Journal of Clinical Tuberculosis and Other Mycobacterial Diseases 21 (2020) 100200

Contents lists available at ScienceDirect

Journal of Clinical Tuberculosis and Other Mycobacterial Diseases

journal homepage: www.elsevier.com/locate/jctube

Prevalence and risk factors of depression in patients with drug-resistant tuberculosis in Nepal: A cross-sectional study

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ARTICLE INFO

Keywords:
Drug-Resistant Tuberculosis
Depression
Prevalence
Patient Health Questionnaire 9

ABSTRACT

Background: Patients with drug-resistant tuberculosis (DR TB) have a protracted course of illness and the available treatment has a low success rate. These factors combined with the associated stigma and financial implications put the patients with DR TB at an increased risk of depression. The psychiatric side effects of anti-tuberculosis drugs further aggravate the problem. This study aimed to estimate the prevalence of depression among patients with DR TB in Nepal and identify risk factors.

Methods: We conducted this cross-sectional study in April 2018 at all the functioning 11 programmatic DR TB treatment centers across Nepal. We selected 129 patients aged ≥ 16 years receiving treatment for DR TB by non-probability quota sampling. Six trained data collectors conducted face-to-face interviews and administered the Nepali language version of Patient Health Questionnaire 9 (PHQ-9) to screen for depression. We summarized sociodemographic and treatment characteristics with median (Interquartile Range [IQR]) and proportions as appropriate. We performed univariate analysis for the variables hypothesized as risk factors for depression. We fitted a multivariable binary logistic regression model with depression as the outcome variable and the variables with a significance level of < 0.25 as explanatory variables. We regarded a *p*-value of < 0.05 as significant for individual variables in the logistic regression model.

Results: Of the 129 patients studied, 92 (71.3%) were male and the median age was 36 years (IQR 25–48). The majority (109, 84.4%) had multi-drug resistant tuberculosis (MDR TB). We identified 81 patients (62.7%, 95% Confidence Interval [CI] 53.7–71) with the PHQ-9 score of 10 or more signifying probable depressive disorder. In univariate analyses, age, treatment center location, DR TB treatment duration, and duration of current illness had a *p*-value lower than the pre-specified cut-off of 0.25. In the multivariable logistic regression model, we found a statistically significant association of depression with the duration of illness (adjusted Odds Ratio 1.15, 95% CI 1.07–1.26, $p < 0.001$).

Conclusion: This study has found that a large proportion of the patients with DR TB screened have depression suggesting the need for screening and management of comorbid depression within the National TB Control Program.

1. Background

Drug-resistant tuberculosis (DR TB) is a growing public health problem worldwide, particularly in developing countries. Globally, there were an estimated 484,000 new cases of Tuberculosis (TB) in 2018 that were resistant to one of the crucial first-line antitubercular drugs - Rifampicin (RR TB), which requires treatment with the second line antitubercular drugs. Among these, 78% had TB resistant to both Rifampicin and Isoniazid (MDR TB). On an average, 6.2% (95% Confidence Interval [CI] 4.4–8.2%) of the MDR TB cases were resistant to further two second-line TB drugs, termed Extensively Drug-Resistant TB (XDR TB) – resistant to at least one Fluoroquinolone and a second line

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https://doi.org/10.1016/j.jctube.2020.100200

Available online 29 October 2020

injectable anti-TB agent in addition to Rifampicin and Isoniazid. >90% of these cases are from 30 high MDR TB burden countries that belong to low or middle-income settings.[1]

The drug-resistant forms of TB have a protracted course of illness. They also require treatment for a longer duration, yet the outcomes are often poor. A systematic review and meta-analysis of 14 studies assessing the MDR TB treatment outcomes under programmatic settings has found that only 55.6% of the patients treated had remitted.[2] Also, the drugs used for DR TB treatment have significant adverse events. These adverse events include the adverse drug reactions as well as those untoward effects which do not necessarily have a causal relationship with the DR TB treatment. In a review of 5346 patients receiving treatment for MDR TB, more than half of the patients (57.3%) were found to have experienced at least one adverse event. The three most common adverse events reported were gastrointestinal disorders (32.1%), ototoxicity (14.6%), and psychiatric disorders (13.2%).[3] Furthermore, the higher plasma level of proinflammatory cytokines, a family of signaling molecules released by immune cells including T cells and macrophages in the setting of chronic inflammation such as DR TB, adds to the risk of depression among these patients.[4,5] These factors, along with the associated psychosocial stress and financial burden, put the patients with DR TB at an increased risk of depression.[6] Comorbid depression among patients with DR TB, in turn, results in increased mortality, disability, and poor quality of life.[7] An additional concern is the amplification of drug resistance - patients with depression are less likely to adhere to their treatment which contributes to the propagation of resistance against antitubercular drugs.[8] Therefore, addressing depression among these patients may help achieve optimal treatment outcomes, prevent the development of further drug resistance as well as improve quality of life.

Knowledge of the burden of depression is a pre-requisite for its optimal management. Studies suggest that the prevalence of depression among patients with DR TB is high. A systematic review and meta-analysis of 32 studies from 20 countries has reported the pooled prevalence of depression among patients with MDR TB as 25% (95% CI 14–39). Significant heterogeneity was reported among the estimates which ranged from 3% to 70%.[9] No studies from Nepal were included in this meta-analysis. In a study from two urban TB clinics in Nepal, investigators screened 135 patients with MDR TB using 25-item Hopkins Symptom Checklist (HSCL-25) and found the period prevalence of depression as 22.2% (95% CI 15.9–30.1).[10] However, this study has considered the patients only from two urban centers with no representation from the rural parts of the country. In addition, no patients with Pre-XDR and XDR TB were considered. Therefore, despite providing an important insight into the burden of depression among the patients with MDR TB, the findings from this study cannot be generalized to represent that of the entire country or the patients with all forms of DR TB. More accurate information on the burden of comorbid depression among patients with DR TB could help devise an appropriate intervention strategy for addressing depression under programmatic conditions.

In this study, we aimed to supplement the prior work by estimating the prevalence of comorbid depression among patients with all forms of DR TB. We further aimed to identify the risk factors associated with depression among these patients.

2. Methods

2.1. Study design and setting

We conducted this cross-sectional study in the DR TB treatment centers in Nepal in April 2018. DR TB treatment in Nepal is ambulatory care provided through DR TB treatment centers under the programmatic management of the DR TB unit within the National TB Control Program. These centers evaluate the presumptive cases of DR TB in close collaboration with the national TB reference laboratories, enroll the diagnosed patients into the treatment program, and monitor them. All the patients diagnosed with DR TB are enrolled at one of these centers. During the study period, the regimen used was a 20-month long standard regimen consisting of Kanamycin, Levofloxacin, Pyrazinamide, Cycloserine and Ethionamide for MDR TB and individualized regimen based on the culture and drug sensitivity results for Pre-XDR (defined as resistant to at least one Fluoroquinolone or a second-line injectable anti-TB agent but not both in addition to Rifampicin and Isoniazid) and XDR TB. Of the 18 DR TB treatment centers across the country, we included 11 centers that had patients enrolled and were receiving treatment during the data collection period. The remaining seven centers did not have patients enrolled for DR TB treatment during the data collection period.

2.2. Participants

We calculated the sample size by the formula $Z^2P(1\text{-}P)/d^2$. With Z as 1.96 for 95% level of confidence, expected prevalence P of 69.55%, and precision d of 10%, we obtained the sample size as 82.[11] Because the participants from each treatment center could be similar to each other, we multiplied the sample size by (design effect) 1.5 to take this loss of variance into account. We determined the number of participants from each center that was proportionate to the existing caseload of the patients and rounded off to the nearest high number. The final sample size required was 129 (Table 1). Patients aged $\geq$ 16 years and receiving treatment for DR TB at the time of data collection were eligible for the study. We used non-probability quota sampling and invited the eligible patients to participate in the study until the quota for each treatment center was filled.

2.3. Measurements

We conducted a one-day training session and trained six paramedics on the details of patient selection, the process of obtaining informed consent, and data collection using the pre-structured data collection tool. The data collectors visited the study centers and conducted face-to-face interviews to collect the relevant data on demographics, history of prior TB, the duration of current illness, and the duration of DR TB treatment at the time of data collection, the type of current drug-resistant TB, and any comorbidity. We defined the duration of current illness as the time between the onset of symptoms that lead to the

Table 1
Number of participants included from each Drug-Resistant Tuberculosis treatment center.

Province Name	Name of drug-resistant Tuberculosis treatment centers	Number of patients enrolled for treatment	Number of patients included
Province Number 1	Nepal Anti TB Association, Biratnagar	52	13
	BP Koirala Institute of Health Sciences, Dharan	11	3
Province Number 2	Lalgadh Leprosy Hospital, Dhanusha	19	5
	National Medical College, Birgunj	17	5
Province Number 3	German Nepal TB Project, Kalimati	97	24
	National TB Center, Bhaktapur	50	13
Gandaki Province	Regional Tuberculosis Centre, Pokhara	46	12
Province Number 5	Lumbini Zonal Hospital, Butwal	87	21
Karnali Province	TB Referral Center TB Nepal, Nepalgunj	56	14
Sudurpaschim Province	Seti Zonal Hospital, Dhangadi, Kailali	60	15
	Mahakali Zonal Hospital, Mahendranagar	15	4
	Total	510	129

diagnosis of DR TB and the data collection time and duration of DR TB treatment as the time between the initiation of DR TB treatment and data collection time. The data collectors obtained the height and weight of the participants to calculate the body mass index (BMI) and administered the Nepalese version of the Patient Health Questionnaire 9 (PHQ-9) to screen for depression. The PHQ-9 is a nine-item questionnaire designed to screen for depression in primary care. It obtains the patient-reported response on the symptoms of depression over the past 2 weeks on a scale of 0 to 3 (0 - not at all, 1 - several days, 2 – more than half the days, 3 - nearly every day) and sums them to obtain a composite score. [12] The cut-off score of $\geq$ 10 in PHQ-9 identifies the probable major depressive disorder with a sensitivity of 88% (95% CI 0.83 to 0.92) and the specificity of 85% (95% CI 0.85 to 0.82) when compared with the semi-structured interview as the reference standard.[13] The Nepali language version of PHQ-9 has been validated in primary care patients in Nepal which showed that the cut-off of $\geq$ 10 had a sensitivity of 94% (95% CI 0.73 – 0.99) and the specificity of 80% (95% CI 0.71–0.86) with the Composite International Diagnostic Interview (CIDI) as the reference standard.[14] We classified the patients who scored $\geq$ 10 in PHQ-9 as having a probable depressive disorder and regarded it as the binary outcome variable. We further classified the patients with depression according to depression severity into moderate depression (PHQ-9 score 10 – 14), moderately severe depression (PHQ-9 score 15 – 19), and severe depression (PHQ-9 score 20 – 27).[12]

2.4. Data management and analysis

We entered the data in Microsoft Excel (Microsoft Office 2016, Microsoft Corporation, Washington, United States) and analyzed in R statistical software (R Core Team. R: A language and environment for statistical computing. Vienna, Austria). We summarized the socio-demographic and treatment characteristics using mean (Standard Deviation [SD]) or median (Interquartile Range [IQR]) and proportions as appropriate. We performed univariate analysis for all the potential variables hypothesized as the risk factors for depression (age, sex, qualification, previous history of TB, location of the treatment center, duration of DR TB treatment, duration of current illness, type of current TB, comorbidity, and BMI) using univariate logistic regression. We used a purposeful selection of covariates as the model building strategy to build a multivariable logistic regression model.[15] We selected the variables with a significance level of $<$ 0.25 in the univariate analyses and fitted the multivariable logistic regression model. We removed the variables not contributing significantly to the model at the significance level of 0.05 and not confounding as signified by a change in the remaining parameter estimate by 20%. We refitted a new model with the remaining variables and repeated the process until the model contained significant covariates and confounders. We introduced the variables not included in the initial stage and retained the ones that had a significant contribution to the model or were confounding variables. We checked the linearity of logit of the continuous variables included in the model. Also, we checked for collinearity between the explanatory variables in the model and regarded it as present if the variance inflation factor (VIF) was $>$ 10. For the final model, we used a likelihood ratio test for the overall evaluation of the final model against the intercept only model and Wald $\chi 2$ statistics to test the significance of individual coefficients in the model. We reported the coefficient and associated standard error, adjusted odds ratio with its 95% CI, and *p*-value for each variable included in the final model. We considered a p-value of $<$ 0.05 in the final model as significant.

3. Results

All the 129 patients approached for the study agreed to participate. There were no missing values. There were 92 (71.3%) male patients. The median age was 36 years (IQR 25–48) and 33 (25.5%) patients reported receiving no formal education. Most patients (101, 78.29%) had a history of TB in the past, of which 15 patients had MDR TB. The current episode was MDR TB for most of the patients (109, 84.4%). There were 10 (7.75%) patients each of Pre-XDR TB and XDR TB. The patients had a median duration of the current illness of 11 months (IQR 7–16) and the median duration of TB treatment received was 8 months (IQR 5–12) at the time of data collection. The median BMI was 18.37 Kg/m2 (IQR 17.1–20.7) and 21 (16.2%) patients had comorbidities. Diabetes mellitus was the most common comorbidity reported by 13 patients.

We identified 81 patients (62.7%, 95% CI 53.7–71) with the PHQ-9 score of 10 or more signifying probable depressive disorder. Of these, 53 (65.4%) had moderate depression (PHQ-9 score of 10–14), 21 (25.9%) had moderately severe depression (PHQ-9 score of 15–19) and the remaining 7 (8.6%) had severe depression (PHQ-9 score of 20–27).

Table 2
Risk factors associated with the probable depression among patients with drug-resistant tuberculosis.

Risk Factors	n (%)		*p* value	Odds Ratio (95% Confidence Interval)
	Probable depression (n = 81)	Without probable depression (n = 48)		
Age in years (Mean ± SD*)	36.78 (±15.62)	40.02 (±13.51)	0.233	0.98 (0.96–1)
Sex				
Female	25	12	0.476	1
Male	56	36		0.75 (0.33–1.67)
Qualification				
Illiterate	18	15	0.256	1
Literate	63	13		1.59 (0.71–3.56)
Previous history of TB				
No	16	12	0.485	1
Yes	65	36		1.35 (0.58–3.17)
Treatment center location				
Province number 1	9	8	–	1
Province number 2	4	4	0.891	0.88 (0.15–4.93)
Province number 3	22	16	0.732	1.22 (0.38–3.8)
Gandaki Province	9	3	0.234	2.66 (0.56–15.36)
Province number 5	16	5	0.139	2.84 (0.73–12.07)
Karnali Province	9	5	0.525	1.60 (0.37–7.15)
Sudurpaschim Province	12	7	0.536	1.52 (0.40–5.93)
Duration of Drug-Resistant Tuberculosis treatment in months (Mean ± SD)	9.8 (±6.8)	8.4 (±4.7)	0.211	1.03 (0.97–1.1)
Duration of current illness in months (Mean ± SD)	13.6 (±6.3)	9.3 (±4.4)	< 0.001	1.15 (1.07-1.26)
Current Tuberculosis				
Multi-Drug Resistant Tuberculosis	67	42	0.616	
Pre/Extensively Drug-Resistant Tuberculosis	14	6		1.46 (0.47–5)
Comorbidity				
No	68	40	0.99	1
Yes	13	8		0.96 (0.33–2.9)
Body Mass Index in Kg/m2 (Mean ± SD)	18.82 (±3.1)	19.25 (±3.6)	0.472	0.96 (0.86–1.07)

*SD - Standard Deviation.

In univariate analyses (Table 2), age, the duration of current illness, duration of DR TB treatment, and treatment center location (for two categories) had a *p*-value lower than the pre-specified cut-off of 0.25. We fitted a multivariable binary logistic regression model with these variables as the independent variables and depression as the outcome variable. The model we obtained had a duration of current illness and duration of DR TB treatment as the significant covariates. However, these two variables correlated significantly (Spearman's ρ 0.69, $p < 0.001$) leading to collinearity in the model as indicated by VIF > 10 for each of these variables. We removed the variable DR TB treatment duration and retained the variable duration of current illness in the regression model. This is because, in addition to the duration of DR TB treatment, the variable duration of the current illness also included the periods between symptom onset and diagnosis of DR TB as well as that between diagnosis of DR TB and initiation of DR TB treatment which are potential areas for improvement. In the final model thus obtained, only the duration of the current illness remained as the significant covariate (Table 3). We verified the linearity of the logit of the duration of current illness. In the likelihood ratio test, the final model was a better fit to the data than the intercept only model ($\chi 2 = 17.005$, df = 1, $p < 0.001$).

4. Discussion

This study aimed to estimate the burden of depression among the patients receiving treatment for DR TB under the National TB Control Program in Nepal. We used PHQ-9 as the tool to screen for depression. PHQ-9 performs similarly regardless of being administered by an interviewer either in person or by phone or even if it is self-administered, can classify the severity of depression, and can be used to monitor the treatment response.[12,16,17] We found that 62.7% of our study participants had a probable depressive disorder and we identified the duration of current illness as an independent risk factor for depression.

Our estimate of depression burden is higher than that reported in the previous work from Nepal (22.2%).[10] This higher prevalence observed could be attributed to several possible explanations. First, unlike the previous study where the participants from only two urban centers were studied, the participants in our study were from 11 treatment centers representing all seven provinces across the country. The participants in different treatment centers came from different geographic locations and socio-economic backgrounds which could have impacted the rate of depression. Although not observed in our study, the previous study has reported a statistically significant association of depression with the treatment center location. Cross-sectional studies on depression among the patients with DR TB in Pakistan have also reported an association of depression with treatment locations and settings thus further supplementing this argument.[11,18] Second, investigators in the previous study screened only 69% of the patients from the two study centers. At least a subset of the patients not screened could have had depression, thus resulting in the lower depression prevalence observed in the study participants. Third, the participants in our study were selected by the non-probability sampling technique. This could have introduced a bias resulting in a higher number of depressed patients being included in the study. Fourth, different screening tools with different sensitivities were used for screening depression. In the studies for validation of Nepali language versions against CIDI, the sensitivity of the HSCL-25 depression module, used in the previous study, had a sensitivity of 87% while that of PHQ-9 was 94%.[14,19] This could have contributed to the higher detection rate in our study. Studies from other settings have found that the prevalence of depression among the patients with DR TB range from 3% to 70% which reflects the significant heterogeneity in the patient population as well as screening tools used.[9]

We found that each month's increase in the duration of current illness increased the odds of being depressed by 1.15 (95% CI 1.07–1.26) (Table 3). The duration of current illness in our study included the time between the symptom onset and treatment initiation as well as between treatment initiation and data collection time. A longer interval between symptom onset and treatment initiation signifies the delay in the DR TB diagnosis and initiation of its effective treatment. Patients with such delays experience the physical symptoms of DR TB and the associated stigma for a longer duration of time. A longer delay in treatment initiation also allows for the plasma levels of proinflammatory cytokines to remain elevated due to ongoing inflammation. These factors increase the risk of depression among patients with DR TB in whom there is a delay in its treatment initiation. Similar findings have been reported in a study from Pakistan, in which investigators screened 289 MDR TB patients for depression at the time of treatment initiation and observed a significant association of depression with the duration of illness.[9] Early diagnosis of DR TB and prompt initiation of its treatment reduce not only the odds of depression but also the transmission of DR TB and therefore, should be a priority area for improvement.

On initiation of the appropriate treatment, the symptoms due to DR TB start to resolve, and the ongoing chronic inflammation begins to subside. As a result, the risk of depression becomes lower as the treatment progresses. However, in the setting of DR TB treatment, additional factors come into play that continue to mediate depression in at least in a subset of these patients. As the DR TB treatment is offered only in a limited number of centers in Nepal, many patients need to relocate for their treatment which often results in absence from work adding to the financial burden and separation from the family. Also, depression is an important side effect of some of the drugs used in DR TB treatment, for example, Cycloserine.[20] The net effect of duration of DR TB treatment on depression is therefore variable. In our study, we did not find a significant association of DR TB treatment duration with depression (Table 2). In a prospective study from Pakistan, investigators found that the MDR TB treatment had a positive impact on the patients' Health-Related Quality of Life – a scale that measures the extent to which patient's subjective perception of physical, mental, and social wellbeing are affected by a disease and its treatment. However, mental health remained compromised even at the end of the treatment.[21] Several approaches could help mitigate this risk of depression during DR TB treatment – decentralization of DR TB treatment services across the country, care and support to the patients receiving DR TB treatment, including vocational training to help generate income during and after treatment as well as using DR TB treatment regimens with drugs not known to cause depression.

There are important limitations in our study to be considered. Though we selected all the DR TB treatment centers across the country, the use of the non-probability sampling technique to select the participants from each center could have introduced a selection bias resulting in limited generalizability of our findings. Because different data collectors administered the PHQ-9 questionnaire, there could be issues with inter-rater reliability as well thereby impacting the estimates of depression. Because it is a cross-sectional study, no distinction could be made if the depression detected was incident depression or present at baseline. The number of special patient populations, for example, patients with diabetes and other comorbidities, have been poorly represented in our study sample. This has limited our assessment of their impact on depression among our study patients. Further studies with larger representation from different patient populations are recommended.

Table 3
Logistic regression results of depression among the patients with drug-resistant tuberculosis.

Variables	Coefficients	SE*	z value	p value	OR (95% CI)
Intercept	−1.138	0.469	−2.426	0.015	
Duration of current illness	0.148	0.041	3.631	<0.001	1.15 (1.07 – 1.26)

*SE – Standard Error.

5. Conclusion

This study has found that a large proportion of the patients with DR TB screened have depression suggesting the need for screening and management of comorbid depression within the National TB Control Program. In addition, increased efforts on early diagnosis of DR TB and initiation of appropriate treatment are warranted to reduce the burden of depression among these patients.

Ethical statement

We obtained ethical approval for the study from Nepal Health Research Council (registration number 110/2018, approval reference number 2327/2018).

We obtained written informed consent from the patients for participation in the study and publication of the findings. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Funding

This work was supported by the National TB Control Program, Nepal through Save the Children, Nepal (Award No. 025/CRF0392018). The funding agency had no role in the study design; collection, management, analysis, and interpretation of data; writing of the manuscript; and the decision to submit the manuscript for publication.

CRediT authorship contribution statement

Sailesh Kumar Shrestha: Conceptualization, Methodology, Software, Investigation, Data curation, Formal analysis, Writing - original draft, Project administration. **Sulochana Joshi:** Conceptualization, Data curation. **Ratna Bahadur Bhattarai:** Investigation, Resources, Project administration, Funding acquisition. **Lok Raj Joshi:** Investigation, Resources. **Nilaramba Adhikari:** Investigation, Resources. **Suvesh Kumar Shrestha:** Investigation, Resources. **Rajendra Basnet:** Validation, Funding acquisition. **Kedar Narsingh KC:** Supervision.

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.

Acknowledgments

We thank Mr. Siddhartha Dhungana for inputs in data analysis and interpretation.

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