Public Health.* 2015; **15**(1): 980.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

11. Cox H, Dickson-hall L, Ndjeka N, *et al.*: **Delays and loss to follow-up before treatment of drug-resistant tuberculosis following implementation of Xpert MTB/RIF in South Africa: A retrospective cohort study.** *PLoS Med.* 2017; **14**(2): e1002238.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

12. **Balochistan | province, Pakistan | Britannica.com**. [cited 2018 Mar 31].
    Reference Source

13. **DIVISION , DISTRICT / CENSUS DISTRICT BALOCHISTAN PROVINCE**. 1.
    Reference Source

14. Units A, Pakhtunkhwa K: **PROVINCE WISE PROVISIONAL RESULTS OF CENSUS - 2017 ADMINISTRATIVE UNITS POPULATION 2017 POPULATION 1998 KHYBER PAKHTUNKHWA PUNJAB residing with the local population.** 2017; 1–18.
    Reference Source

15. Kurd S: Pre-Treatment Loss to Follow-up among Patients with Rifampicin-Resistant Tuberculosis in Baluchistan, Pakistan, 2012-17: A Retrospective Cohort Study. *OSF*. Web. 2018.
    http://www.doi.org/10.17605/OSF.IO/9UP87

16. Rami K, Thakor N, Patel A: **Awareness and knowledge about tuberculosis in patient of tuberculosis at GMERS Medical College and Hospital Dharpur, Patan, Gujarat.** *Int J Med Sci Public Health.* 2015; **4**(7): 906–909.
    Publisher Full Text

17. Desalu OO, Adeoti AO, Fadeyi A, *et al.*: **Awareness of the Warning Signs, Risk Factors, and Treatment for Tuberculosis among Urban Nigerians.** *Tuberc Res Treat.* 2013; **2013**: 369717.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

18. Thapa B, Prasad BM, Chadha SS, *et al.*: **Serial survey shows community intervention may contribute to increase in knowledge of Tuberculosis in 30 districts of India.** *BMC Public Health.* 2016; **16**(1): 1155.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

19. Cremers AL, de Laat MM, Kapata N, *et al.*: **Assessing the consequences of stigma for tuberculosis patients in urban Zambia.** *PLoS One.* 2015; **10**(3): e0119861.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

20. Courtwright A, Turner AN: **Tuberculosis and Stigmatization: pathways and interventions.** *Public Health Rep.* 2010; **125 Suppl 4**: 34–42.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

21. Shewade HD, Nair D, Klinton JS, *et al.*: **Low pre-diagnosis attrition but high pre-treatment attrition among patients with MDR-TB: An operational research from Chennai, India.** *J Epidemiol Glob Health.* 2017; **7**(4): 227–33.
    PubMed Abstract | **Publisher Full Text**

22. von Elm E, Altman DG, Egger M, *et al.*: **The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies.** *Lancet.* 2007; **370**(9596): 1453–7.
    PubMed Abstract | **Publisher Full Text**

Open Peer Review

Current Peer Review Status: ✕ ?

Version 1

Reviewer Report 26 April 2019

? **Amer Hayat Khan**

Department of Clinical Pharmacy, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Minden, Malaysia

- Table 1: Socio-demographic… "Address" - what does it mean and what is its impact on the findings?

- Table 1: Xpert results (RR+VE)…I think it is Inclusion criteria, I will suggest to omit this from the table.

- Table 2: PTLF and P-Value…For the "Age less than 15 years" group, PTLF is 00, so how is the P-value 0.24?

- Table 2: It is confusable, Urban and Rural P-values for both, while Address P-values only once? Uniformity must be brought to the article and its format.

- Do the researchers want to prove that such defaulter is due to distance? There are no further reasons?

- The discussion needs to be improved.

- The conclusion seems like a general statement, it should be based on the study findings.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Research in Infections & Nephrology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 04 March 2019

https://doi.org/10.5256/f1000research.18647.r44665

❌   **Hemant Deepak Shewade** 🆔

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[3] Karuna Trust, Bengaluru, India

Overall there is lack of clarity of what the study population is. Are they all RR-patients irrespective of their address? Of them, how was the outcome ascertained? A clear operational definition of "not initiated on treatment" is missing. Death has been excluded which should not be done. It should be included under pre-treatment loss to follow-up or reported separately. Detailed comments below:

First two lines of abstract:
- Please check the English.

- May not be relevant for this paper.

Abstract – Background:
- "implementation of Xpert MTB/RIF assay, which is a rapid molecular based test and more sensitive than conventional microscopy which detects MTB even present in small limit of 136 MTB/ml of sputum" - may not be relevant for this paper.

Abstract – Background:

- Why is this study not clear? Is it because there is no information in Pakistan on this topic?

Abstract – Methods:
- Avoid using the term "retrospective" (please follow STROBE guidelines).

Abstract – Methods:
- How can patients enrolled into PMDT sites (I assume this means starting MDR-TB treatment) be included in the denominator? This is the outcome of interest and is included in the numerator.

Abstract - Results:
- 84 out of 396? Of 84, 6 were started on treatment. So the remaining 78, were they not considered pre-treatment LTFU? Making it 78+78?

Introduction - first line:
- "continues", not "continue".

Introduction – paragraph 2:
- 13% RR-TB are missed from care - is this a repetition? Wasn't the point already made before?

- "Missed from care" is not clear. Do you mean after diagnosis? The reasons mentioned below also include reasons for pre-diagnosis LTFU.

Introduction - paragraph 2:
- Clarity of operational definitions:
  1) Not initiated on treatment - within the district? In a province or anywhere in the country?
  2) Not initiated on treatment - within how many days of diagnosis?

Introduction - paragraph 3:
- WHO recommends (not "recommend").

Introduction - paragraph 3:
- "Xpert MTB/RIF assay should be used rather than conventional microscopy as the initial diagnostic test in presumptive TB cases (PTC)," - is this relevant for this study?

Introduction - paragraph 3:
- "In 2014; about 3243 cases of RR-TB were detected in Pakistan, while 2662 were enrolled for treatment[6]." - why share 2014 data here when 2017 data has been shared before?

Introduction - last line:
- "that could be investigated thoroughly." - may be removed.

Study design:
- Same comment as in the abstract (may mention cohort study involving secondary data).

Study settings:
- Are there three Xpert sites for 33 districts in Balochistan? If yes, please stress this point. Is this sufficient or are these too few? Please make this judgement call in the setting (can bring this later in the discussion).

- 2 million (Quetta population) appears to be more than 1.2 million (province population).

- So there were three PMDT sites. Were these also the Xpert sites? Of these three sites, only two were functional.

- Please mention, to which population did these sites cater to? Are they for the whole of the province (Balochistan)?

Study population:
- For RR-TB patients detected in Xpert sites with an address out of the province, were they included or excluded?

- The way I would frame study population is as follows: "RR-TB patients detected at the two Xpert sites in Balochistan during 2012-17 and belonging to Balochistan were included in the study."

- Study population should not include the enrolled patients.

- All diagnosed patients (RR-TB) from the Xpert sites should be included. Enrolment at PMDT is your outcome of interest.

- "RR-TB patients referred out for enrolment at other than the study PMDT sites were also included." - this should not be mentioned under study population.

- Death is one of the reasons for pre-treatment loss to follow up and therefore should be considered as pre-treatment LTFU. First of all, this statement again (that deaths were excluded) should not be mentioned here in study population. It should be mentioned under outcome ascertainment.

Sources of data and data collection:
- The authors need to mention the operational definitions here (may be a separate paragraph after this paragraph).

- Clarity of operational definitions:
  1) Not initiated on treatment - within the district? In a province or anywhere in the country?
  2) Not initiated on treatment - within how many days of diagnosis?

- Deaths should be considered as pre-treatment loss to follow up. In other words, if patients do not get initiated on treatment, we should also document how many of them died before treatment initiation.

- "Out of district or within district" - should this not be "province"? There is no description of district before. These sites cater to Balochistan. Also there are 33 districts in Balochistan.

- Also why were the dates not collected (diagnosis and treatment)? This way the authors could have calculated the pre-treatment delay among patients initiated on treatment

Data confidentiality:
- This paragraph is not required.

Ethics:

- Mention the name of the ethics committee providing approval (approval number and date).

- Mention whether administrative approval was obtained.

- Put this paragraph after analysis.

- "validated" may not be the right word to use.

Statistical analysis:
- As this is a cohort study, please mention (should be clarified earlier) what the duration was of follow up for each patient before he/she was declared as pre-treatment loss to follow up.

- May then summarize the association between factors and pre-treatment LTFU using relative risk (cumulative incidence ratio if follow period was consistent for each patient).

Results:
- As the study population lacks clarity I am not clear how to interpret this.

- There were 396 patients (I assume you included all RR-TB patients irrespective of their addresses). Of them how did you decide how many started treatment? Where did they start? Was it anywhere in these three sites? Was it anywhere in the country?

- Regarding the 84 that were referred out: Are these 84 out of 396? Of 84, 6 were started on treatment. So the remaining 78, were they not considered pre-treatment LTFU? Making it 78+78?

- For "factors associated", please present a table with RR and aRR (for risk factor analysis).

Discussion - third line:
- Just say Balochistan, as you included all sites in Balochistan.

Discussion:
- All discussions around risk factors based on the aRR and their 95% Cis.

- Another point for consideration - Results/Discussion: There are three Xpert sites and three PMDT sites. If both are located in the same hospital, then if the patient belongs to the population covered under the PMDT site and is diagnosed in the Xpert facility in the PMDT site, then treatment initiation should not be a problem. If the patient belongs to a population covered under another PMDT site, then the patient has to be referred for treatment to other sites and here loss to follow up is common. Should this be considered as one of the factors (for analysis) for pre-treatment LTFU? However, the larger question is the operational definition of study population and operational definition of outcomes (treatment initiation).

- If the patient belongs to the population covered under the PMDT site and is diagnosed in the Xpert facility in the PMDT site, then treatment initiation should not be a problem. This should be included as one of the factors (for analysis) for pre-treatment LTFU.

Is the work clearly and accurately presented and does it cite the current literature?
No

Is the study design appropriate and is the work technically sound?
No

Are sufficient details of methods and analysis provided to allow replication by others?
No

If applicable, is the statistical analysis and its interpretation appropriate?
Not applicable

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: This paper is from Pakistan's national Operational research course (SORT IT course). I work as a senior mentor in similar operational research courses (SORT IT) in India, Myanmar, Zimbabwe and Asia regional. I was not involved with the Pakistan national Operational Research Course. One of the co-authors, though we have not published anything together for the last five years, recently we worked together in the Asia regional operational research course. This is a WHO TDR accredited SORT IT course. I don't believe the above influences my views of the article.

Reviewer Expertise: MDR-TB, TB, TB-DM, Primary health care, ACF for TB

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

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