Original Research Article

Impact of adverse drug reaction on quality of life in drug resistant tuberculosis

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Received: 11 January 2024
Accepted: 08 February 2024

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ABSTRACT

Background: India has largest population of drug resistant tuberculosis, the treatment of which is long and full of adverse drug reactions. Despite the ongoing research in clinical and pharmacological aspects, quality of life in drug-resistant tuberculosis remains less explored. This study aims to study the quality of life in drug-resistant tuberculosis patients before and after treatment of the adverse drug reactions.
Methods: This hospital based cross-sectional study done in the at tertiary care center in Surat, from January 2019 to February 2020, enrolling patients above 18 years, with multi-drug/ extensively drug resistant tuberculosis, who suffered > 1 adverse drug reaction after commencing treatment. SF-36 was administered at start of treatment and after treatment of first adverse drug reaction, and scores compared. Paired Student T Test was used for comparison of pre - post scores. p -value < 0.05 is considered statistically significant.
Results: Among the 120 patients studied, majority (87.5%) were had pulmonary tuberculosis. 92.5% and 7.2% were multi-drug resistant and extensively drug resistant respectively. A significant improvement in QOL scores was seen in all 3 domains post treatment of adverse drug reaction- physical domain: After vs. Before: 55.2±6.8 vs. 25.2±4.2; (p-value < 0.0001), mental domain: After vs. Before: 66.8±6.7 vs. 39.4±2.1; (p-value < 0.0001) and social domain After vs. Before: 65.4±5.5 vs. 39.7±2.0; p-value < 0.0001).
Conclusions: Drug-resistant tuberculosis along with its associated adverse drug reactions greatly impacts the quality of life in all domains. However, prevention and effective treatment of such adverse effects, especially in systematic protocolised manner can do wonders in improving the life of these patients.

Keywords: Adverse drug reactions, Drug-resistant tuberculosis, Quality of life

INTRODUCTION

Tuberculosis is considered one of the significant menaces in the domain of public health in many countries. In 2019 alone, an estimated 10 million people were sick with tuberculosis(TB), and 1.4 million deaths contributed by the same.[1]Among those diagnosed with TB, 465,000 cases were resistant to rifampicin and at least to both rifampicin and isoniazid (Multi-drug resistant TB).[1] This huge disease burden poses a persistent threat to global tuberculosis care, control, and prevention. What is more devastating is that almost two-third of global TB burden is accounted for by eight developing countries with India contributing 27% of 10.4 million cases. In fact, India has the highest incidence of new and MDR-TB cases in the world.[2,3] Drug resistant TB (DR-TB) is usually treated for 9-20 months,[4]and its treatment requires a course of second- line regime that is more toxic and expensive,

including prolonged periods of injectable medications.[1,5] Despite this expensive and lengthy treatment, only 57% of the DR-TB cases have been successfully treated as com- pared to 85% of the Drug sensitive TB cases at the global level, mainly due to high rates of lost to follow-up, death, and treatment failures.[1] Furthermore, MDR-TB patients experience serious psychosocial problems due to the disease and its treatment complications, which negatively impacts patients' health- related quality of life (HRQoL).[6]

Adverse drug reactions (ADRs) associated with these drugs further complicate the picture, resulting in dropouts, insufficient treatment, and thereby affect success rate. The management of ADRs as well as the cost of treating ADRs is an essential component and needs to be addressed.[7]

Despite the considerable attention given to traditional microbiological and clinical indicators, the effect of MDR-TB on the HRQoL of patients has largely been neglected.[8] The review of English language literature revealed very few studies which have evaluated the HRQoL of MDR-TB patients. Though many factors can be implicated to affect the quality of life in DR-TB, there is evidence available that shows adverse drug effects from the treatment regimen severely impacts and lowers the HRQoL of such patients. Not only that, but these adverse drug reactions (ADR) also affect the adherence to the therapeutic recommendations.[9-11]

Despite this, there is paucity of literature which take into account the QoL, if the ADRs receive treatment, which is of value since many of the ADR can be mild to moderate and treatable, if detected early. A significant improvement would prove to be of much utility in modelling the new measures in programmes and treatment protocols, which attempt to improve the QOL or adherence to treatment in these patients. Keeping all this in mind, the study attempts to study the quality of life in patients with DR-TB, having ADR and the QOL post-treatment of the ADR.

This study aimed to study Health Related Quality of Life (HRQOL) in patients having Multidrug Resistant Tuberculosis (MDR-TB) and Extensive Drug Resistant Tuberculosis (XDR-TB) suffering from adverse drug reactions from the treatment

METHODS

This was a hospital based cross-sectional study done in the Respiratory Medicine department, at tertiary care center, SMIMER Medical College, Surat, during period January 2019 to February 2020.

Inclusion criteria

Patient with age > 18 years, patients diagnosed as MDR-TB & XDR TB based on drug susceptibility testing under RNTCP and suffered 1 or more adverse drug reaction after commencing treatment for TB were included.

Exclusion criteria

Pregnant women, adverse drug reactions from the drugs other than anti tubercular drugs, in the same patient and not consenting for MDR & XDR TB regimen were excluded.

Data collection

Those patients diagnosed as MDR/XDR-TB based on CBNAAT, counselled and started under RNTCP drug regimen, were enrolled in the study, after obtaining informed consent. Data was collected using predesigned, structured and pretested questionnaire (SF-36) to enter the patient details, detailed clinical history and examination, along with previous tubercular or prior hospitalisation history. All patients who were started on treatment were asked to follow up after 1 month or earlier if occurrence of any clinical worsening or illness.

Study tool

The short form SF-36 health questionnaire. SF-36 consists of eight scales that measure eight domains of HRQoL, namely, physical functioning (PF, 10 items), role-physical (RP, four items), bodily pain (BP, two items), general health (GH, five items), vitality (VT, four items), social functioning (SF, two items) role-emotional (RE, three items) and mental health (MH, five items).

For sake of convenience, in our study, physical functioning, role-physical, pain, vitality and general health were clubbed as physical domain, mental health and role-emotional as mental domain and social functioning.

A maximum of 100 and a minimum of 0 is considered for each question. The scores considered for two-option, three-option and five option are (50 and 100), (0, 50 and 100), (0, 25, 50, 75 and 100) respectively. The mean of total scores of all studied scopes will be calculated to measure the total score of individuals' quality of life. The mean of every scope will be calculated for every individual and, if the mean is lower than 50, the quality of related scope will be considered low and if it is higher than 50, it will be considered high.

The SF-36 questionnaire was filled up by the patients during start of treatment and first follow up at 1 month or earlier in case of occurrence of any adverse drug reaction. Pre-treatment and follow-up scores were recorded.

Data analysis

The analysis included profiling of patients on different demographic, Co morbidities, clinical findings as well as HRQOL score. Quantitative data were presented in terms

of means and standard deviation. Qualitative/categorical data were presented as absolute numbers and proportions. Cross tables were generated and Chi Square Test was used for testing of association. Paired Student T Test was used for comparison of pre-post HRQOL scores. p value <0.05 is considered statistically significant.

Definitions used in the study[12]

MDR-TB (Multiple Drug Resistance TB): MTB resistant to both isoniazid and rifampicin with or without resistance to other drugs.

XDR-TB (Extensive Drug Resistance TB): A rare type of multidrug-resistant tuberculosis (MDR TB) that is resistant to isoniazid and rifampin, plus any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin.

Cured: A microbiologically confirmed patient at the beginning of treatment, who was smear negative at the end of the complete treatment and on at least one previous occasion.

Treatment failed: A patient whose biological specimen is positive by smear at 5 months or later. Loss to follow up: A patient whose treatment was interrupted for continuous 1 month or more. Died: A patient who has died due any reason during anti-TB treatment.

Treatment completed: A patient who has completed the treatment according to guidelines but does not meet the definition for cure or treatment failure due to lack of microbiological results.

RESULTS

Among the 120 patients studied, 77 (64.2%) were male, with male: female ratio being 1.8, with almost half the population belonging to the age group between 21years to 40 years (44.2%). The demographic characteristics of the study are further mentioned in Table 1. Majority were diagnosed with pulmonary tuberculosis (87.5%) and 92.5% were multi-drug resistant (MDR) tuberculosis (Table 2). Around 5% of the patients expired by end of the study and 4.2% contributed to treatment failure.

The HRQOL was determined for all the patients with resistant Tuberculosis suffering from adverse drug reaction before treatment and post treatment of ADR. The descriptive statistics of the same is illustrated in Table 3.

In the physical domain, the HRQOL score was significantly higher after treatment for adverse reactions as compared to before treatment (After vs. Before: 55.2±6.8 vs. 25.2±4.2; p-value <0.0001).

Similarly, the HRQOL assessed for mental score was significantly higher after treatment for adverse reactions

as compared to before treatment for adverse reactions (After vs. Before: 66.8±6.7 vs. 39.4±2.1; p-value <0.0001).

Table 1: Socio-demographic characteristics of the study population.

Characteristics	Number of subjects	Percentage
Gender		
Male	77	64.2
Female	43	35.8
Age group (years)		
< 21	6	5
21-40	53	44.2
41-60	38	31.7
> 60	23	19.2
Employment status		
Employed	55	45.8
Unemployed	65	54.2
Smoking and drinking habits		
Smoking	9	7.5
Drinking	23	19.2
Both	12	10
Associated co-morbidities		
Diabetes mellitus type 2	30	25
HIV	18	15
Both	11	9.2
None	61	50.8

Table 2: Details of the tuberculosis status in study population.

	Number of subjects	Percentage
Type of tuberculosis based on site		
Extra-pulmonary TB	15	12.5
Pulmonary TB	105	87.5
Site of extrapulmonary TB		
TB lymph node	7	46.7
TB pleural effusion	4	26.7
TB abdomen	2	13.3
TB spine	2	13.3
Type of tuberculosis based on resistance		
Multidrug resistant TB	111	92.5
Extensively drug resistant TB	9	7.5
Outcomes at the end of study		
Expired	6	5
Treatment failure	5	4.2
Cured	71	59.2
Lost to follow-up	8	6.7
Still on treatment at the end of the study	30	25

The HRQOL assessed for social score, also improved from 39.7±2.0 to 65.4±5.5 after treatment of the ADR,

which was statistically highly significant (p-value <0.0001).

On sub-group analysis, similar trend was noted in the patients who got cured at the end of the study, regardless of site of tuberculosis, and the domain of HRQOL. On comparison of the pre and post treatment scores of those 59 patients who had pulmonary TB and were subsequently cured, physical scores were 25.5±4.5 versus 56.8±1.9 (difference=-31.3±4.9; p-<0.0001), mental scores being 39.3±2.0 versus 39.3±2.0 (difference=-

28.8±3.3, p-<0.0001) and social domain scores being 39.7±2.2 versus 39.7±2.2 (difference=-26.7±3.7, p-<0.0001).

Likewise, the post-treatment scores were higher in physical domain (25.3±3.9 against 56.9±1.6), social domain (39.2±1.6 against 66.5±2.3) and mental (39.4±1.9 against 69.5±2.0), in the 12 patients with extra-pulmonary TB who were cured. All of these showed a statistical significant rise in QOL scores (p-value <0.0001).

Table 3: Health related quality of life (HRQOL) of study population pre- and post-treatment of adverse drug reaction (ADR).

| | Quality of life (HRQOL) | | | | | | | | |
| | Physical | | | Mental | | | Social | | |
	Pre-treatment of ADR	Post-treatment of ADR	Diff. (pre-Post)	Pre-treatment of ADR	Post-treatment of ADR	Diff. (pre-post)	Pre-treatment of ADR	Post-treatment of ADR	Diff. (pre-post)
Mean	25.1	55.2	-30.1	39.5	66.8	-27.4	39.5	65.4	-25.8
Median	23.6	56.8	32.4	38.9	67.4	28.4	39.0	66.5	26.6
SD	4.2	6.8	7.9	2.1	6.7	6.8	1.9	5.5	5.9
Minimum	21.0	23.3	-1.8	37.0	38.2	0.1	37.1	39.6	0.9
Maximum	35.9	60.0	38.5	44.6	73.9	36.4	44.9	70.0	32.4

SD-Standard deviation, Diff.-Difference

Upon considering the effect of treatment of ADR, specifically in XDR TB patients, though a statistical significant difference was observed between pre-and post-treatment scores in all 3 aspects of QOL, (physical: p-value= 0.036, mental p-value= 0.034 and social p-value= 0.011). However, there is a relatively narrower gap between the scores as illustrated in Figure 1.
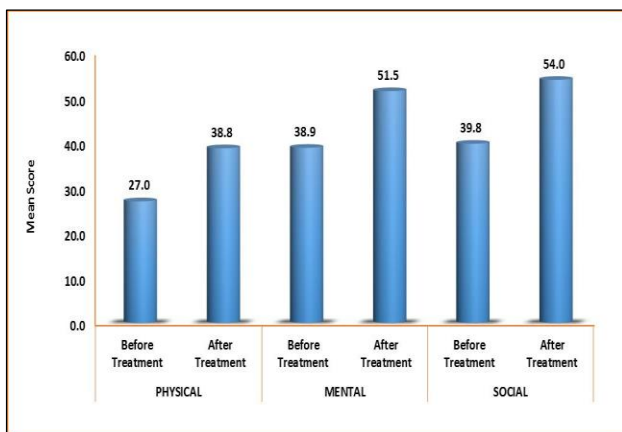
Figure 1: Comparison of HRQOL parameters before and after treating adverse reactions in XDR resistance study subjects.

Contrary to the above, no significant difference could be established in those patients who had expired in any domain (physical: p-value= 0.443, mental p-value= 0.638 and social p-value= 0.243) nor in those patients who had treatment failure (physical: p-value= 0.916, mental p-value= 0.463 and social p-value= 0.249).

Further, the gender of the patient, past history of TB, Site of TB did not affect the HRQOL caused by ADR in any of the domains.

DISCUSSION

The challenges to the treatment of tuberculosis have further worsened with the increasing emergence of multidrug resistant (MDR) and extensively drug resistant (XDR) strains. With the continuing focus on efficient methods of early and effective diagnosis and newer better drug regimens, much of the focus of management is limited to traditional microbiological and clinical parameters. Consequently, not much focus has been given to the quality of life of these patients or what reforms could be done to improve the same.

Be it the social stigma associated with disease, or the compliance to the treatment regimen for long durations along with multiple injections, health care visits or the various side-effects of the second-line or third line agents, the life of drug-resistant tuberculosis suffers from multiple reasons that could contribute to poor quality of life. In this study, an attempt has been made to judge the impact of adverse drug reactions to quality of life in MDR and XDR TB patients and compare the scores before and after treatment of the ADR.

In our study, 120 patients with MDR and XDR-TB were enrolled, who had experienced or detected to have adverse drug reaction. In general, the quality of life in MDR-TB and XDR-TB was poor, with the mean score in physical domain being 25.1, mental and social domains

being 39.5 each. Similarly, studies done by Ahmad et al and Tembeka showed low scores in the mental health component, social functioning, and physical component summary.[13,14] In fact, in a study done by Sharma et al, where QOL scores of pulmonary TB and MDR TB were compared showed a generalized worsening in MDR-TB patients, especially in the psychological domain.[11]

DR-TB had a substantial impact on patients' quality of life, but the presence of ADR during the early months on treatment may be responsible for reducing HRQoL even further. A study done in South Africa reported SF-36 domains and summary scores (MCS and PCS)to be lower in those who reported an ADR compared to those who did not, and both were lower than healthy adults. Compared to those who did not report an ADR, patients who reported ADRs were more likely to have a low MCS (aRR 2.24 95% CI 1.53–3.27) and PCS (aRR 1.52 95% CI 1.07–2.18) summary score. HRQoL was lower among those on DR-TB treatment for 6 months or less.[14]

Till the discovery and approval of newer drugs that can combat resistance and simultaneously reduce the various ADRs associated with current second line and third line anti-tubercular agents, adverse drug reactions will continue to be inevitable in the treatment of MDR and XDR-TB. However, many of the ADR s of the drugs can be predicted, detected early and effectively treated, before much of the quality of life is potentially lost.

Such was the case noticed in our study, where the QOL scores in all domains were significantly improved post-treatment of the ADR as compared to pre-treatment. In the physical domain, the HRQOL score was significantly higher after treatment for adverse reactions as compared to before treatment (After vs. Before: 55.2±6.8 vs. 25.2±4.2; p-value <0.0001). Similarly, the HRQOL assessed for mental score was significantly higher after treatment for adverse reactions as compared to before treatment for adverse reactions (After vs. Before: 66.8±6.7 vs. 39.4±2.1; p-value <0.0001). The HRQOL assessed for social score, also improved from 39.7±2.0 to 65.4±5.5 after treatment of the ADR, which was statistically highly significant (p-value <0.0001).

A study from western India found that psychological and physical health domains were the most affected among patients receiving treatment for MDR TB, and that loss of work adversely affected the social relationships and environmental domains.[15]

This observation highlights two things- the immense role that ADR solely have in affecting the QOL in these patients, and that treating the ADR alone can improve the QOL from a poor score to a good score (>50), nearing the scores of general populations. It also suggests that the impact of ADR in our population was overcome by most people with treatment, without much residual impact in all the physical, mental and social components. This is important to note since most studies done in tuberculosis patients focus on the impact of ADR on quality of life and adherence to treatment, whereas there is paucity of literature studying the change in the quality-of-life scores upon treatment of these ADRs. A study in Gujrat done by Dela et al showed majority (77.87%) ADRs were mild to moderate while only 23.12% ADRs were severe, thus making them amenable to treatment.[16] Hence, improving vigilance and protocolized treatment for ADRs can significantly improve the impact on treatment.

Further, the improvement in the QOL scores in all 3 domains remained unaffected by the site of tuberculosis (EPTB or PTB), the gender, age group or past history of TB. This was against what was anticipated by the studies by Salehitali and Jaber et al, where QOL was different based on gender and age group of the patients.[17,13]

On assessing the sub-group of XDR- TB patients, an equivalent significant increase in QOL scores were noted, in all the domains. Social domain showed the highest improvement (After- before= 14.2±13.0, p-value=0.011), followed by mental domain (After- before = 12.6±14.8, p-value= 0.034) and lastly physical domain (After-Before= 11.8±14.0, p-value= 0.036).

Unfortunately, the same could not be extrapolated to those cases of treatment failure. Among the 5 patients who had treatment failure, there was almost nil improvement of the QOL scores in physical (before 25.3±3.4 versus 25.9±2.2 after) and mental (38.2±1.1 before vs 38.9±0.8 after). Though minimal improvement was seen in the social domain from 39.6±1.1 to 45.3±9.6 post treatment of the adverse drug reactions, the p-value remained insignificant (0.243). This implies that the burden of DR-TB patients who are treatment failures are probably far more diverse, and QOL is less dependent on adverse drug reactions alone. The continuing low physical scores could be due to suboptimal relief of the primary symptoms and restrictions of health due to the same. On the other hand, anxiety and stress secondary to non-resolution of primary disease along with worry and uncertainty of being in the minority group of treatment failures, with lesser support system can affect the mental component scores. All these factors probably out shadow the ADR situation in these sub-group of people.

A similar argument could be put forward for the 6 patients who expired in the study, where no difference was noted in QOL pre and post treatment of ADR. However, the other way of thinking would be to say those patients with non-improvement of QOL scores after the treatment of ADRs were more likely to fall in the treatment failure or death group. However, establishing evidence for the same is beyond the scope of this study and practically, more robust indicators would be evident during course of treatment.

It is interesting to note that in the DR-TB patients overall, in those who were cured from extra-pulmonary TB or

pulmonary TB , the greatest impact after treatment of ADR was in the physical domain, even though a significant improvement was seen in all domains. The social domain, comparatively showed a lesser upliftment. Contrary to this trend, in patients with XDR-TB, in treatment failure cases and those who later on expired, showed a reverse trend, where physical domain was least affected even after treatment of the ADR. This could be helpful in planning rehabilitation measures for such patients, in the form of physical rehabilitation therapy, pulmonary rehabilitation, whole body physiotherapy, drainage procedures, nutritional rehabilitation and diet counselling in priority to other reforms, whereas in the former group of patients, there is urgent need to detect and treat adverse drug reactions, which itself has the most significant impact in improving the quality of life.

The study, however, had few limitations. All the patients in the study were on the oral longer regimen, not shorter regimen. The study took into account the QOL scores pre and post treatment of first detected ADR, the timing of which slightly varied patient to patient, and also did not take into account the QOL post treatment of tuberculosis or recurrent ADR. However, the study uses a standard questionnaire for computing QOL scores and is one of the few studies which attempts to compare objectively the impact of treated ADR in DR-TB patients.

With rising incidence of MDR-TB and XDR-TB, not just clinical management but quality of life has also come into the limelight. Considering the enormous impact of various drugs and their side effects on the quality of life, and further the drastic improvement upon treatment of the same, utmost care needs to be taken to detect and treat these drug reactions.

Protocols need to be in place with programmes which cover patient education about the possible side- effects and danger signs. Patient counselling about ADRs, introducing incentives for reporting of such ADRs and standard regimens for treatment at subsidized rates will help in improving the quality of life in these drug-resistant tuberculosis.

CONCLUSION

Drug-resistant tuberculosis along with its associated adverse drug reactions greatly impacts the quality of life in all domains, rendering patients with life of burden with the disease. However, prevention and effective treatment of such adverse effects, especially in systematic protocolised manner can do wonders in improving the life of these patients, such that they can contribute more to society.

ACKNOWLEDGEMENTS

REFERENCES

1. World Health Organization. Global Tuberculosis Report, 2020. Available at: https://www.who.int/publicationsdetailredirect/9789 240013131. Accessed on 10 February 2020.
2. Pai M., Bhaumik S., Bhuyan S.S. India's plan to eliminate tuberculosis by 2025: converting rhetoric into reality. BMJ Glob Health. 2017;2(2).
3. World Health Organization. Global Tuberculosis Report, 2016. Available at: https://www.who.int/publicationsdetailredirect/9789 241565394. Accessed on 10 February 2020.
4. World Health Organization. Consolidated Guidelines on Drug- Resistant Tuberculosis Treatment, 2019. Available at: https://www.who.int/publications/i/item/978924155 0529. Accessed on 10 February 2020.
5. Seung KJ, Keshavjee S, Rich ML. Multidrug-resistant tuberculosis and extensively drug- resistant tuberculosis. Cold Spring Harb Perspect Med. 2015;5(9):a017863.
6. Thomas BE, Shanmugam P, Malaisamy M, Ovung S, Suresh C, Subbaraman R, et al. Psycho-socio-economic issues challenging multidrug resistant tuberculosis patients: a systematic review. PLoS One. 2016;11(1):e0147397.
7. Verma R, Mahor GR, Shrivastva A, Pathak P. Adverse drug reactions associated with first line antitberculosis drugs in a tertiary care teaching hospital: A study of clinical presentations, causality and severity. Asian J Pharm Clin Res. 2014;7(5):140-3.
8. Jaber AAS, Khan AH, Sulaiman SAS. Evaluation of health-related quality of life among tuberculosis patients in two cities in Yemen. PLoS One. 2016;11(6):48:1-19.
9. Brown J, Capocci S, Smith C, Morris S, Abubakar I, Lipman M. Health status and quality of life in tuberculosis. Int J Infect Dis. 2015;32:68-75.
10. Louw J, Peltzer K, Naidoo P, Matseke G, McHunu G, Tutshana B. Quality of life among tuberculosis (TB), TB retreatment and/or TB-HIV co-infected primary public health care patients in three districts in South Africa. Health Qual Life Outcomes. 2012;10(1):77.
11. Sharma R, Yadav R, Sharma M, Saini V, Koushal V. Quality of life of multi drug resistant tuberculosis patients: a study of North India. Acta Medica Iranica. 2014;52(6):448-53.
12. Central TB Division, Directorate General of Health Services, Ministry of Health & Family Welfare, Government of India, New Delhi. RNTCP Technical and Operational Guidelines for TB Control in India, 2016. Available at: https://tbcindia.gov.in/index1.php?sublinkid=4573&

level=2&lid=3177&lang=1. Accessed on 10 February 2020.

13. Ahmad N, Javaid A, Syed Sulaiman SA, Basit A, Afridi AK, Jaber AA, et al. Effects of multidrug resistant tuberculosis treatment on patients' health related quality of life: results from a follow up study. PloS one. 2016;11(7):e0159560.

14. Sineke T, Evans D, Schnippel K, van Aswegen H, Berhanu R, Musakwa N, et al. The impact of adverse events on health-related quality of life among patients receiving treatment for drug-resistant tuberculosis in Johannesburg, South Africa. Health Qual Life Outcomes. 2019;17(1):94.

15. Laxmeshwar C, Stewart AG, Dalal A, Kumar AMV, Kalaiselvi S, Das M. Beyond 'cure' and 'treatment success': quality of life of patients with multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2019;23(1):73-81.

16. Dela AI, Tank NKD, Singh AP, Piparva KG. Adverse drug reactions and treatment outcome analysis of DOTS-plus therapy of MDR-TB patients at district tuberculosis centre: A four year retrospective study. Lung India. 2017;34(6):522-6.

17. Salehitali S, Noorian K, Hafizi M, Dehkordi AH. Quality of life and its effective factors in tuberculosis patients receiving directly observed treatment short-course (DOTS). J Clin Tuberc Other Mycobact Dis. 2019;15:100093.