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Adverse treatment outcomes in multidrug resistant tuberculosis are beyond the microbe drug interaction: results of a multiple correspondence analysis

Desenlaces adversos en el tratamiento para tuberculosis multi-fármaco resistente sobrepasan la relación fármaco-microorganismo: resultados de un análisis de correspondencia múltiple

Treatment outcomes in MDR-TB patients

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Introduction: Multidrug-resistant tuberculosis treatment is effective in 50% of patients, due to several factors including the antibiotic susceptibility of the microorganism, adverse treatment reactions, social factors, and associated comorbidities.

Objectives: Here we describe the demographics, clinical characteristics, and factors associated with treatment outcomes in multidrug-resistant tuberculosis (MDR-TB) patients in Medellín, Colombia.

Materials and methods: A retrospective analysis was performed of data from patients diagnosed with MDR-TB attending Hospital La María in Medellin-Colombia, who were treated between 2010-2015. Patients were categorized as having a successful (cured) or poor (failure, lost to follow-up, and death) treatment outcome. Associations between demographic, clinical factors, laboratory results, treatment outcomes, and follow-up information were evaluated by univariate, multivariate and multiple correspondence analyses (MCA).

Results: 128 patients with MDR-TB, 77 (60%) had successful outcomes. Of those with poor outcomes, 26 were lost to follow-up, 15 died, and 10 were treatment failures. Irregular treatment, the presence of comorbidities, and positive cultures beyond >2 months of treatment were associated with poor outcomes compared to successful outcomes ($p<0.05$ for all). MCA grouped patients lost to follow-up with HIV and drug addiction, and patients with treatment failure with irregular treatment and chronic obstructive pulmonary disease.

Conclusion: the recognition of factors affecting treatment outcomes is essential and was associated with treatment outcomes in this series of patients. Early

identification of these factors should increase the rates of treatment success and contribute to MDR-TB control.

Keywords: Tuberculosis, multidrug-resistant; extensively drug-resistant tuberculosis; treatment outcome.

Introducción. El tratamiento de la tuberculosis multi-fármaco resistente tiene una efectividad del 50%, asociado con múltiples factores como la susceptibilidad del microorganismo, las reacciones adversas, los factores sociales y las comorbilidades.

Objetivo. Describir la demografía, las características clínicas y los factores pronósticos asociados con el desenlace de tratamiento en pacientes multi-fármacoresistente (TB-MDR) en Medellín, Colombia.

Materiales y métodos. Se realizó un análisis retrospectivo de los datos de pacientes con TB-MDR atendidos en el Hospital La María de Medellín, Colombia que fueron tratados entre 2010 y 2015. Los pacientes se categorizaron con tratamiento exitoso (curados) o con tratamiento fallido (falla en el tratamiento, perdida durante seguimiento y muerte). Se determinó la asociación entre características demográficas y clínicas, resultados de laboratorio, desenlaces en el tratamiento e información de seguimiento utilizando análisis univariado, multivariado y de correspondencia múltiple (ACM).

Resultados. De 128 pacientes con TB-MDR, 77 (60%) tuvieron un tratamiento exitoso. De los que tuvieron un tratamiento fallido, 26 pacientes se perdieron en el seguimiento, 15 murieron y 10 tuvieron falla en el tratamiento. Tratamiento irregular, comorbilidades y cultivos positivos más allá de 2 meses de tratamiento se asociaron significativamente con tratamientos fallidos ($p<0.05$). ACM agrupó los pacientes con pérdida en el seguimiento, con VIH y tratamientos irregulares. Los pacientes con tratamientos irregulares y enfermedad pulmonar obstructiva crónica con falla en el tratamiento y muerte.

Conclusión. El reconocimiento temprano de factores que afectan el desenlace de tratamiento en pacientes con TB-MDR es esencial, la identificación de esos factores debe incrementar el éxito del tratamiento y contribuir al adecuado control de la TB-MDR.

Palabras clave: tuberculosis resistente a múltiples medicamentos; tuberculosis extensivamente resistente a drogas; resultado del tratamiento.

Multidrug-resistant tuberculosis (MDR-TB) continues to be an obstacle to disease control. It has been estimated that, globally, 4.1% of new TB cases and 19% of previously treated cases have MDR-TB. In other words, there are 490.000 new MDR-TB cases worldwide. Also, 6.2% of MDR-TB cases are extensively drug-resistant (XDR) (1).

Colombia with a population of 45.5 million, reported 13.870 TB cases in 2017, 420 cases were reported as drug-resistant, 108 as MDR-TB, of them 2.4% were new cases and 14% were previously treated (2). According to the national TB program, 32 XDR-TB cases have been diagnosed in the country to date (3). The Department of Antioquia reported a fifth of the national MDR-TB cases and half of these cases were reported in Medellin; the capital city (4).

MDR-TB cases pose problems for TB control programs: expensive treatment, longer duration of treatment and lesser efficacy. Also, this treatment is associated with more adverse effects than the one required for a regular TB patient. Adverse effects, in turn, are accompanied by drug availability constraints, lack of treatment compliance, and administrative barriers for delivering and treatment follow-up (5). In this context, the global treatment cure rate for MDR-TB is 54%, which is mostly affected by mortality and lack of follow up. For XDR-TB, only 30% of patients completed successful treatment in the 2014 cohort reported from 138 countries (1).

From 2000 onwards, the World Health Organization (WHO) and the Stop TB Partnership provided support to countries for MDR-TB management through the Green Light Committee (GLC). This initiative was created to evaluate, lend

guidance, and facilitate access of TB control programs to second-line drugs at reduced price with an assured quality (5).

In Colombia, a program for MDR-TB treatment was initiated to improve the management of these patients with second-line antituberculosis drugs. It was supported by GLC and the national TB program (a public-private alliance formed by Dirección Seccional de Salud, Secretaría de Salud de Medellin, Hospital La María, Corporación para Investigaciones Biológicas, Liga Antituberculosa de Antioquia, and Fundación Red de Apoyo Social RASA). This program was located in Medellin and started in 2010. In this study, we describe the demographics, clinical characteristics, and prognostic factors associated with treatment outcomes in these MDR-TB patients. Due to the lack of published studies on treatment results of patients with MDR-TB in the country, this study describes a cohort of patients treated for MDR-TB and analyze the socio-demographic factors associated with their outcomes.

Materials and methods

A descriptive retrospective study was done based on data on diagnosis, treatment, and outcomes of MDR-TB patients enrolled in a national program for improving MDR-TB treatment and management. It included 146 patients diagnosed with MDR-TB at Hospital La María in Medellin, who started and received treatment from November 2010 to June 2015. Data from 128 patients were finally included in the analysis, their final treatment outcome defined as follows: patients with a successful treatment were those cured by microbiological and clinical parameters, and patients with a poor treatment outcome included those who failed treatment,

those who died (associated with TB condition) and those that were lost to follow-up (6).

Patients included in the program were previously diagnosed with MDR-TB using a molecular test GenoType MTBDR*plus* (Hain Life science GmbH, Nehren, Germany) at the Regional Public Health Laboratory. After diagnosis and before starting treatment, a new sputum sample was processed using a decontamination procedure standard method (7). From the digested sputum a direct smear was stained with auramine-rhodamine, in addition, 0.1 mL and 0.5 mL were inoculated in Löwenstein-Jensen medium (L-J) and in a mycobacterial growth indicator tube (MGIT) respectively (Becton, Dickinson, and Company, Sparks, MD, USA). In cultures identified as positive, a smear stained by Kinyoun was performed and subcultured on thin layer agar (TLA). Final identification of *Mycobacterium tuberculosis* (MTB) was based on inhibition of MTB complex growth by *p*-nitrobenzoic acid in TLA and a standard phenotypic test; resistance to isoniazid and rifampin was also confirmed using TLA (8).

Seventy-nine MDR-TB isolates were tested for susceptibility to second-line drugs using the BD Bactec MGIT 960 system (9). Drug stock concentrations were prepared following standard recommendations (10,11). Patients were started on standard treatment (12), with kanamycin, levofloxacin, cycloserine, pyrazinamide, and ethionamide, for 18 to 24 months. A clinical and laboratory follow-up was done monthly, as well as an audiometry test at three months and at the end of the administration of injectable medication, thorax PA and lateral X-ray were performed every six months. Changes in treatment were done due to drug intolerance, drug

resistance or the presence of serious adverse effects. Alternative drugs used were *p*-aminosalicylic acid, ethambutol, moxifloxacin, amoxicillin-clavulanate, and linezolid.

Demographic characteristics, clinical results, laboratory results, treatment outcomes, and follow-up information were collected from each patient´s clinical record. A data collection form was used to extract data from medical records. All data were entered into a Microsoft Excel database. To identify differences in means, Student´s t-test or Mann-Whitney U test was used. Odds Ratio (OR), and their 95% confidence intervals (CI) were calculated. A *p*-value of less than 0.05 defined significant differences. Variables with a $p < 0.05$ were used in a logistic regression model to adjust independent factors associated with treatment outcome. We performed a multiple correspondence analysis (MCA) to evaluate the relationships among treatment outcomes and patient's baseline conditions; human immunodeficiency virus (HIV) infection, drug addiction, irregular treatment (as evidenced by failing to finish treatment or intermittent treatment without completion of a full treatment scheme), Chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM) and undernourishment. This analysis considers the level of significance (weight) of each factor, to explain total sample variability (inertia). All analyses were performed using EPIDAT 3.1 and STATA 11.0.

The study was done under national public health law as part of a pilot program for MDR-TB treatment supported by GLC and the national TB program, as such no additional ethical approval was necessary. Individual participants gave written informed consent before starting treatment according to country regulations, and

institutional consent was obtained for record review. All patient information was anonymized before analysis.

Results

Data from 128 patients treated for MDR-TB and with a treatment outcome were analyzed. The patients had a mean age of 40 years, and 69% (n = 88) were male. Among the 128 patients, 51 (40%) had an irregular treatment for MDR-TB (41 with poor adherence, seven due to problems in drug supply and three with booth causes concomitantly) and 112 (88%) had risk factors for MDR before being treated for MDR-TB; of these patients, 49 (44%) received irregular previous anti-tuberculosis treatment, 46 (41%) regular previous anti-tuberculosis treatment, and 17 (15%) had contact with a TB patient. A variety of adverse effects were found in these patients; more common were diarrhea (three patients), vomitus (4 patients), hypoacusis (13 patients), and gastritis (15 patients). Thoracic surgery was performed in eight patients (6%), and six of them had a successful outcome. The type of surgery practiced was upper lobectomy in four patients, upper bilobectomy in one, and pneumonectomy in three. Forty-eight percent of patients had an associated comorbidity: drug addiction (n = 18; 14%), DM (n = 16; 13%), HIV co-infection (n = 14; 11%), COPD or undernourished (n = 10; 8% each), and other comorbidities (n = 16; 13%). A total of 77 (60%) MDR-TB patients had successful treatment outcomes, 26 (20%) were lost to follow-up, 15 (12%) died, and 10 (8%) had a failure during treatment (table 1 and figure 1).

In the univariate analysis, irregular treatment and presence of comorbidities had a significant association with poor outcome (OR: 5.14; $p<0.001$ and 4.05; $p<0.001$,

respectively), as well as drug addiction and HIV infection (OR: 4.92; *p*=0.005 and 4.45; *p*=0.017, respectively). Patients with poor outcome took more than two months to achieve microbiological sterilization (OR: 1.26; *p*<0.026) (table 2). Sixty-five patients (85%) with a successful outcome had negative cultures at two months in contrast with 30 patients (60%) with poor outcomes (p= 0.0015). In particular, the subgroup of patients with DM needed more than two months for negative culture conversion compared with those who did not have DM (*p*=0.028). Nine patients with DM had a successful outcome, and seven had poor outcomes; of these seven patients, four patients died, two had treatment failure, and one was lost to follow-up.

Using a forward selection stepwise logistic regression model, we identified two factors associated with poor outcome: previous irregular treatment (OR: 9.38, 95% CI: 2.30-38.2, *p*=0.002) and time (months) of positive culture after treatment initiation (OR: 1.85, 95% CI: 1.29-2,64, *p*=0.001). Time of TB treatment for 18 months was associated with a successful outcome (OR: 0.79, 95% CI: 0.73-0.85, *p*=0.001) (table 2).

Out of 128 patients, 79 (62%) had a susceptibility test for second-line drugs. Of these, 9 (11%) showed resistance exclusively to isoniazid and rifampicin. Seventy patients (89%) showed additional resistance to one or more second-line drugs, 54 (68%) were resistant to ethionamide, 49 (62%) were resistant to pyrazinamide, and 12 (15%) were resistant to both drugs concomitantly. We found a pre-XDR-TB condition in 12 (15%) patients, and five patients had developed XDR-TB; four of them died including one diabetic patient who had XDR-TB since his admission. All

XDR-TB patients had a positive culture at the time of death or loss to follow-up. Seventy-seven patients completed successful treatment; 68 of them received cycloserine, 60 received levofloxacin, and 53 patients received kanamycin. Due to resistance to ethionamide or to pyrazinamide, or cycloserine adverse effects, scheme changes were necessary; 13 patients received linezolid, 41 amoxicillin/clavulanate, and 2 XDR-TB patients received imipenem.

Four groups were identified using the MCA analysis (Figure 2). The first group (a) comprised patients that were lost to follow up; these patients' associated baseline conditions were HIV infection and drug addiction. The second group (b) included patients that died or presented a treatment failure; this group showed an association with irregular previous treatment and COPD. The third group (c) comprised patients with diabetes and undernourished; those patients were not directly associated with any of the outcome categories defined in this study. Finally, the fourth group (d) contained patients with a successful outcome; this group was not associated with any baseline conditions analyzed in this study (Figure 2).

Discussion

In this study, 60% of 128 MDR-TB patients had a successful outcome. Overall, treatment outcomes for this population are consistent with previously reported outcomes. In a systematic review of 26 trials with a total of 4959 MDR-TB patients, 62% of patients met the definition of successful treatment (13). The 60% treatment success rate for our population was higher than the 54% reported worldwide by WHO (1), but it is less than 86% success rate achieved by individualized MDR-TB treatment published by *Bolhuis et al.* (14). In the present study, 26 (20%) patients

were lost to follow-up, and seven of these re-initiated their treatment until completion. WHO reported a global rate for lost to follow-up of 15% (1). The MCA analysis in the present study showed that loss to follow-up is a poor treatment outcome associated with HIV infection and drug addiction. One study in Africa reported that 56% of HIV patients were lost to follow-up during MDR-TB treatment, suggesting that better patient tracking activities, an improved understanding of the reasons that generate loss to follow-up outcomes and an earlier initiation of antiretroviral therapy are needed to improve treatment completion (15). In Georgia, drug addiction was reported to be significantly associated with a higher risk of loss to follow-up (16). For our study, the non-inclusion of patients lost to follow-up in the analysis would increase the success of the treatment rate from 60% (77/128) to 75% (77/102). MCA analysis also identified poor treatment outcomes associated with COPD and previous irregular treatment. Several studies have associated COPD (17) and previous treatment as independent predictors of death in MDR-TB patients (18) or poor treatment outcomes (19).

Surgery has been recommended for the treatment of patients with MDR-TB who do not respond to drug treatment, and have a persistent cavitary well-localized lesion, an adequate respiratory function, and when not enough active drugs are available to design a curative scheme (20). In our study, eight patients underwent lung resection surgery, and six of them had successful outcomes. A systematic review and meta-analysis done with data from 24 studies revealed a significant association between surgical intervention and successful treatment compared to non-surgical intervention (OR 2.24, 95%CI 1.68–2.97) (21).

Sputum smear and culture are direct indicators of bacteriological load, the patient's infectious status, and ultimately the success of treatment. Conversion of initial sputum culture in the first three months is essential to label the patient as non-infectious, which in turn is an important indicator to determine whether or not it is necessary to extend the time of treatment (22). In this study, most patients with a successful outcome (85%) had a sputum culture negative conversion at two months, while 60% of patients with a poorer outcome had negative cultures in the same period of time. This is consistent with studies in which sputum culture conversion within two months was considered as a marker of a successful outcome in HIV negative patients (23). In our study, patients with DM needed more than two months for negative culture conversion compared with those who did not have DM (*p*=0,028). This finding suggests that in addition to optimal control of DM, it would be necessary to extend the recommended duration of treatment in order to avoid treatment failure, relapses, and deaths. This situation should be addressed when considering the use of a new standardized shorter treatment regimen for patients with MDR-TB (24).

Despite effective anti-tuberculosis chemotherapy, case-fatality rates up to 25% have been described in patients with MDR-TB in both industrialized and resource-poor settings (25). In our study, 16% of MDR-TB patients died, and four of these patients had XDR-TB. The cause of the increased death risk in patients with MDR-TB is diverse, commonly associated with HIV infection, DM, and particular lifestyles including alcohol abuse, smoking, and illicit drugs use (25). Among 20 patients in

our study who died while on anti-tuberculosis treatment, 17 had comorbidities, mainly HIV, DM, and illicit drugs use.

A common characteristic of isolates from patients in our study was the increased resistance to pyrazinamide (62%) and ethionamide (68%). A systematic review and meta-analysis found that 61% of patients with confirmed MDR-TB have pyrazinamide resistance (26). Ethionamide resistance was found in 13% to 87% of MDR-TB patients according to the world region (27,28). Other studies in Medellin reported that 33% of MDR isolates have cross-resistance between isoniazid and ethionamide, suggesting the need to confirm the susceptibility to ETH and PZA before considering their use in the treatment of MDR-TB patients (29). In this study, 8% of MDR-TB isolates became XDR during treatment or were XDR-TB at the beginning of it. These patients had high mortality (66%), which is similar to that reported in other studies, and were associated with DM, malnutrition, and drug addiction (30).

We could not assess a clear relationship between the MDR-TB treatment scheme and its outcome due to the variability of schemes used prompted by drugs availability, adverse reactions, and initial drug resistance which is a limitation of the study. Despite a moderate treatment success obtained in this cohort, a flaw to integrate medical, nutritionist, psychologist, and social work care, needed for the integral management of patients, was observed. Nevertheless, this program served the purpose of increasing the availability of second-line drugs needed for the proper management of MDR-TB patients.

In conclusion, early recognition of factors that can influence the treatment outcomes is essential for the successful treatment of patients with MDR-TB. Knowing these factors will help to focus on the care of these patients and should become a high priority in a TB program. The interdisciplinary attention to the patient, besides an expert medical management and the support of an experienced laboratory, should take care of nutritional patient status, comorbid conditions, and social and psychological factors that affect the final success of treatment. In the quest for better drugs and treatment schemes for MDR-TB, it is also essential to pay attention to factors beyond the interaction microbe-drug, to improve the beneficial impact of new developments in the treatment of these patients and the future of MDR-TB control.

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Conflict of interest

Conflict of interest: none.

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References

1. **World Health Organization.** Global tuberculosis report – 2012. Fecha de consulta: 5 diciembre de 2018. Disponible en:

https://apps.who.int/iris/handle/10665/75938

2. **World Health Organization.** Global tuberculosis report – 2017. Fecha de consulta: 8 de noviembre de 2018. Disponible en: https://www.who.int/tb/publications/global_report/gtbr2017_main_text.pdf

3. **Lucía M, Martínez O, Enrique M, Duran M, Pacheco García OE, Bonilla HQ, *et al.*** Protocolo de vigilancia en salud publica tuberculosis – 2016. Fecha de consulta: 12 de noviembre de 2018. Disponible en: http://www.saludpereira.gov.co/medios/Tuberculosis_PROTOCOLO_farmacoresistente2016.pdf

4. **Secretaria de Salud y Protección Social de Antioquia.** Situación de la tuberculosis en el departamento de Antioquia 2015 - 2016. Boletín Información para la Acción – 2017. Fecha de consulta: 5 de octubre de 2018. Disponible en: https://www.dssa.gov.co/images/Bia_%20Tuberculosis_Mayo2017.pdf

5. **Gupta R, Cegielski JP, Espinal MA, Henkens M, Kim JY, Lee JW,** *et al*. Increasing transparency in partnerships for health--introducing the Green Light Committee. Trop Med Int Health. 2002;7:970-6. https://doi.org/10.1046/j.1365-3156.2002.00960.x

6. **World Health Organization.** Definitions and reporting framework for tuberculosis 2013 revision – 2014. Fecha de consulta: 11 de julio de 2018. Disponible en: https://www.who.int/tb/publications/definitions/en/

7. **Pfyffer GE, Palicova F.** *Mycobacterium*: General Characteristics, Laboratory Detection, and Staining Procedures. Manual of Clinical Microbiology, 10th

Edition. Washington, D.C.: American Society of Microbiology; 2011. p. 472-502.

8. **Robledo J, Mejia GI, Paniagua L, Martin A, Guzmán A.** Rapid detection of rifampicin and isoniazid resistance in Mycobacterium tuberculosis by the direct thin-layer agar method. Int J Tuberc Lung Dis. 2008;12:1482-4.

9. **Rodrigues C, Jani J, Shenai S, Thakkar P, Siddiqi S, Mehta A.** Drug susceptibility testing of Mycobacterium tuberculosis against second-line drugs using the Bactec MGIT 960 System. Int J Tuberc Lung Dis. 2008;12:1449-55.

10. **Clinical and Laboratory Standards Institute.** M24-A2 Susceptibility Testing of Mycobacteria, Nocardiae, and Other Aerobic Actinomycetes. 2nd edition. Wayne (PA): Clinical and Laboratory Standards Institute; 2011.

11. **Rusch-Gerdes S, Pfyffer GE, Casal M, Chadwick M, Siddiqi S.** Multicenter Laboratory Validation of the BACTEC MGIT 960 Technique for Testing Susceptibilities of Mycobacterium tuberculosis to Classical Second-Line Drugs and Newer Antimicrobials. J Clin Microbiol. 2006;44:688–92. https://doi.org/10.1128/JCM.44.3.688-692.2006

12. **Instituto Nacional de Salud.** Lineamientos para el manejo programático de los pacientes con tuberculosis farmacorresistente – 2013. Fecha de consulta: 15 de julio de 2018]. Disponible en: https://www.minsalud.gov.co/sites/rid/Lists/BibliotecaDigital/RIDE/VS/PP/ET/lineamientos-tb-farmacorresistente.pdf

13. **Johnston JC, Shahidi NC, Sadatsafavi M, Fitzgerald JM.** Treatment

outcomes of multidrug-resistant tuberculosis: a systematic review and meta-analysis. PLoS One. 2009;4:e6914. https://doi.org/10.1371/journal.pone.0006914

14. **Bolhuis MS, Akkerman OW, Sturkenboom MG, de Lange WC, van der Werf TS, Alffenaar J-WC**. Individualized treatment of multidrug-resistant tuberculosis using therapeutic drug monitoring. Int J Mycobacteriol. 2016;5:S44-5. https://doi.org/10.1016/j.ijmyco.2016.07.003
15. **Fox MP, Rosen S.** Patient retention in antiretroviral therapy programs up to three years on treatment in sub-Saharan Africa, 2007-2009: systematic review. Trop Med Int Health. 2010;15:1-15. https://doi.org/10.1111/j.1365-3156.2010.02508.x
16. **Kuchukhidze G, Kumar AM, de Colombani P, Khogali M, Nanava U, Blumberg HM**, *et al*. Risk factors associated with loss to follow-up among multidrug-resistant tuberculosis patients in Georgia. Public Health Action. 2014;4:S41-6. https://doi.org/10.5588/pha.14.0048
17. **Surya PI, Davies FL, Bruchfeld J, Hak E, Alffenaar J-W.** Risk factors of multidrug-resistant tuberculosis: A global systematic review and meta-analysis. J Infect. 2018;77:469-78. https://doi.org/10.1016/j.jinf.2018.10.004
18. **Dheda K, Shean K, Zumla A, Badri M, Streicher EM, Page-Shipp L,** *et al*. Early treatment outcomes and HIV status of patients with extensively drug-resistant tuberculosis in South Africa: a retrospective cohort study. Lancet. 2010;375:1798-807. https://doi.org/10.1016/S0140-6736(10)60492-8
19. **Tang S, Tan S, Yao L, Li F, Li L, Guo X, *et al*.** Risk factors for poor

treatment outcomes in patients with MDR-TB and XDR-TB in China: retrospective multi-center investigation. PLoS One. 2013;8:e82943. https://doi.org/10.1371/journal.pone.0082943

20. **Caminero JA.** Treatment of multidrug-resistant tuberculosis: evidence and controversies. Int J Tuberc Lung Dis. 2006;10:829-37.
21. **Marrone MT, Venkataramanan V, Goodman M, Hill AC, Jereb JA, Mase SR.** Surgical interventions for drug-resistant tuberculosis: a systematic review and meta-analysis. Int J Tuberc Lung Dis. 2013;17:6-16.
22. **Jain K, Desai M, Solanki R, Dikshit RK.** Treatment outcome of standardized regimen in patients with multidrug-resistant tuberculosis. J Pharmacol Pharmacother. 2014;5:145-9. https://doi.org/10.4103/0976-500X.130062
23. **Kurbatova EV., Cegielski JP, Lienhardt C, Akksilp R, Bayona J, Becerra MC**, *et al*. Sputum culture conversion as a prognostic marker for end-of-treatment outcome in patients with multidrug-resistant tuberculosis: a secondary analysis of data from two observational cohort studies. Lancet Respir Med. 2015;3:201-9. https://doi.org/10.1016/S2213-2600(15)00036-3
24. **World Health Organization.** The shorter MDR-TB regimen – 2016. Fecha de consulta: 3 de diciembre de 2018. Disponible en: https://www.who.int/tb/Short_MDR_regimen_factsheet.pdf
25. **Waitt CJ, Squire SB.** A systematic review of risk factors for death in adults during and after tuberculosis treatment. Int J Tuberc Lung Dis. 2011;15:871-85. https://doi.org/10.5588/ijtld.10.0352

26. **Whitfield MG, Soeters HM, Warren RM, York T, Sampson SL, Streicher EM**, *et al*. A Global perspective on pyrazinamide resistance: systematic review and meta-analysis. PLoS One. 2015;10:e0133869. https://doi.org/10.1371/journal.pone.0133869

27. **Ghafoor T, Ikram A, Abbasi SA, Zaman G, Ayyub M, Palomino JC**, *et al*. Sensitivity pattern of second line anti-tuberculosis drugs against clinical isolates of multidrug-resistant *Mycobacterium tuberculosis*. J Coll Physicians Surg Pak. 2015;25:250-3.

28. **Simpson G, Coulter C, Weston J, Knight T, Carter R, Vincent S,** *et al*. Resistance patterns of multidrug-resistant tuberculosis in Western Province, Papua New Guinea. Int J Tuberc Lung Dis. 2011;15:551–2. https://doi.org/10.5588/ijtld.10.0347

29. **Rueda J, Realpe T, Mejia GI, Zapata E, Rozo JC, Ferro BE,** *et al*. Genotypic analysis of genes associated with independent resistance and cross-resistance to isoniazid and ethionamide in *Mycobacterium tuberculosis* clinical isolates. Antimicrob Agents Chemother. 2015;59:7805-10. https://doi.org/10.1128/AAC.01028-15

30. **Pietersen E, Ignatius E, Streicher EM, Mastrapa B, Padanilam X, Pooran A**, *et al*. Long-term outcomes of patients with extensively drug-resistant tuberculosis in South Africa: a cohort study. Lancet. 2014;383:1230-9. https://doi.org/10.1016/S0140-6736(13)62675-6

Table 1. Demographics, clinical characteristics, and treatment outcomes of 128 patients with multidrug-resistant tuberculosis

Characteristics	Patients n (%)
Total	128
Male	88 (69)
Age, years, median (range)	40 (16-80)
Time of treatment in months, median (range)	18 (1-28)
Time of positive culture in months, median (range)	1 (1-10)
Irregular treatment	
Yes	51 (40)
No	77 (60)
Risk factors for MDR-TB	
Yes †	112 (88)
No	16 (12)
Thoracic Surgery	
Yes	8 (6)
No	120 (94)
Co-morbidities	
HIV	14 (11)
Diabetes	16 (13)
Drug addiction	18 (14)
COPD	10 (8)
Undernourished	10 (8)
Other	16 (13)
Patient outcome	
Successful outcome	77 (60)
The lost to follow up	26 (20)
Failure *	10 (8)
Dead	15 (12)

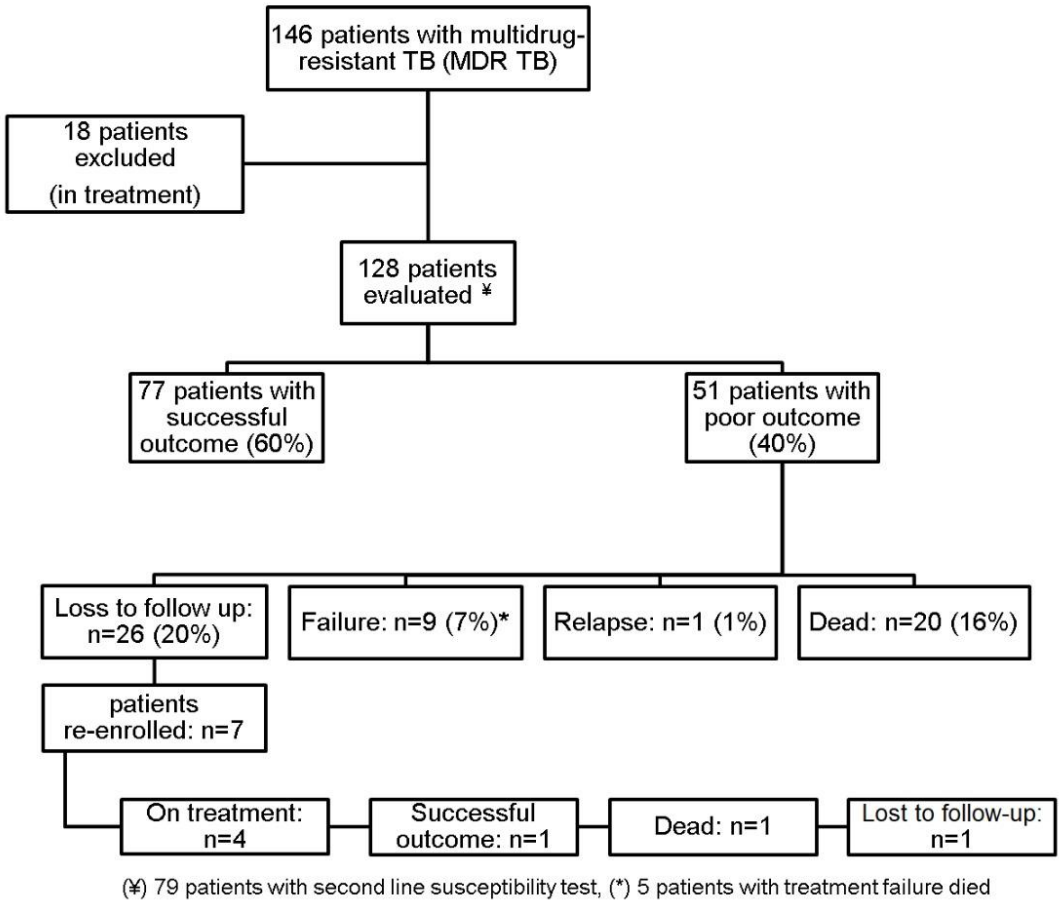
† The risk factors were irregular prior anti-tuberculosis treatment or regular prior anti-tuberculosis treatment and contact with a TB patient.
*Five patients died while receiving treatment.
MDR-TB: Multidrug-resistant tuberculosis
HIV: Human immunodeficiency virus
COPD: Chronic obstructive pulmonary disease

Table 2. Characteristics of 128 patients with multidrug-resistant tuberculosis and their association with treatment outcomes

Variable	Poor outcome (n=51)	Successful outcome (n=77)	Univariate		Multivariate	
			OR (IC 95%)	*p*	OR (IC 95%)	*p*
Age (years)*	41 (15)	40 (14)	1.00 (0.98-1.02)	0.737	-	
Sex (male)†	33 (65)	55 (71)	0.73 (0.34-1.56)	0.422	-	
Irregular treatment†	32 (63)	19 (25)	**5.14 (2.38-11.1)**	**>0.001***	**9.38 (2.30-38.2)**	**0.002***
Time of treatment (months)*	5 (12)	18 (2)	**0.79 (0.73-0.85)**	**>0.001***	**0.66 (0.57-0.77)**	**>0.001***
Risk factor of MDR†	46 (90)	66 (86)	1.53 (0.49-4.70)	0.455	-	
Co-morbidities†	35 (69)	27 (35)	**4.05 (1.90-8.61)**	**>0.001***	2.33 (0.88-5.65)	0.089
HIV†	10 (20)	4 (5)	**4.45 (1.31-15.1)**	**0.017***	3.26 (0.77-13.78)	0.108
Diabetes†	7 (14)	9 (12)	1.20 (0.41-3.46)	0.733	-	
Drug addiction†	13 (25)	5 (6)	**4.92 (1.63-14.8)**	**0.005***	1.56 (0.42-5.73)	0.089
COPD†	2 (4)	8 (10)	0.35 (0.07-1.73)	0.199	-	
Undernourished†	6 (12)	4 (5)	2.43 (0.65-9.09)	0.186	-	
Thoracic Surgery†	2 (4)	6 (8)	0.48 (0.09-2.49)	0.385	-	
Time of positive culture (months)*	2 (3)	1 (1)	**1.26 (1.02-1.56)**	**0.026***	**1.85 (1.29-2.64)**	**0.001***

[*] median (interquartile range); [†] Number (%).
(OR) Odds Ratio, (CI) 95% confidence interval, (**) statistically significant differences ($p < 0.05$).

Figure 1. Flow chart of analyzed patients with MDR-TB.



(¥) 79 patients with second line susceptibility test, (*) 5 patients with treatment failure died

Figure 2. Multiple correspondence analyses between treatment outcomes and patient's base line conditions

Based on the patient's baseline conditions the Multiple Correspondence Analysis (MCA) shows several patterns: (a) Lost of follow-up was associated with HIV infection and drug addiction. (b) Dead and treatment failure were associated with patients with irregular treatment and COPD. (c) Diabetes and undernourished were not directly associated with any of the outcome categories defined in this study. (d) The successful outcome was not associated with any of the patient's baseline conditions described in this study. The horizontal and vertical axes represent the first and second principal components.