

Psychological Distress Symptoms among Adults with Multidrug-Resistant Versus Drug-Sensitive Pulmonary Tuberculosis: A Comparative Cross-Sectional Study at Mardan Medical Complex, Pakistan

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Abstract

Background: Tuberculosis and its treatment are associated with significant psychological burden, especially in multidrug-resistant tuberculosis (MDR-TB) due to treatment regimens, treatment effects, stigma and socio-economic disruption. Evidence from other parts of the world, such as Khyber Pakhtunkhwa, Pakistan, is still scarce.

Objective: To compare the burden and severity of depression, anxiety, and stress symptoms among adults with MDR-TB and drug-sensitive tuberculosis (DS-TB) attending Mardan Medical Complex.

Methods: A comparative cross-sectional study was conducted in the Tuberculosis Services of Mardan Medical Complex, Mardan, Khyber Pakhtunkhwa, Pakistan from January 2022 to December 2025. Total 156 adults were consecutively recruited, there were 104 cases of DS-TB and 52 cases of MDR-TB. The 21 item Depression Anxiety Stress Scales (DASS-21) was used to measure psychological symptoms. Welch's t-test was used to compare group means and Pearson's chi-square or Fisher's exact test (where appropriate) to compare categorical distributions.

Results: Depression, anxiety, and stress scores were higher in the MDR-TB group than in the DS-TB group: 24.0 ± 6.0 vs 12.0 ± 5.0 , 20.0 ± 8.0 vs 13.0 ± 5.0 , and 26.0 ± 7.0 vs 13.0 ± 5.0 , respectively. The corresponding mean differences (MDR-TB minus DS-TB) were 12.0 (95% CI 10.1-13.9), 7.0 (95% CI 4.6-9.4), and 13.0 (95% CI 10.8-15.2); all $p < 0.001$. Severe or extremely severe depression occurred in 65.4% of MDR-TB versus 5.8% of DS-TB participants, extremely severe anxiety in 59.6% versus 11.5%, and severe or extremely severe stress in 57.7% versus 1.0%.

Conclusion: Adults with MDR-TB had significantly higher depression, anxiety and stress symptom burden compared to adults with DS-TB at this tertiary-care facility. It is recommended that routine, confidential mental-health screening, assessment and referral is considered as part of TB care, especially for TB patients undergoing MDR-TB treatment.

Keywords: Tuberculosis, multidrug-resistant tuberculosis, drug-sensitive tuberculosis, psychological distress, DASS-21, Pakistan

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Introduction

Tuberculosis (TB) is still a leading cause of morbidity and mortality from infectious diseases worldwide. According to the World Health Organization (WHO) Global Tuberculosis Report 2025, Pakistan falls into the top 8 countries that contribute to nearly two-thirds of all incident TB cases in the world, with estimated Pakistan contributing approximately 6.3% of the estimated incident cases in 2024.¹ Multidrug-resistant TB (MDR-TB) is TB due to *Mycobacterium tuberculosis* that is resistant to at least isoniazid and rifampicin. The current WHO guidance

is to provide shorter all-oral treatment to those patients who are eligible for the treatment of MDR/rifampicin-resistant TB; however, drug-resistant TB takes a more complicated clinical approach and requires ongoing care from health providers.² Psychological distress is clinically relevant in TB as it is possible that stigma, social isolation, loss of income, uncertainty about recovery, persistent physical symptoms and adverse effects of treatment can lead to symptoms of depression, anxiety and stress. In turn, psychological symptoms can have a

negative impact on quality of life, treatment involvement and compliance.^{3,4} MDR-TB might be exacerbated by these pressures, as patients have a higher likelihood of having been treated before, more complex treatment regimens and significant social and financial upheaval. A significant mental health burden has been reported in TB-seekers by Pakistani studies. Walker et al. reported depression in 42.8% of 1,279 MDR-TB patients across 12 sites in Punjab.⁵ whereas a study conducted by the Programmatic Management of Drug-Resistant TB unit in Lady Reading Hospital, Peshawar, reported 65.5% of patients to be depressed at baseline.⁶ More recently, a feasibility study conducted in Peshawar showed that around 35% of the TB patients screened in were in depression, and that a depression-care pathway could be integrated in regular TB care.⁷ Systematic reviews and international comparative studies indicate that there is also high burden of anxiety and depressive symptoms in DR-TB, although this varies depending on the screening tool used, the treatment phase and the setting.⁸⁻¹¹

Despite this evidence, there is a lack of comparative data of directly comparing the depression, anxiety, and stress symptomology in adults with DS-TB and MDR-TB in a tertiary-care setting. The key limitation of the current study is the same DASS-21 assessment and severity framework used for both resistance groups for the opportunity to directly compare three psychological symptom domains. The main aim was to assess the mean depression, anxiety and stress scores to compare between MDR-TB and DS-TB group. Other secondary aims were to explore the difference in the distributions of severity of DASS-21 scores and to characterize the groups in terms of socio-demographic and clinical data.

Methods

It was a comparative cross sectional Study carried out in tuberculosis service center of the Department of Pulmonology in Mardan Medical Complex, Mardan Pakistan with programmatic service center of DR TB. Recruitment of 156 participants was done from January 2022 to December 2025. The study protocol was approved by the Ethical Committee of Association for Community Development (ACD), Peshawar, Khyber Pakhtunkhwa, Pakistan (approval/reference no.: 104/ERC/ACD) and written informed consent was obtained prior to data collection. The

study recruited the consecutive eligible patients who came to the routine TB service. Eventually, 156 patients were analyzed: 104 DS-TB and 52 MDR-TB. No study group allocation was done by investigators and participants were classified based on documented molecular and/or phenotypic drug-susceptibility testing. As a result, the difference in the number of participants was due to the respective availability of eligible DS-TB and MDR-TB patients during the recruitment process. A two-sample mean compare-son was considered with an allocation ratio of 2:1, 2 sided $\alpha=0.05$ and 80% statistical power to ascertain if the obtained sample was adequate to make the primary between group comparison. The study achieved a power of 100% to detect a standardized mean difference (Cohen's *d*) of approximately 0.48 or larger between the groups with 104 DS-TB and 52 MDR-TB participants.

The inclusion criteria were age of ≥ 18 years, bacteriologically confirmed pulmonary TB, classification as DS-TB or MDR-TB based on molecular and/or phenotypic drug susceptibility testing, and ability to participate in the interview; and willingness to provide informed consent. Patients those who were critically ill and could not be interviewed, those with major cognitive impairment (prevented reliable interview despite reasonable assistance) and those with incomplete DASS-21 data were excluded. If present, a prior psychiatric history was noted but did not automatically exclude an individual. No imputation was done, the available complete observations were analysed with regard to variables reported in Tables 1-3.

Pulmonary TB was diagnosed using sputum smear microscopy and/or Xpert MTB/RIF or Xpert MTB/RIF Ultra or mycobacterial culture and/or drug-susceptibility testing as clinically indicated. MDR-TB was considered to be TB due to *M. tuberculosis* resistant to at least isoniazid and rifampicin.² DS-TB meant that the TB was bacteriologically confirmed and resistant TB as per the MDR definition on available test was not documented. Patients were treated as per national TB programme and current recommendation of WHO.

A standardised case-report form was used to collect data on age, sex, urban or rural dwelling area, smoking status, occupational status, height, weight for body mass index (BMI) and HIV status. The instrument used in the study, the DASS-21 was

presented orally by trained study staff in a private location, with the use of the participant's chosen language of Pashto/urdu and consistent wording and response options.

The DASS-21 consists of 21 items, comprising of 7 items each in the three subscales of depression, anxiety and stress.¹² Each item is rated on a four point scale (0-3) based on the presence of symptoms in the week prior to rating. Each item on the seven subscales is added together and each subscale total doubled to enable the conventional severity cut-offs to be used. The depression categories were 0-9 normal, 10-13 mild, 14-20 moderate, 21-27 severe and ≥ 28 extremely severe, while the anxiety categories were 0-7 normal, 8-9 mild, 10-14 moderate, 15-19 severe and ≥ 20 extremely severe and the stress categories were 0-14 normal, 15-18 mild, 19-25 moderate, 26-33 severe and ≥ 34 extremely severe. The categories on the DASS-21 are not psychiatric diagnoses, but rather provide information on the severity of symptoms. For participants, the DASS-21 items were administered in Urdu and Pashto language as per participants' language preference. Mean and standard deviation (SD) were used for continuous variables while frequency and percentage were used for categorical variables. Since the two groups (DS-TB and MDR-TB) were not equal and equal variances were not assumed, Welch's two-sample t-test was used to compare the means for age and the DASS-21 subscales. Mean differences were computed for DASS-21 subscales as follows: MDR-TB - DS-TB, and are presented with 95% confidence intervals (CIs). Pearson's Chi-square test was used to compare the categorical variables while Fisher's exact test was used for sparse cells. Fisher's exact test was used to compare the severity distributions for the DASS-21. All tests were two sided and $p < 0.05$ was taken as statistically significant.

Each participant was assigned an identifier that was kept away from study data and confidentiality was upheld. The site safety protocol was followed in the clinical assessment and referral of those participants who were distressed or who had other significant safety issues.

Results

A total of 156 participants were included: 104 (66.7%) with DS-TB and 52 (33.3%) with MDR-TB. The overall mean age was 52 ± 13 years; mean age was 51 ± 13

years in the DS-TB group and 53 ± 14 years in the MDR-TB group ($p = 0.391$). Overall, 110 participants (70.5%) were male and 85 (54.5%) lived in urban areas. Smoking status distribution and BMI category were statistically different between groups ($p < 0.001$ for both); while residence, sex, occupational status, HIV status and mean age were not statistically different between groups (Table 1).

Table 1: Baseline Characteristics

Characteristic	Overall N=156	DS-TB N=104	MDR-TB N=52	p-value
Age, years; mean (SD)	52 (13)	51 (13)	53 (14)	0.391
Residence, n (%)				0.460
Urban	85 (54.5)	54 (51.9)	31 (59.6)	
Rural	71 (45.5)	50 (48.1)	21 (40.4)	
Sex, n (%)				0.291
Male	110 (70.5)	70 (67.3)	40 (76.9)	
Female	46 (29.5)	34 (32.7)	12 (23.1)	
Smoking status, n (%)				<0.001
Ex-smoker	14 (9.0)	6 (5.8)	8 (15.4)	
Current smoker	111 (71.2)	68 (65.4)	43 (82.7)	
Never-smoker	31 (19.9)	30 (28.8)	1 (1.9)	
Occupational status, n (%)				0.091
Employed	60 (38.5)	46 (44.2)	14 (26.9)	
Retired	33 (21.2)	20 (19.2)	13 (25.0)	
Student	7 (4.5)	2 (1.9)	5 (9.6)	
Daily-wage worker	18 (11.5)	12 (11.5)	6 (11.5)	
No occupation	38 (24.4)	24 (23.1)	14 (26.9)	
HIV coinfection, n (%)				0.108
No	152 (97.4)	103 (99.0)	49 (94.2)	
Yes	4 (2.6)	1 (1.0)	3 (5.8)	
BMI category, n (%)				<0.001
Underweight	4 (2.6)	0 (0.0)	4 (7.7)	
Normal	106 (67.9)	66 (63.5)	40 (76.9)	
Overweight	45 (28.8)	37 (35.6)	8 (15.4)	
Obese class I	1 (0.6)	1 (1.0)	0 (0.0)	

Table 1 p values: age was compared using Welch's t-test; categorical variables were compared with Pearson's chi-square test when expected counts were adequate and Fisher's exact test for sparse tables (including HIV status and BMI category).

All three DASS-21 subscale means were significantly higher in the MDR-TB group. Mean depression scores were 24.0 ± 6.0 in MDR-TB versus 12.0 ± 5.0 in DS-TB (mean difference 12.0, 95% CI 10.1-13.9; $p < 0.001$). Mean anxiety scores were 20.0 ± 8.0 versus 13.0 ± 5.0 (mean difference 7.0, 95% CI 4.6-9.4; $p < 0.001$), and mean stress scores were 26.0 ± 7.0 versus 13.0 ± 5.0 (mean difference 13.0, 95% CI 10.8-

15.2; $p < 0.001$) (Table 2). Figure 1 shows the higher mean symptom scores and large absolute differences in the MDR-TB group.

Table 2: DASS-21 Subscale Scores by Tuberculosis Resistance Group

Subscale score	Overall N=156	DS-TB N=104	MDR-TB N=52	p-value	Mean difference (95% CI) MDR-TB - DS-TB
Depression, mean (SD)	16.0 (7.8)	12.0 (5.0)	24.0 (6.0)	<0.001	12.0 (10.1-13.9)
Anxiety, mean (SD)	15.3 (7.0)	13.0 (5.0)	20.0 (8.0)	<0.001	7.0 (4.6-9.4)
Stress, mean (SD)	17.3 (8.4)	13.0 (5.0)	26.0 (7.0)	<0.001	13.0 (10.8-15.2)

Values are mean (SD). Mean difference = MDR-TB minus DS-TB. Group means and 95% CIs were estimated using Welch's two-sample t-test

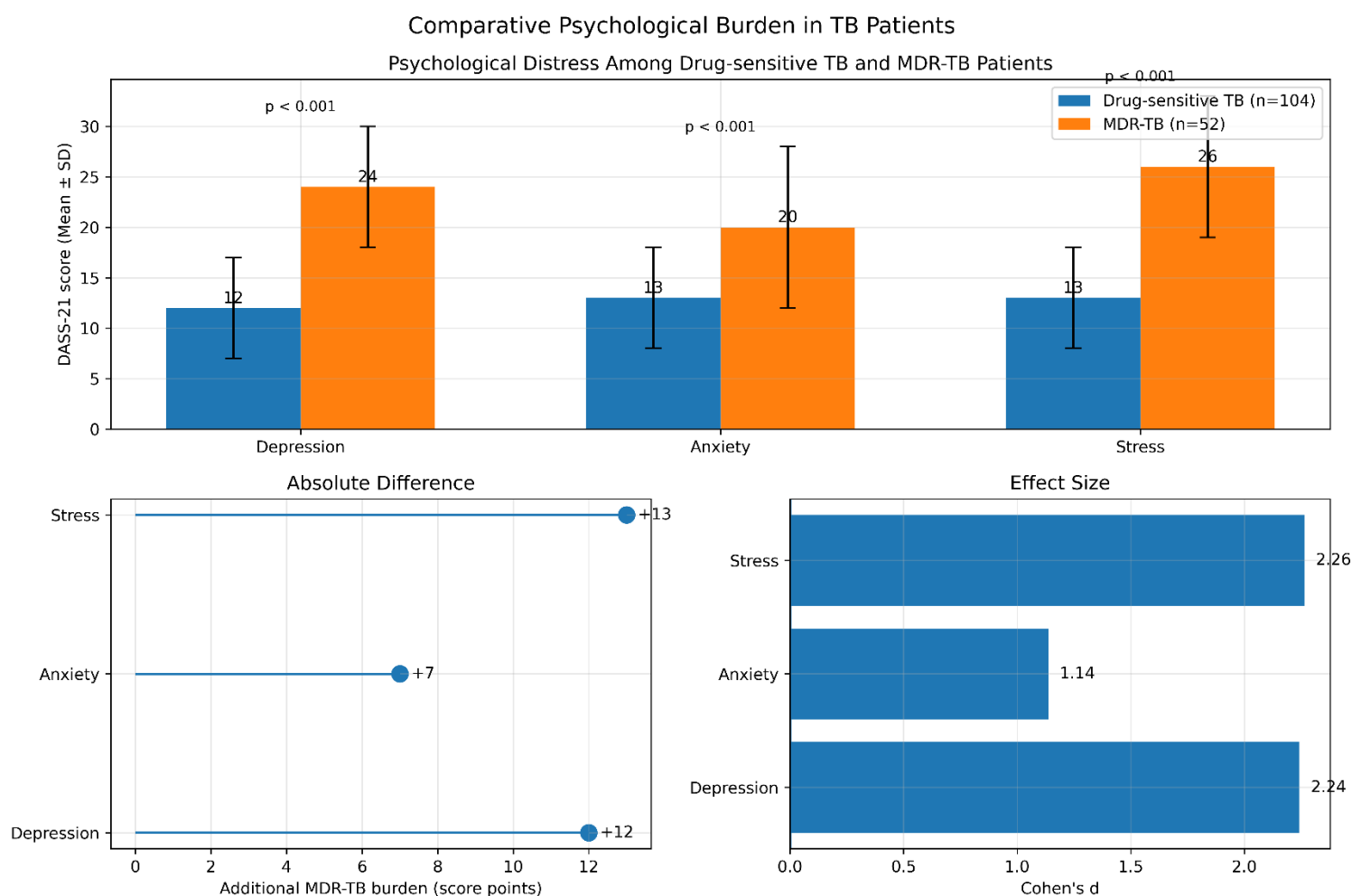


Figure 1: Differences in Depression, Anxiety, and Stress Scores between DS-TB and MDR-TB Participants

DASS-21 (all $p < 0.001$ by Fisher's exact test; Table 3). Of the 52 MDR-TB participants, 34 (65.4%) had severe or extremely severe depression compared to 6 (5.8%) of 104 DS-TB participants. A total of 31 of 52 MDR-TB participants (59.6%) had extremely severe anxiety compared with 12 of 104 DS-TB participants (11.5%). Among all the MDR TB participants (52), severe or

extremely severe stress was reported in 30 (57.7%) participants compared to 1 (1.0%) among all DS TB participants (104). A remarkable difference between MDR-TB group and its respective controls was observed in terms of symptom-severity categories, as shown in Figure 2.

Table 3. Distribution of DASS-21 Severity Categories by Tuberculosis Resistance Group

Domain and severity	Overall N=156	DS-TB N=104	MDR-TB N=52	p-value
Depression category, n (%)				<0.001
Normal	36 (23.1)	35 (33.7)	1 (1.9)	
Mild	31 (19.9)	31 (29.8)	0 (0.0)	
Moderate	49 (31.4)	32 (30.8)	17 (32.7)	
Severe	24 (15.4)	5 (4.8)	19 (36.5)	
Extremely severe	16 (10.3)	1 (1.0)	15 (28.8)	
Anxiety category, n (%)				<0.001
Normal	16 (10.3)	16 (15.4)	0 (0.0)	
Mild	14 (9.0)	10 (9.6)	4 (7.7)	
Moderate	57 (36.5)	45 (43.3)	12 (23.1)	
Severe	26 (16.7)	21 (20.2)	5 (9.6)	
Extremely severe	43 (27.6)	12 (11.5)	31 (59.6)	
Stress category, n (%)				<0.001
Normal	72 (46.2)	71 (68.3)	1 (1.9)	
Mild	32 (20.5)	24 (23.1)	8 (15.4)	
Moderate	21 (13.5)	8 (7.7)	13 (25.0)	
Severe	21 (13.5)	1 (1.0)	20 (38.5)	
Extremely severe	10 (6.4)	0 (0.0)	10 (19.2)	

P values for depression, anxiety, and stress severity distributions were obtained using Fisher's exact test because several cells contained small or zero counts.

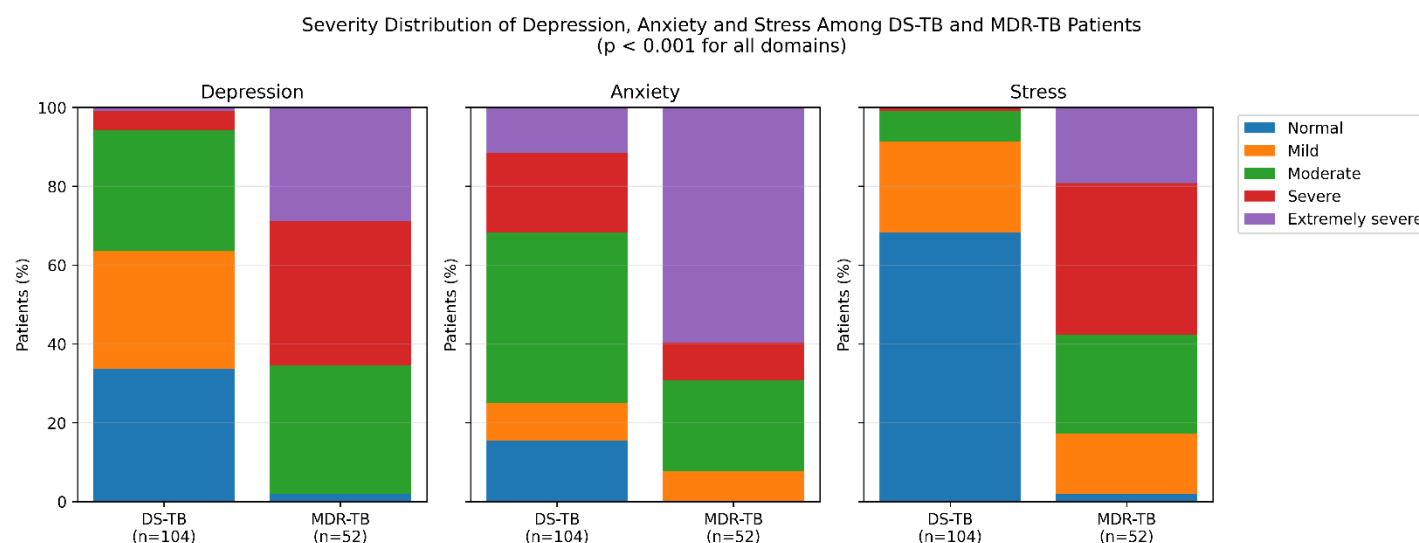


Figure 2: Shift in Psychological Distress Severity Profiles among DS-TB and MDR-TB Participants

Discussion

When making comparison of the 156 adults receiving TB services at Mardan Medical Complex, the results indicated that participants with MDR-TB had significantly more symptom scores of depression, anxiety and stress than the DS-TB. For all three DASS-21 domains there was a large separation between groups and the symptom distributions were skewed towards severe and extremely severe symptoms in

the individuals with MDR-TB. The results suggest that there were a lot of psychological symptoms associated with the MDR-TB group and therefore should not be considered as psychiatric diagnosis. This pattern may be due to several mechanisms. MDR-TB is often a result of prior treatment failure or drug exposure, treatment is more complex, there is uncertainty of cure, more frequent healthcare

encounters, stigma and socioeconomic disruptions compared to DS-TB.¹³⁻¹⁵ All of these factors may be reasonably accounted for as increasing emotional distress. However, the present cross sectional comparisons were unadjusted, and differences in treatment stage, adverse drug effects, socioeconomic status, comorbidities and previous mental-health history might have played a role in the present between-group differences; causal attribution is therefore not possible.

The size of the findings is broadly consistent (although not a direct comparison) with previous evidence from Pakistan and other countries. Walker et al found depression in 42.8% of the MDR-TB patients at all the treatment sites of Punjab⁵ and Mehreen et al found depression in 65.5% of patients at the time of registration in MDR-TB in Peshawar.⁶ Of the participants in the present study, 65.4% were in the severe or extreme severe category of depression on the DASS-21. Percentages cannot be compared as the studies have employed different instruments, case definitions and time of assessment. A more recent study conducted in Peshawar revealed that approximately 35% of TB patients who were routinely screened for depression had depression symptoms.⁷ A large burden of anxiety and depressive symptoms has also been reported in drug-resistant TB patients in China, Indonesia, and in systematic reviews.^{8-10,16,17} The point is that the implication of using the DASS-21 is not that it is diagnosing a psychiatric disorder, but that it could serve as a screening tool to identify patients who might require further evaluation. A practical approach in TB services could involve screening for the symptoms in a non-stigmatizing way at registration and at selected follow-up visits, training staff to communicate in a non-stigmatizing way, establishing clear thresholds for clinical review, and providing clear links to psychiatry, psychology, social welfare and treatment-support services. Feasibility findings from Pakistan indicate that screening for mental health is possible as part of TB care, provided there is a plan in place for staffing, supervision and referrals.^{7,18} The use of screening should therefore be coupled with a clinical action, and not used as a standalone questionnaire.

There are a number of strengths to this study. It assessed depression, anxiety, and stress simultaneously with a standardized 21-item tool, applied

consistent threshold for severity to both groups of patients, and provided both continuous scores and clinically interpretable symptom-severity categories for both DS-TB and MDR-TB patients. The number of consecutive recruitment also lowered the number of eligible attendees to have selective choice of investigators. However, the results need to be viewed in the context of key caveats. The single-centre design restricts the applicability to other TB facilities and populations in Pakistan, and the recruitment at the tertiary-care level may have led to selection bias to recruit patients with more complicated TB. The cross-sectional study design does not allow analysis of temporality or causality. It is important to remember that DASS-21 is a self-reported symptom measure and not a diagnostic interview, thus response and reporting bias may occur. There was an unequal number of participants in the groups, which may impact precision for some of the estimates of subgroups; Welch's t-test was used for continuous outcomes. Analyses were unadjusted, meaning that they did not control for other factors such as adverse effects of the drugs, socioeconomic factors, comorbidities, or other unmeasured factors.

Future multicentre longitudinal studies assessing psychological symptoms at specific treatment milestones with multivariable analyses taking into account clinical and socioeconomic factors are warranted. Structured diagnostic assessment to differentiate symptom severity from diagnosable mental disorders, and the impact of integrated mental-health care on adherence, quality of life, and TB treatment outcomes, should be used wherever possible.

Conclusion

Adult TB patients receiving services from Mardan Medical Complex who had MDR-TB had significantly higher depression, anxiety and stress symptom scores and higher percentage of severe symptom categories as compared to adults with DS-TB. Adding confidential psychological symptom screening, using appropriate clinical assessment and referral can enhance comprehensive TB care, especially when combined with MDR-TB treatment.

Ethical Approval: The Ethical Committee of Association for Community Development (ACD), Peshawar, Khyber Pakhtunkhwa, Pakistan approved this study vide Ref No: 104/ERC/ACD.

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Authors' Contribution:

MMK: Conception and design, critical revisions for important intellectual content

SZ: Conception and design, Acquisition of data, analysis and interpretation of data, drafting of article final approval of the version to be published

R: Acquisition of data, drafting of article

MNS: Acquisition of data, critical revisions for important intellectual content

AAS: Drafting of article

NUI: Final approval of the version to be published

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