talenta PUBLISHER

JETROMI
Journal of Endocrinology, Tropical Medicine, and Infectiouse Disease
Journal homepage: https://jetromi.usu.ac.id

FACTORS ASSOCIATED WITH TREATMENT OUTCOME OF SHORTER TREATMENT REGIMEN (STR) FOR MULTIDRUG-RESISTANT TUBERCULOSIS (MDR-TB)

Gwanita Nawariantina Perangin-angin[1], Bintang Yinke Magdalena Sinaga[*1], Parluhutan Siagian[1], Putri Chairani Eyanoer[2]

[1] *Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Sumatera Utara, Adam Malik Hospital, Medan, Indonesia.*
[2] *Department of Preventive and Community Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia*

[*]Corresponding Author: bintang@usu.ac.id

ARTICLE INFO

Article history:
Received 04 April 2024
Revised 10 September 2024
Accepted 15 November 2024
Available online xxx

E-ISSN: 2686-0856
P-ISSN: 2686-0872

How to cite:
Sinaga, Bintang Y M. (2024). Factors Associated With Treatment Outcome Of Shorter Treatment Regimen (STR) for Multidrug-Resistant Tuberculosis (MDR-TB). Journal of Endocrinology, Tropical Medicine, an Infectiouse Disease, 6(4), 131-137. (make in IEEE style)

http://doi.org/10.32734/jetromi.v6i4.16123

ABSTRACT

Background: Indonesia ranked 2nd around the world for TB cases with the case population continue increasing. In 2018, the Shorter Treatment Regimen (STR) was introduced as a new regimen for treating MDR-TB patients. This study aims to determine factors associated with the treatment outcome of MDR-TB patients treated with the Shorter Treatment Regimen

Methods: This is a descriptive-analytic study using cross-sectional design which was conducted at Adam Malik Hospital Medan. Subjects were 150 patients with drug-resistant Pulmonary TB at MDR-TB polyclinics according to inclusion and exclusion criteria

Results: MDR-TB patients treated with STR were mostly < 50 years old (65.2%) and 107 subjects (70.4%) were male. The majority of subjects with comorbidity were 94 subjects (61.8%); 43 subjects (28.3%) with DM, 5 subjects (3.3%) with CHF, 3 subjects (2.0%) with HIV, 1 subject (0.7%) with DM & CHF, and 1 subject (0.7%) with DM & HIV. When evaluating the patient's treatment outcome, 47.4% were cured, 6.6% failed, 34.8% were defaulted and 11.2% were death. A chi-square test was conducted to assess the association between age with treatment outcome. Age was significantly associated with treatment outcome (p=0.038) but gender and comorbidity were not associated with treatment outcome with p-values 0.152 and 0.497 (p>0,05) respectively.

Conclusions: There is a significant association between age and treatment outcome but no significant association between gender and comorbidity with treatment outcome.

Keyword: Treatment Outcome, Shorter Treatment Regimen, MDR-TB

ABSTRAK

***Latar Belakang**: Indonesia menduduki peringkat ke-2 dunia untuk kasus TBC dengan populasi kasus yang terus meningkat. Pada tahun 2018, Shorter Treatment Regimen (STR) diperkenalkan sebagai rejimen baru untuk mengobati pasien TB-MDR. Tujuan dari penelitian ini adalah untuk mengetahui faktor-faktor yang berkorelasi dengan hasil pengobatan pasien TB-MDR yang diobati dengan Regimen STR.*

***Metode**: Penelitian ini merupakan penelitian deskriptif-analitik dengan desain cross-sectional yang dilakukan di Rumah Sakit Adam Malik Medan. Subyek penelitian adalah 150 pasien TB Paru Resisten Obat di poliklinik TB MDR sesuai kriteria inklusi dan eksklusi.*

***Hasil**: Pasien TB-MDR yang diobati dengan STR sebagian besar berusia <50 tahun (65,2%) dan berjenis kelamin laki-laki sebanyak 107 subjek (70,4%). Mayoritas subjek dengan penyakit penyerta sebanyak 94 orang (61,8%); 43 orang (28,3%) DM, 5 orang (3,3%) CHF, 3 orang (2,0%) HIV, 1 orang (0,7%) DM & CHF, dan 1 orang (0,7%) DM & HIV. Hasil pengobatan adalah 47,4% sembuh, 6,6% gagal, 34,8% putus berobat dan 11,2% meninggal. Uji chi square dilakukan untuk menilai hubungan antara usia dengan hasil pengobatan dan didapatkan nilai p = 0,038 yang menunjukkan adanya hubungan yang signifikan namun berdasarkan jenis kelamin dan penyakit penyerta ditemukan nilai p masing-masing 0,152 dan 0,497 (p>0,05) yang menunjukkan tidak ada hubungan antara jenis kelamin dan penyakit penyerta terhadap hasil pengobatan.*
***Kesimpulan**: Terdapat hubungan yang signifikan antara usia dan hasil pengobatan namun tidak ada hubungan yang signifikan antara jenis kelamin dan penyakit penyerta dengan hasil pengobatan.*

***Kata Kunci**: Hasil Pengobatan, Regimen STR, MDR-TB*

1. Introduction

Tuberculosis (TB) is an infectious disease, the leading cause of health problems, one of the top 10 causes of death worldwide, and the leading cause of death cause of infectious agents (ranked above HIV/AIDS). In 2019, around 10 million people were infected and 1.4 million died. Indonesia ranked 2nd around the world for TB cases with the case population continue increasing from 331,703 cases in 2015 to 562,049 cases in 2019 (69%) [1].

Drug-resistant TB continues to be a public health threat. Worldwide in 2019, close to half a million people developed rifampicin-resistant TB (RR-TB), of which 78% had multidrug-resistant TB (MDR-TB). The three countries with the largest share of the global burden were India (27%), China (14%) and the Russian Federation (8%). Globally in 2019, 3.3% of new TB cases and 17.7% of previously treated cases had MDR/RR-TB. The highest proportions (>50% in previously treated cases) were in countries of the former Soviet Union. Despite these improvements, the number of people enrolled in treatment in 2019 was equivalent to only 38% of the estimated number of people who developed MDR/ RR-TB in 2019. Closing this wide gap requires one or more of the following: improving the detection of TB; increasing bacteriological confirmation among those diagnosed with TB; expanding the coverage of testing for drug resistance among those with bacteriologically confirmed TB; and ensuring that all those diagnosed with MDR/RR-TB are enrolled in treatment. Ten countries accounted for 77% of the global gap between treatment enrolments and the estimated number of new cases of MDR/RR-TB in 2019 and thus will have a strong influence on progress in closing this gap. China and India accounted for 41% of the global gap. The latest treatment outcome data for people with MDR/RR-TB show a global treatment success rate of 57%. Three examples of high MDR-TB burden countries with relatively high TB treatment coverage that have higher treatment success rates for MDR/RR-TB (≥75%) are Ethiopia, Kazakhstan, and Myanmar [1].

MDR-TB cases increased by about 30,000 cases per year, but only 1848 (6%) cases received treatment in 2016. The economic burden in Indonesia for 1 year to tackle TB was US$5.46 million. Based on the 2017 Joint External TB Monitoring Mission (JEMM), there were many lost to follow-up TB and died cases in Indonesia and not well-reported. The treatment success rate will decrease if death and loss of follow-up cases are included [2].

Hardini et al report treatment outcomes lost to follow-up cases are more prevalent in the shorter-term regimen group (49.2%) compared to the Bedaquiline (BDQ) regimen (29.4%). Whereas, the duration of treatment with a shorter-term regimen (STR) was 9–11 months, much shorter than the 18–24-month duration of Bedaquiline (BDQ) treatment. The cause of the high case of loss to follow-up cases in MDR therapy is due to drug adverse events [3]. Adverse events are common with existing regimens for multidrug-resistant tuberculosis and can lead to major morbidity, including blindness, deafness, myelosuppression, renal failure, or liver failure, with resultant hospital admission or even death, as well as treatment interruptions or failure [4].

Many factors can correlate with treatment success. The purpose of this study was to determine the factors correlated with the treatment success of drug-resistant TB patients who received a Shorter Treatment Regimen (STR).

2. Methods

This study is a retrospective study using cross-sectional design which was conducted at Adam Malik General Hospital Medan. The subjects were 140 patients with inclusion criteria age > 18 years, multi-drug-resistant TB patients based on molecular rapid test and drug sensitivity test results, pulmonary TB cases, and exclusion criteria were Pre-XDR / XDR TB patients, history of drug-resistant treatment > 1 month, history of drug-resistant treatment failure. The sampling technique used was non-probability sampling with consecutive sampling techniques.

The data was obtained from medical records of MDR patients in Adam Malik Hospital Medan from January 2017 to September 2019. Data collection information also included the patient's age, gender, comorbidity, and treatment outcome.

Statistical analysis

Data processing was carried out using SPSS statistical software version 20, with a p-value <0.05 indicating a significant correlation. The data also will be analyzed descriptively to determine the demographic distribution of subjects and analyze the factors correlated with treatment success.

This study was approved by the Health Research Ethical Committee of North Sumatera, Faculty of Medicine, Universitas Sumatera Utara, Medan, with approval number 529/KEP/USU/2021 on June 16, 2021.

3. Results

Based on age, the proportion of MDR-TB patients treated with STR was mostly < 50 years old (65.2%) and 107 subjects (70.4%) were male. The majority of subjects with comorbidity were 94 subjects (61.8%); 43 subjects (28.3%) with DM, 5 subjects (3.3%) with CHF, 3 subjects (2.0%) with HIV, 1 subject (0.7%) with DM & CHF, and 1 subject (0.7%) with DM & HIV. The treatment outcome was 47.4% cured, 6.6% failed, 34.8% default, and 11.2% death (Table 1).

Table 1. Characteristics of Subjects

Characteristics		**n (%)**
Age (years old)	20-30	34 (22.4 %)
	31-40	34 (22.4%)
	41-50	31 (20.4%)
	51-60	36 (23.7%)
	> 60	17 (11.1%)
Gender	Male	107 (70.4%)
	Female	45 (29.6%)
Comorbidity	Yes	90 (59.2 %)
	No	62 (40.8 %)
Treatment Outcomes	Cured	72 (47.4%)
	Default	53 (34.8%)
	Failed	10 (6.6%)
	Death	17 (11.2)
Comorbidity	No Comorbid	91 (59.8%)
	DM	51 (33.6%)
	CHF	5 (3.2%)
	HIV	3 (2.0%)
	DM, & CHF	1 (0.7%)
	DM & HIV	1 (0.7%)

DM=Diabetes Mellitus; CHF=Congestive Heart Failure; HIV=Human Immunodeficiency Virus

A chi-square test was conducted to assess the association between age and treatment outcomes with p-value = 0.038 ($p<0.05$) which indicated a significant association between age and treatment outcomes, which aged 31-40 years group had the highest success treatment, namely 21 cases. Most default cases are in the age of 51-60 years group, with as many as 16 cases (Table 2).

Table 2. Association of Age with Treatment Outcome of MDR-TB Patients

Age (yr)	Total	Treatment Outcomes				p-value
		Cured (%)	Default (%)	Failed (%)	Death (%)	
20-30	34	19 (55.9)	10 (29.4)	4 (11.8)	1 (2.9)	
31-40	34	21 (61.8)	9 (26.5)	1 (2.9)	3 (8.8)	
41-50	31	16 (51.6)	9 (29.0)	0 (0.0)	6 (19.4)	0.038*
51-60	36	13 (36.1)	16 (44.4)	4 (11.1)	3 (8.3)	
> 60	17	3 (17.6)	9 (52.9)	1 (5.9)	4 (23.5)	

*chi-square test

Bivariate analysis with a chi-square test was conducted to assess the association between gender and treatment outcomes and obtained p-value = 0.152 (p>0.05), which means that there was no significant association between age and treatment outcomes (table 3).

Table 3. Association of gender with treatment outcome of MDR-TB patients

Gender	Total	Treatment Outcomes				p-value*
		Cured (%)	Default (%)	Failed (%)	Death (%)	
Male	107	53 (49.5)	38 (35.5)	8 (7.5)	8 (7.5)	0.152
Female	45	19 (42.2)	15 (33.3)	2 (4.4)	9 (20.0)	

*chi-square test

There was also no significant association found between comorbidity and treatment outcomes of MDR-TB patients with a p-value of 0.497 (p>0.05) (table 4).

Table 4. Association of comorbidity with treatment outcome of MDR-TB patients

Comorbidity	Total	Treatment Outcomes				p-value
		Cured (%)	Default (%)	Failed (%)	Death (%)	
Yes	94	49 (52.1)	30 (31.9)	6 (6.4)	9 (9.6)	0,497
No	58	23 (39.7)	23 (39.7)	4 (6.9)	8 (13.8)	

*chi-square test

4. Discussions

This study found MDR-TB patients treated with STR were mostly < 50 years old (65.2%) and 107 subjects (70.4%) were male. The majority of subjects with comorbidity were 94 subjects (61.8%). Trubnikov study in MDR-TB patients treated with STR regimen showed mean (SD) age of subjects was 45.6 (16.1) years old and 67 subjects (70.5%) were male. The majority of patients with comorbidity were 56 patients (58.9%) and 11 patients (11.6%) were co-infected with HIV [5]. Trebucq study in nine countries in West and Central Africa in MDR-TB patients treated with STR regimen found majority of patients were <45 years old (76.7%) and 667 subjects (66.3%) were male with a median age was 34 years old (between 18-80 years old). Trebucq showed 806 patients (80.1%) were HIV negative and only 200 subjects (19,9%) were HIV positive. Among the 1006 MDR-TB patients included in the study, 200 (19.9%) were infected with the human immunodeficiency virus (HIV) [6].

Our study for outcome treatment found that 47.4% were cured, 6.6% of patients failed, 34.8% defaulted, and 11.2% died. Of 95 rifampicin-resistant patients enrolled and treated with STR regimen in Tashkent, 66.3% were successfully treated, 17.9% suffered failed treatment, 7.4% died, 5.3% were lost to follow-up and 3.2% were not evaluated. No recurrence was identified in 54 patients after 12 months of successful treatment completion [5]. Ciza showed of the 225 patients, 209 (92.9%) were cured (185, 82.2%) or completed treatment (25, 10.7%) without evidence of recurrence, one (0.4%) experienced treatment failure, three (1.3%) were lost to follow-up, 11 (4.9%) died during treatment and one (0.4%) relapsed six months after being declared cured.5 Trébucq et al. report death occurred in 8.5% of participants in the short regimen group and 6.4% in the long

regimen group, and acquired resistance to fluoroquinolones or aminoglycosides occurred in 3.3% and 2.3%, respectively. Outcomes were as follows: 728 (72.4%) cured, 93 (9.2%) treatment completed (81.6% success), 59 (5.9%) failures, 78 (7.8%) deaths, and 48 (4.8%) lost to follow-up [6].

This research found a significant association between age and treatment outcomes. Older patients (>55 years) have the lowest cure rate and highest treatment drop-out rate compared to younger patients and patients > 60 years have the highest death proportion treatment-outcome [7]. A study by Myemba showed MDR-TB mortality was associated with gender, age, long-term concurrent drug use, and HIV co-infection. A greater mortality rate was observed in patients aged >45 years old and women, HIV-positive patients, patients taking the short regimen, concomitant long-term drug use, and patients who had comorbidity. Cox regression analysis found that patients aged >45 years had a 10.82-fold increased risk of death with MDR-TB compared to those aged <24 years [8]. The presence of age-related health conditions such as underlying malignant conditions, immunosuppressive therapies, malnutrition, and others make the elderly population susceptible to TB disease and its complications [9–11].

Genwas der found to be not significantly associated with the treatment outcomes in our study. In contrast, Myemba's study showed that female patients were 5.92 times more likely to die from MDR-TB than male patients [8]. Soeroto from West Java, Indonesia, from 315 MDR-TB patients treated with STR regimen, the success rate was 64.5% and multivariate analysis showed male gender increased the chance of successful outcome, while malnutrition, history of previous TB treatment, and time of culture conversion >2 months decreased the chance of successful outcome [12]. An analysis of surveillance data from 2002–2011 in 250,854 cases of MDR-TB patients treatment outcomes in the European Union and European Economic Area found males were likely to develop unsuccessful MDR/ RR-TB treatment OR = 1.40, 95% CI: 1.28–1.52 compared to females. The factor that may play an important role is the behaviors of drinking alcohol and drug abuse [13]. This is to The European Monitoring Centre for Drugs and Drug Addiction report that stated these behaviors are more common in men [14]. Males were also associated with poor outcomes of treatment due to delayed and non-compliance treatment [15].

Comorbid is also not significantly associated with the treatment outcomes in our study. Behring found that HIV-positive patients were associated with poorer treatment outcomes and higher mortality. Bilateral disease and previous treatment for MDR-TB were almost twice as likely to result in poorer treatment outcomes [16]. Myemba found the overall mortality rate was 5.7 per 1000 MDR-TB patients. A higher mortality rate was associated with being ≥45 years, female, on a short anti-TB regimen, HIV co-infected, on concomitant long-term medication use, and having other co-morbidities [8]. Other studies found the proportion of deaths was much higher among HIV-infected patients (19.0% vs. 5.0%). Treatment success did not differ by HIV status among survivors. Fluoroquinolone resistance was the main cause of failure, while resistance to PZA, ethionamide, or EMB did not influence bacteriological outcomes [6]. Of 2,269 MDR and XDR-TB patients in Brazil, the proportion of unfavorable outcomes was 41.9% among MDR-TB and 81.5% among XDR-TB. Having less than 8 years of schooling, being an Afro-Brazilian, being under 40 years old, and drug user was associated with unfavorable outcomes and default. Bilateral disease, HIV positive, and comorbidities were associated with death. XDR-TB cases had 4.7-fold higher odds of an unfavorable outcome [16].

A study by du Cros in Uzbekistan of 128 MDR-TB patients, 67 female (52.3%), median age 30.1 (interquartile range 23.8–44.4) years. At the end of treatment, 71.9% (92 out of 128) of patients achieved treatment success, with 68% achieving recurrence-free cure at 1 year following completion. Unsuccessful outcomes during treatment included 22 (17.2%) treatment failures with fluoroquinolone-resistance amplification in 8 patients (8 out of 22, 36.4%); 12 (9.4%) lost to follow-up; and 2 (1.5%) deaths. Recurrence occurred in one patient. Fourteen patients (10.9%) experienced serious adverse events. Baseline resistance to both pyrazinamide and ethambutol (adjusted OR 6.13, 95% CI 2.01; 18.63) and adherence <95% (adjusted OR 5.33, 95% CI 1.73; 16.36) were associated with unsuccessful outcomes in multivariable logistic regression [17]. Khan's study, 669 out of 796 MDR-TB patients treated with STR were successfully treated (83.0%, 95% CI 71.9–90.3%). In IPD meta-regression (three studies, n=497), failure/relapse was associated with fluoroquinolone resistance (crude OR 46, 95% CI 8–273), pyrazinamide resistance (OR 8, 95% CI 2–38) and no culture conversion by month 2 of treatment (OR 7, 95% CI 3–202) [18].

Samuel conducted a systematic review and meta-analysis to examine the effect of human immunodeficiency virus (HIV), diabetes, chronic kidney disease (CKD), alcohol misuse, and smoking on MDR/XDRTB treatment outcomes. In this systematic review and meta-analysis, alcohol misuse and HIV were associated with higher pooled OR of an unsuccessful outcome in MDR/XDR-TB treatment [19].

In this research, the patient cure rate was 47.7%, the treatment drop-out rate was 34.8%, and the treatment failure rate was 6.6%, 11.2% death, and the factor associated with success treatment outcome is the age of the patients. Adherence interventions are needed to reduce the number of deaths and loss to follow-up MDR-TB cases. Regular evaluation of treatment regimens and treatment administration options can be substantial in reducing unfavorable treatment outcomes.

Before this study, there was a study by Manurung et al that also reported in 2016 that the success rate of drug-resistant TB treatment in H. Adam Malik Hospital from 2012-2015 was 48%. The study reports that age and resistance pattern prove to influence the success of drug-resistant TB treatment ($p<0.05\%$), while gender, comorbidity, and conversion time did not significantly ($p>0.05$) [20].

The strength of this study is that it uses the shorter-term regimen drug, while a same earlier study by Manurung et al in 2016 at Adam Malik General Hospital used the older regimen of drug that has been left out. This study

has some limitations. The major limitation was being the retrospective cohort study design caused the use of secondary data, so we could not access the full factors for treatment outcomes like patient data on sociodemographics, smoking, alcohol consumption, and other behaviors. Our study also did not analyze clinical factors such as sputum culture, drug sensitivity test, and manifestation of Chest X-ray with treatment outcome.

5. Conclusions

There is a significant association between age and treatment outcome ($p<0.05\%$) but there is no significant association between gender and comorbidity with treatment outcome. A prospective cohort study is needed to investigate other potential causes of unfavorable outcomes.

References

[1]. World Health Organization. World Health Organization. Geneva; 2020. Global Tuberculosis Report 2020. Available from: https://www.who.int/publications/i/item/9789240013131

[2]. World Health Organization. The Joint External TB Monitoring Mission (JEMM TB) [Internet]. Jakarta; 2017 [cited 2021 Dec 20]. Available from: https://www.who.int/docs/default-source/searo/indonesia/non-who/2017-joint-external-tb-monitoring-system-indonesia.pdf?sfvrsn=a10eb522_2

[3]. Indarti, Tri H, Krtistin E, Soedarsono S, Endarti D. Treatment Outcomes of Multidrug-Resistant Tuberculosis Patients in East Java, Indonesia. Int J Mycobacteriol [Internet]. 2022;11(3):261–7. Available from: https://pubmed.ncbi.nlm.nih.gov/36260444/

[4]. WHO. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis [Internet]. World Health Organization. Geneva: World Health Organization; 2014. 1–446 p. Available from: http://apps.who.int/iris/bitstream/10665/75146/1/9789241548441_eng.pdf

[5]. Trubnikov A, Hovhannesyan A, Akopyan K, Ciobanu A, Sadirova D, Kalandarova L, et al. Effectiveness and safety of a shorter treatment regimen in a setting with a high burden of multidrug-resistant tuberculosis. Int J Environ Res Public Health. 2021;18(8):4121. Available from: https://doi.org/10.3390/ijerph18084121

[6]. Trébucq A, Schwoebel V, Kashongwe Z, Bakayoko A, Kuaban C, Noeske J, et al. Treatment outcome with a short multidrug-resistant tuberculosis regimen in nine African countries. Int J Tuberc Lung Dis. 2018;22(1):17–25. Available from: https://doi.org/10.5588/ijtld.17.0498

[7]. Ciza F, Gils T, Sawadogo M, Decroo T, Roggi A, Piubello A, et al. Course of adverse events during short treatment regimen in patients with rifampicin-resistant tuberculosis in Burundi. J Clin Med. 2020;9(6):1–15. Available from: https://doi.org/10.3390/jcm9061873

[8]. Myemba DT, Bwire GM, Sambayi G, Maganda BA, Njiro BJ, Ndumwa HP, et al. Clinical characteristics and treatment outcomes of patients with MDR tuberculosis in Dar Es Salaam region, Tanzania. JAC-Antimicrobial Resist. 2020;2(4):1–8. Available from: https://doi.org/10.1093/jacamr/dlaa108

[9]. Byng-Maddick R, Noursadeghi M. Does tuberculosis threaten our aging populations? BMC Infect Dis [Internet]. 2016;16(119):1–5. Available from: http://dx.doi.org/10.1186/s12879-016-1451-0

[10]. Schaaf HS, Collins A, Bekker A, Davies PDO. Tuberculosis at extremes of age. Respirology. 2010;15(5):747–63. Available from: https://doi.org/10.1111/j.1440-1843.2010.01784

[11]. Rajagopalan S. Tuberculosis and aging: A global health problem. Clin Infect Dis. 2001;33(7):1034–9. Available from: https://doi.org/10.1086/322671

[12]. Soeroto AY, Nurhayati RD, Purwiga A, Lestari BW, Pratiwi C, Santoso P, et al. Factors associated with treatment outcome of MDR/RR-TB patients treated with shorter injectable based regimen in West Java Indonesia. PLoS One. 2022;20(49):1–13. Available from: http://dx.doi.org/10.1371/journal.pone.0263304

[13]. Karo B, Hauer B, Hollo V, Van der Werf MJ, Fiebig L, Haas W. Tuberculosis treatment outcome in the European Union and European economic area: An analysis of surveillance data from 2002–2011. Eurosurveillance. 2015;20(49):1–10. Available from: https://doi.org/10.2807/1560-7917.ES.2015.20.49.30087

[14]. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). A gender perspective on drug use and responding to drug problems. Belgium; 2006. Available from: https://www.euda.europa.eu/html.cfm/index34880EN.html_en

[15]. Nair D, Valeyutham B, Kannan T, Tripathy JP, Harries AD, Natrajan M, et al. Predictors of unfavorable treatment outcome in patients with multidrug-resistant tuberculosis in India. Public Heal Action. 2017;7(1):32–8. Available from: https://doi.org/10.5588/pha.16.0055

[16]. Bhering M, Duarte R, Kritski A. Predictive factors for unfavorable treatment in MDR-TB and XDR-TB patients in Rio de Janeiro State, Brazil, 2000-2016. PLOS ONE. 2019;14(11):1–14. Available from: https://doi.org/10.1371/journal.pone.0218299

[17]. du Cros P, Khamraev A, Tigay Z, Abdrasuliev T, Greig J, Cooke G, et al. Outcomes with a shorter multidrug-resistant tuberculosis regimen from Karakalpakstan, Uzbekistan. ERJ Open Res. 2021;7(1):1–12. Available from: http://dx.doi.org/10.1183/23120541.00537-2020

[18]. Khan FA, Salim MAH, du Cros P, Casas EC, Khamraev A, Sikhondze W, et al. Effectiveness and safety of standardized shorter regimens for multidrug-resistant tuberculosis: Individual patient data and aggregate data meta-analyses. Eur Respir J. 2017;50(1):1–13. Available from: http://dx.doi.org/10.1183/13993003.00061-2017

[19]. Samuels JP, Sood A, Campbell JR, Ahmad Khan F, Johnston JC. Comorbidities and treatment outcomes in multidrug-resistant tuberculosis: A systematic review and meta-analysis. Sci Rep. 2018;8(1):1–13. Available from: http://dx.doi.org/10.1038/s41598-018-23344-z

[20]. Manurung MPF, Siagian P, Sinaga BYM, Mutiara E. Factors related to successful treatment of drug-resistance tuberculosis in H. Adam Malik hospital, Medan, Indonesia. In: IOP Conf Series: Earth and Environmental Science. 2018. p. 1–6. Available from: https://doi:10.1088/1755-1315/125/1/012148 - 023-07678-7