A highly effective and inexpensive standardized treatment of multidrug- resistant tuberculosis: A muticenter prospective study in china

Wenwen Sun
Tongji University Affiliated Shanghai Pulmonary Hospital
Zheyuan Wu
Shanghai Municipal Center for Disease Control and Prevention
Zhou Ying
Shanghai Xuhui Central Hospital
Xia Fan
905th Hospital of PLA Navy
Qin Tang
Tongji University Affiliated Shanghai Pulmonary Hospital
Jie Wang
Tongji University Affiliated Shanghai Pulmonary Hospital
Jinhui Yang
Tongji University Affiliated Shanghai Pulmonary Hospital
Fangyou Yu
Tongji University Affiliated Shanghai Pulmonary Hospital
Hua Yang
Tongji University Affiliated Shanghai Pulmonary Hospital
Heping Xiao
Tongji University Affiliated Shanghai Pulmonary Hospital
Lin Fan (fanlinsj@163.com)
Tongji University Affiliated Shanghai Pulmonary Hospital https://orcid.org/0000-0002-9411-496X

Research article

Keywords: MDR-TB, treatment regimen, MIC, treatment outcome, adverse effects

Posted Date: April 1st, 2021

DOI: https://doi.org/10.21203/rs.3.rs-366277/v1

Version of Record: A version of this preprint was published at BMC Infectious Diseases on August 19th, 2021. See the published version at https://doi.org/10.1186/s12879-021-06553-2.

Abstract

Background

To verify the efficacy and safety of an inexpensive standardized treatment for multidrug-resistant tuberculosis (MDR-TB) based on minimum inhibitory concentration (MIC) drug sensitivity test(DST), a multicenter prospective study was conducted in eastern China.

Methods

Patients diagnosed as MDR-TB with isoniazid resistance at low concentration and rifampicin resistance, second-line/injectable agents sensitive) were prospectively enrolled, given the regimen of Ak Mfx(Lfx)CsPtoPaZ for six months followed by 12 months of Mfx(Lfx)CsPtoPaZ and followed up for treatment outcomes and adverse events (AEs).

Results

A total of 114 patients were enrolled into the study. The overall rate of favorable treatment rate was 79.8% (91/114), among 91 cases with favorable treatment, 86(75.4%)cured and 5 (4.4%) completed treatment. 23 cases got unfavorable outcome including 10 8.8% (10/114) failures, 8.8% (10/114) losing follow up ,0.9%(1/114) withdrawing treatment due to intolerance to drugs and 1.8%(2/114) died. Treatment favorable rate was significantly higher in newly treated MDR-TB (91.7%, 33/36) than that in retreated MDR-TB (74.4%, 58/78, p = 0.03). The investigators recorded 42 AEs occurrences in 30 of 114 patients□26.3%). Clinicians rated most AEs as mild or moderate (95.24%, 40/42) .

Conclusions

The regimen was proved to be effective, safe and inexpensive. It is suitable for specific drug resistant population, especially for newly-treated patients, which could be expected to be developed into a short-course regimen.

Clinical Trials Registration

China Clinical Trial Registry ChiCTR- OPC-16009380

Introduction

Multidrug-resistant tuberculosis (MDR-TB) is a major global health problem with treatment success rate less than 60% (1). The 2019 WHO consolidated guidelines recommended three kinds of therapeutic options(all-oral long/short or injection included)for countries and programs treating MDR-TB (1). However, varied status in different areas or countries resulted in varied outcomes, depending on different factors such as financial support, management, protocol, drug quality, newly included drugs, patient compliance and tolerance. Therefore, how to achieve the best treatment outcome for MDR-TB and ensure

its high safety has become the most important issue for clinicians. The all-oral regimen containing bedaquiline (BDQ) instead of injectable agent recommended in 2019 guideline (2) may be effective but difficult to be implemented in resource-poor areas due to its high price. It was pointed out that the explicit recommendations for the use of Linazolamide (LZD) and BDQ might bring some disadvantages to the global TB control program (3).MDR-TB treatment should be Ideally effective,less adverse events cheaply, easily available and drugs affordable (4).

According to the WHO 2019 report, the treatment coverage rate of MDR-TB in China was only 13.6% (1). Delayed DST, unaffordable treatment costs and adverse drug reactions were the main reasons (5). The WHO guideline in 2016 recommended a short-range regimen for patients without second-line drug resistance which had been proved to be effective in multiple countries, called “Bangladesh regimen” (6, 7). On the other hand, MDR-TB had multiple factors which can influence treatment outcome including, previous treatment history or resistance patterns (8). Therefore, we designed a treatment regimen similar to the regimen recommended by the 2016 WHO guidelines according to national conditions based on Drug sensitivity test (DST)results.

In the present study, a prospective clinical trial was conducted in a national TB specialist hospital in China to evaluate the safety and efficacy of a Pa containing regimen on patients with INH low resistance, Rifampin resistance and no second-line drug or injection resistance. We hope to explore a relatively inexpensive and effective regimen for MDR-TB patients with specific drug resistance pattern. The results of this study might provide a treatment model for MDR-TB in source limited areas with high TB burden-individualized stratified treatment on MDR-TB.

Methods

Study design

This study is an open-label, prospective cohort study. All patients received treatment for 18 months. They were followed up for at least one year after end of the course. The trial was mainly conducted at a national TB clinical treatment center with nearly 300 beds receiving referral of patients with MDR-TB from eastern China. In addition, the hospital is the only specialized hospital receiving MDR-TB in Shanghai and undertakes the region formulation and management collaborated with Center for Disease Control and Prevention CDC.

Study patients

From January 2017 to January 2018 we enrolled patients between 18 and 65 years diagnosed as MDR-TB confirmed by BACTEC MGIT 960 liquid culture MGIT 960 and Minimum Inhibitory Concentration MIC DST referred from 3 TB specialist hospitals and shanghai CDC.

Inclusion criteria were to include MDR-TB patients confirmed by MIC DST at least resistant to INH at low concentration and rifampicin (R) resistance within 2 months prior to screening; and patients had no

injectable agents or FQs resistance; patients previously only received first-line anti-TB treatment (ATT) or had no previous history of ATT or previous history of second-line ATT less than one month.

Excluded criteria were as follows: XDR-TB patients (resistant to both flquinolones and second-line injection drugs) or pre-XDR (resistant to either flquinolones or second-line injection drugs); patients had poor compliance to any drugs within the regimens; any serious systemic disease or disease of the immune system; coexisted with extrapulmonary tuberculosis; co-infected with HIV and other virus, taking immunosuppressive agents; history of flquinolone use for more than one month in the recent 6 months; pregnant.

We defined the newly diagnosis of MDR-TB as having never been treated for TB or less than one month of treatment history (9); Re-treated cases were defined as registered MDR-TB patients who had previously taken first-line anti-TB drugs for more than one month at the time of history inquiry; or if there is sufficient documentary evidence of having been treated with first-line anti-TB drugs for one month or more in the past.(10)

Inclusion and intervention

Patients satisfied with included criteria were administered by the regimen including Amikacin (Ak), Fluoroquinolones（FQs）, Cycloserine(Cs), Protionamide (Pto), Pyrazinamide (PZA) and Pasiniazine (Pa) for six months with injectable Ak followed by 12 months of oral FQs, Cs, Pto, PZA and Pa.

All patients were screened within one week of receiving the first dose and administered under directly observed therapy (DOT) throughout the treatment course. During the course of treatment, patients were visited by the same specialist every two weeks until the end of the course. Visits were made every 3 months after completion of treatment until 12 months after completion of treatment.

Microbiological assessment

Sputum/bronchoalveolar lavage samples were collected for smear microscopy and MTB culture at the following times: at baseline; Follow-up was followed up at 1, 2, and 3 months, and then once every 3 months until the end of the course.

All MTB positive isolates were transferred to the TB basic laboratory for the determination of MIC were 1μg/mL for Pa , 5μg/mL for Ak（1μg/mL for Rifampicin（R）, 0.2 μg/mL for INH, 0.5μg/mL for Mfx and 1μg/mL for Lfx,.

Treatment efficacy evaluation

Treatment outcomes for MDR-TB were evaluated according to WHO guidelines (11). The patients were examined by Chest CT imaging every three months and sputum culture once a month during the treatment period.

The treatment outcomes were divided into “cured”、“completed treatment”、“failure”、“default”and “death”. The “cured” was referred as patients completed treatment with consistently at least five negative culture results for the final 12 months of the treatment course and without evidence of treatment failure(12); Completed treatment was determined by bacterial negative conversion at the end of the treatment with less than three negative cultures. The “failure” was referred as patients had sputum culture positive in the final 12 months of the treatment course or if any one of the final three cultures was positive or to be discontinued due to clinical or radiological adverse reactions or adverse events. “Death” was patients died from any reason during the course of ATT; “Default” was referred as patients whose TB treatment was interrupted for at least two consecutive months for any reason. Favorable treatment outcomes were defined as sum of cured and treatment completed , unfavorable outcomes included “failure”, “default” and “death”(13).

Safety assessment

Included patients were monitored by blood and urine routine, liver function, renal function at least once a months, hearing test once a month, followed at outpatients department of TB by physicians once a moths or less if possible. Adverse events（AEs）endpoints included all-cause mortality and incidence of adverse events that occurred or worsened during treatment, defined by the Division of Microbiology and Infectious Diseases(14). And the severity of AEs according to whether they were determined by researchers to be related to the drug in question.

Statistical analysis

Statistical analysis was used SPSS 18.0 (IBM Corp, Armonk, NY, USA). Categorical variables such as treatment outcome, sputum conversion rate were analysed using X^2 tests and Fisher’s exact tests, and continuous variables were analysed using independent t-tests and Mann-Whitney U-tests. P value < 0.05 was considered statistically significant.

Results

1. Study population

During the study period, a total of 114 patients were included in the study, including 72 males with median age at 35.7 years (range19-64 years) and 42 females with median age at 32.2 years (range 19-61 years), 36 cases with newly treated MDR-TB and 78 cases with retreated MDR-TB. The general characteristics of included patients was shown in Table 1

Table 1 Clinical characteristics of patients enrolled

2. Treatment outcome of included patients

The overall favorable treatment rate was 79.8% (91/114): 75.4% (86/114) cured, 4.4% (5/114) completed treatment. 20.2%（23/114）got unfavorable outcome（8.8% (10/114) failures, 9.6% (11/114) default

including 8.8% (10/114) losing follow up and 0.9% (1/114) withdrawing treatment due to intolerance to drugs; and 1.8% (2/114) died. The flow diagram of patients included was shown in Figure 1

Fig 1 Flow diagram

Treatment favorable rate was significantly higher in newly treated MDR-TB (91.7%, 33/36) than that in retreated MDR-TB (74.4%，58/78)，p value was 0.03. Sputum culture negative conversion rates at the end of third month and the sixth month were 91.7% (33/36) and 94.4% (34/36) in newly treated group which were significantly higher than that of 69.2%(54/78) and 70.5% (55/78) in retreated group, p value was 0.009 and 0.004, respectively. A total of 51 (44.73%,51/114) patients achieved the standard of stopping medication (11) at the end of the 12th month: among which 26 (72%,26/36) patients were newly treated, and 25 (32%,25/78) were retreated, p value was 0.00. The curve outcome was shown in figure 2 and Table 2.

All patients who completed the course of treatment were followed for 1 year and no recurrence was found.

Table 2 culture conversion in different groups at different times

Figure 2 The differences of time to culture conversion between two groups

3. Safety and side effect monitoring（Adverse events（AEs）

The investigators recorded 42 AEs occurrences in 30 of 114 patients（30/114, 26.3%). Clinicians rated most AEs as mild or moderate (n=40 AEs, 40/42) and no one was caused by Pa（0/114, 0%).

Among them, 22 AEs occurrences in 15 patients (13.16%, 15/114) experienced a change in treatment regimen. Among them, 12 AEs occurrence in 10 patients associated with Ak due to mild hearing loss (n=5) or mild renal dysfunction (n=7). 6 AEs occurrences in 3 patients associated with PZA due to transaminase elevation (n=3, alanine aminotransferase were elevated to 2 times higher than the upper limit of the normal range) and gout (n=3). 4 AEs occurrences in 2 patients associated with Pto due to transaminase elevation (n=2, alanine aminotransferase were elevated two times higher than the upper limit of the normal) and gastrointestinal reaction (n=2). All AEs above were improved after discontinuation of the suspected drugs. 9（60%, 9/15) of these patients returned to the discontinued drug after dosage adjustment and completed the course.

4 AEs in 2 patients（1.75%，2/114）were reported to be severe enough to require permanent discontinuation of the suspected drug: 1 case (0.88%, 1/114) was associated with Ak by hearing loss (n=1) and mild renal insufficiency (n=1). Allergic rash (n=1) and gastrointestinal reaction (n=1) caused by Mfx in 1 case (0.88%，1/114). Patient with allergic skin rash were unable to tolerate and abandoned the treatment.

As the rest 16 AEs occurrences in 13 patients (11.40%, 13/114) were improved after symptomatic treatment, and no treatment plan was changed，4 AEs occurrences in 4 patients suspended Ak due to mild

dizziness (n=4); 12 AEs occurrences in 9 patients suspended PZA and Pto due to mild transaminase elevation (n=8, alanine aminotransferase elevated 2 times lower than the upper limit of the normal range.) and gastrointestinal reaction (n=4).

Discussion

In the present study, we made up a regimen for the treatment on MDR-TB mainly based on guidelines of WHO 2016 and Chinese guidelines (15–17). We included MDR-TB patients with a low concentration INH resistance and without second-line injection and FQs resistance according to MIC DST. The results showed that overall success rate was 79.8% in which treatment favorable rate reached as high as 91.7% in newly treated patients and 74% in retreated patients, the results demonstrated the high efficacy of this regimen against specific MDR-TB patients.

The Bangladesh short range regimen recommended by the 2016 guidelines is suggested for treating MDR patients without FQs and second-line injectable agents resistance,which consisted of an intensive period of four to six months with seven drugs (Ak ,M, Pt, Cfz, PZA, high-dose INH and EMB) followed by a five-month course of M, Cfz, PZA and E (18). But Cfz is expensive in China (about $ 400 / month) and may be unacceptable to most Asian patients, especially young women to accept due to the skin pigmentation. In the present study, under inclusion conditions similar to the short range regimen: we replaced the high dose INH with Pa and replaced Cfz with Cs. The result indicated high favorable treatment outcome rate and the entire treatment regimen costs at only around $300 per month, while the short range regimen costs $450 per month and the all-oral regimen recommended by the 2019 WHO guideline costs more than $2000 per month in China. And the incidence of SAEs in the present study was as extremely low as 1.75%.

For resource-limited areas, the cost of treatment is an important determinant of patient compliance. Costly drugs, even if effective, may cause patients to discontinue treatment,which not only leads to the spread of drug-resistant MTB, but can also lead to more complex drug resistance in individuals. China is a high TB burden country with high financial burden of health care. Therefore, BDQ had not been widely used in China at present for its price. On the other hand, the WHO's clear recommendations on the use of LZD and BDQ could prove a double-edged sword for global TB control programmes (3). Intuitively, the advantages of including LZD and BDQ in standard protocols for all types of MDR-TB may be more conducive to programme implementation and less likely to require DST. The main drawback, however, may be concerns about patient’s safety and tolerability. Lzd is also expensive in China ($600/month) and has significant long-term side effects as an ultra-broad-spectrum antibiotic. About 30–40% of patients stop linezolid treatment because of AEs (19). Therefore, in the present study, patients were selected with inclusion criteria, and only FQs was selected as the included drug among class A drugs which was the most inexpensive and safely.

The rate of INH acetylated is controlled by genetics. Once acetylated, INH is ineffective as an antibiotic against TB bacilli. Rapid acetylation of INH may lead to low serum concentrations of anti-TB drugs,

increasing the risk of treatment failure. Most Asians are of the fast-metabolizing type (20). It had been reported that in the INH -resistant organisms studied, about 50% of INH MIC belong to the category of low concentration resistance with MIC at 0.1-1.0 ug /mL(21–22). A study from China showed that among 109 INH-resistant isolates, only 11.9% and 19.3% showed resistance to PAS and Pa, respectively (23). Pa is a chemical synthesis of isoniazid (INH) and paminosalicylic acid (PAS). PAS effectively delays and blocks the acetylation of INH in vivo. Pa maintains high, prolonged concentration of INH in the blood and reduces toxicity to the liver. It not only enhances the bactericidal action of the drug, but also delays the generation of bacterial resistance. In the present study, patients infected with low concentration INH resistant strains were included, and MIC values showed that all strains were sensitive to Pa. Another advantage of Pa is its low price ($22 per month). Its safety was reflected in the incidence of AEs(0%).

Cycloserine(Cs)in group B has good antibacterial activity and the price in China is lower than Cfz. Due to its low drug resistance rate, low cross-resistance with other anti-TB drugs, and is oftem used as a good alternative drug (24, 25). The present study also verified its safety and efficacy.

Second-line injections (SLIs) were once one of the core drug groups in treatment of MDR-TB (15). However, existing studies have shown that SLIs has high side effects and often leads to withdrawal of patients (26). A retrospective study of 25 countries (27), according to the results of injection therapy (Ak) were better than no injections, but in analysis of comprehensive treatment results, patients who received the injection did worse than those who did not receive the injection. The results provided evidence for 2019 guidelines on use of injection drugs (1). But the article also explained that Ak may be the most widely used injectable drug due to its price and tended to be used in patients with the worst resistance patterns, which may be one of the reasons for poor outcomes rather than the problem with the drug itself. However, the present study showed that 18 AEs occurrences in 15 (13.16%, 15/114) patients suspicious of Ak due to mild hearing loss or mild renal dysfunction. But most of them(66,67%, 10/15) were treated with reduced doses. Only 1 (6.67%, 1/15) patient had Ak permanently disabled. These results suggest that the Chinese population could be moderately tolerant to SLIs and that the cheap drug is certainly effective for certain populations.

Conclusions

The regimen in the present study had the following characteristics: highly effective with favorable treatment rate in newly treatment patients reached 91%, and the patients were followed up for 1 year without recurrence; the use of Pa instead of high-dose INH and Cs instead of Cfz to treat specific MDR-TB population could be more in line with China's national conditions; It proved that the AEs of SLIs are controllable in Chinese population and inexpensive; 72% (26/36) newly treated patients achieved the standard of withdraw medicine at the end of the 12th month. These characteristics suggested that the regimen could be widely used in China, even other resource-poor parts of Asia. Further research on the possibility of short-course treatment in resource-poor areas with high TB burden could be expected.

Declarations

Ethical Approval and Consent to participate

This study was approved by the Ethics Committee of Shanghai Pulmonary Hospital affiliated to Tongji University, the approval number was K16-298. Obtain written informed consent from each eligible MDR-TB participant. An independent safety monitoring committee was established to ensure the continued safety of participants during clinical studies.

Consent for publication

Not applicable

Availability of supporting data

All data regarding the included participants and laboratory data during the study are available from the corresponding author by email request. The clinical study was registered at The China Clinical Trial Registry (ChiCTR, www.chictr.org.cn) with the registration number: ChiCTR-OPC-16009380.

The study followed the CONSORT guidelines.

Competing interests

The authors declare that they have no competing interests.

Funding acknowledgements:

This work was supported by the grant from the Shanghai Natural Science Foundation (Grant No.20ZR1446700). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Author contribution Statement

WS: included the patients, treated and followed up the patients, wrote the manuscript; QT:included the patients, collected the data; JW and HY : culture isolated strain, FY and JY Clinical laboratory for the work of MGIT 960 culture; LF: Research design, included the patients, data collection and revised the manuscript. All authors read and approved the final submitted version.

Acknowledgements

We thank all participants for their time and efforts.

Author information:

Affiliations

Shanghai Clinical Research Center for Tuberculosis, Shanghai Key Lab of Tuberculosis, Department of Tuberculosis, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China

Wenwen Sun, Qin Tang and Lin Fan

Shanghai Clinical Research Center for Tuberculosis, Shanghai Key Lab of Tuberculosis, Shanghai Pulmonary Hospital, Tongji University School of Medicine: Jie Wang and Hua Yang

Shanghai Clinical Research Center for Tuberculosis, Shanghai Key Lab of Tuberculosis, Department of clinical laboratory, Shanghai Pulmonary Hospital, Tongji University School of Medicine: Jinghui Yang, and Fangyou Yu

Corresponding author

Correspondence to Lin Fan; Heping Xiao

References

1. WHO. Global Tuberculosis Report 2019. Geneva, World health organization;. 2019;2019(License):CCBY-NC-SA3.
2. WHO. WHO consolidated guidelines on drug-resistant tuberculosis treatment. world health organization. 2019;2019.
3. Chang K, Yew W. ATS/CDC/ERS/IDSA Clinical Practice Guidelines for Treatment of Drug-Resistant Tuberculosis: A Two-edged Sword? American journal of respiratory and critical care medicine. 2020;202(5):777-8. https://doi: 10.1164/rccm.201912-2460LE.
4. Brouqui P, Quenard F, Drancourt M. Old antibiotics for emerging multidrug-resistant/extensively drug-resistant tuberculosis (MDR/XDR-TB). International journal of antimicrobial agents. 2017;49(5):554-7.https://doi: 10.1016/j.ijantimicag.2017.02.008.
5. Zhang Y, Wu S, Xia Y, Wang N, Zhou L, Wang J, et al. Adverse Events Associated with Treatment of Multidrug-Resistant Tuberculosis in China: An Ambispective Cohort Study. Medical science monitor : international medical journal of experimental and clinical research. 2017;23:2348-56. https://doi: 10.12659/msm.904682.
6. Falzon D, Schünemann H, Harausz E, González-Angulo L, Lienhardt C, Jaramillo E, et al. World Health Organization treatment guidelines for drug-resistant tuberculosis, 2016 update. The European respiratory journal. 2017;49(3). https://doi: 10.1183/13993003.02308-2016.
7. Nunn A, Phillips P, Meredith S, Chiang C, Conradie F, Dalai D, et al. A Trial of a Shorter Regimen for Rifampin-Resistant Tuberculosis. The New England journal of medicine. 2019;380(13):1201-13. https:// doi: 10.1056/NEJMoa1811867.
8. Fan Y, Ding S, Bao Z, Wu L, Zhen L, Xia Q, et al. Prognostic factors for treatment success in patients with multidrug-resistant tuberculosis in China. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2018;22(3):300-5. https://doi: 10.5588/ijtld.17.0183.

9. Ranzani O, Rodrigues L, Bombarda S, Minto C, Waldman E, Carvalho C. Long-term survival and cause-specific mortality of patients newly diagnosed with tuberculosis in São Paulo state, Brazil, 2010-15: a population-based, longitudinal study. The Lancet Infectious diseases. 2020;20(1):123-32. https://doi: 10. 1016/S1473-3099(19)30518-3.
10. Ismail N, Mvusi L, Nanoo A, Dreyer A, Omar S, Babatunde S, et al. Prevalence of drug-resistant tuberculosis and imputed burden in South Africa: a national and sub-national cross-sectional survey. The Lancet Infectious diseases. 2018;18(7):779-87. https://doi: 10.1016/S1473-3099(18)30222-6.
11. Committee WHOGR. Guidelines for the programmatic management of drug-resistant tuberculosis-2011 update. Geneva, Switzerland: World Health Organization, 2011. 2011.
12. Lange C, van Leth F, Mitnick C, Dheda K, Günther G. Time to revise WHO-recommended definitions of MDR-TB treatment outcomes. The Lancet Respiratory medicine. 2018;6(4):246-8. https://doi: 10.1016 /S2213 -2600 (18)30104-8.
13. Duan H, Chen X, Li Z, Pang Y, Jing W, Liu P, et al. Clofazimine improves clinical outcomes in multidrug-resistant tuberculosis: a randomized controlled trial. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2019;25(2):190-5. https://doi: 10.1016/j.cmi.2018.07.012.
14. United States. National Institute of Allergy and Infectious Diseases. Division of Microbiology and Infectious Diseases. United States National Institute of Allergy & Infectious Diseases.
15. WHO. WHO treatment guidelines for drugresistant tuberculosis 2016 update. world health organization. 2016.
16. Association CA-t. the guideline of chemotherapy on MDR-TB in China. 2015; 2015.
17. Association Ca-t. the guideline of chemotherapy on MDR-TB. 2019.
18. A VD, AK M, MA S, PK D, MR S, P D, et al. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. American journal of respiratory and critical care medicine. 2010;182(5):684-92. https://doi: 10.1164/rccm.201001-0077OC.
19. Jaspard M, Butel N, El Helali N, Marigot-Outtandy D, Guillot H, Peytavin G, et al. Linezolid-Associated Neurologic Adverse Events in Patients with Multidrug-Resistant Tuberculosis, France. Emerging infectious diseases. 2020;26(8):1792-800. https://doi: 10.3201/eid2608.191499.
20. Jagielski T, Bakuła Z, Roeske K, Kamiński M, Napiórkowska A, Augustynowicz-Kopeć E, et al. Mutation profiling for detection of isoniazid resistance in Mycobacterium tuberculosis clinical isolates. The Journal of antimicrobial chemotherapy. 2015;70(12):3214-21. https://doi: 10.1093 /jac/dkv253.
21. Parkin D, Vandenplas S, Botha F, Vandenplas M, Seifart H, van Helden P, et al. Trimodality of isoniazid elimination: phenotype and genotype in patients with tuberculosis. American journal of respiratory and critical care medicine. 1997;155(5):1717-22. https://doi: 10.1093/jac/dkv253.
22. Nagel S, Streicher E, Klopper M, Warren R, Van Helden P. Isoniazid Resistance and Dosage as Treatment for Patients with Tuberculosis. Current drug metabolism. 2017;18(11):1030-9. https://doi: 10.2174/1389200218666171031121905.

23. Li G, Zhang J, Jiang Y, Zhao L, Liu H, Li M, et al. Cross-resistance of isoniazid, para-aminosalicylic acid and pasiniazid against isoniazid-resistant Mycobacterium tuberculosis isolates in China. Journal of global antimicrobial resistance. 2020;20:275-81.https://doi: 10.1016/j.jgar.2019.08.005.
24. Wang J, Pang Y, Jing W, Chen W, Guo R, Han X, et al. Efficacy and safety of cycloserine-containing regimens in the treatment of multidrug-resistant tuberculosis: a nationwide retrospective cohort study in China. Infection and drug resistance. 2019;12:763-70.https://doi:10.2147/IDR.S194484.
25. Li Y, Wang F, Wu L, Zhu M, He G, Chen X, et al. Cycloserine for treatment of multidrug-resistant tuberculosis: a retrospective cohort study in China. Infection and drug resistance. 2019;12:721-31.https://doi: 10.2147/IDR.S195555.
26. Shean K, Streicher E, Pieterson E, Symons G, van Zyl Smit R, Theron G, et al. Drug-associated adverse events and their relationship with outcomes in patients receiving treatment for extensively drug-resistant tuberculosis in South Africa. PloS one. 2013;8(5):e63057. https:doi: 10.1371/journal.pone.0063057.
27. J Peter Cegielski, Pei-Chun Chan, Zhiyi Lan,et al.Aminoglycosides and Capreomycin in the Treatment of Multidrug-resistant Tuberculosis: Individual Patient Data Meta-analysis of 12 030 Patients From 25 Countries, 2009–2016, Clinical Infectious Diseases, 2020, ciaa621 https://doi: 10.1093/cid/ciaa621.

Tables

Table 1 Clinical characteristics of patients enrolled

characteristic	Newly treated (n=36)	Retreated (n=78)	P value
median age	32.1±12.4	35.5±11.5	0.13
Male (%)	22(61%)	50(64.1%)	0.34
median BMI	19.8	19.2	0.54
cavities present on Chest CT			
no cavity	18(50%)	36(46.2%)	0.82
unilateral	12(33.3%)	35(44.9%)	0.08
bilateral	5(13.9%)	7(9.0%)	0.14
lesion severity			
≥ 3 fields	22(61.1%)	49(62.8%)	0.55
< 3 fields	14(38.9%)	29(37.2%)	0.76
complications			
DM	5(13.9%)	10(12.8%)	0.35

Table 2 The differences of time to culture conversion between two groups

	Newly treated (n=36)	Retreated (n=78)	P value
Sputum negative conversion rate at month 2 (n, %)	15 (41.67)	18(23.08)	0.00
Sputum negative conversion rate at month 3 (n, %)	33 (91.67)	54(69.23)	0.01
Sputum negative conversion rate at month 6 (n, %)	34 (94.44)	55(70.51)	0.00
Achieve the standard of stopping medicine at the end of 12 month	26(72)	25(32)	0.00

Figures

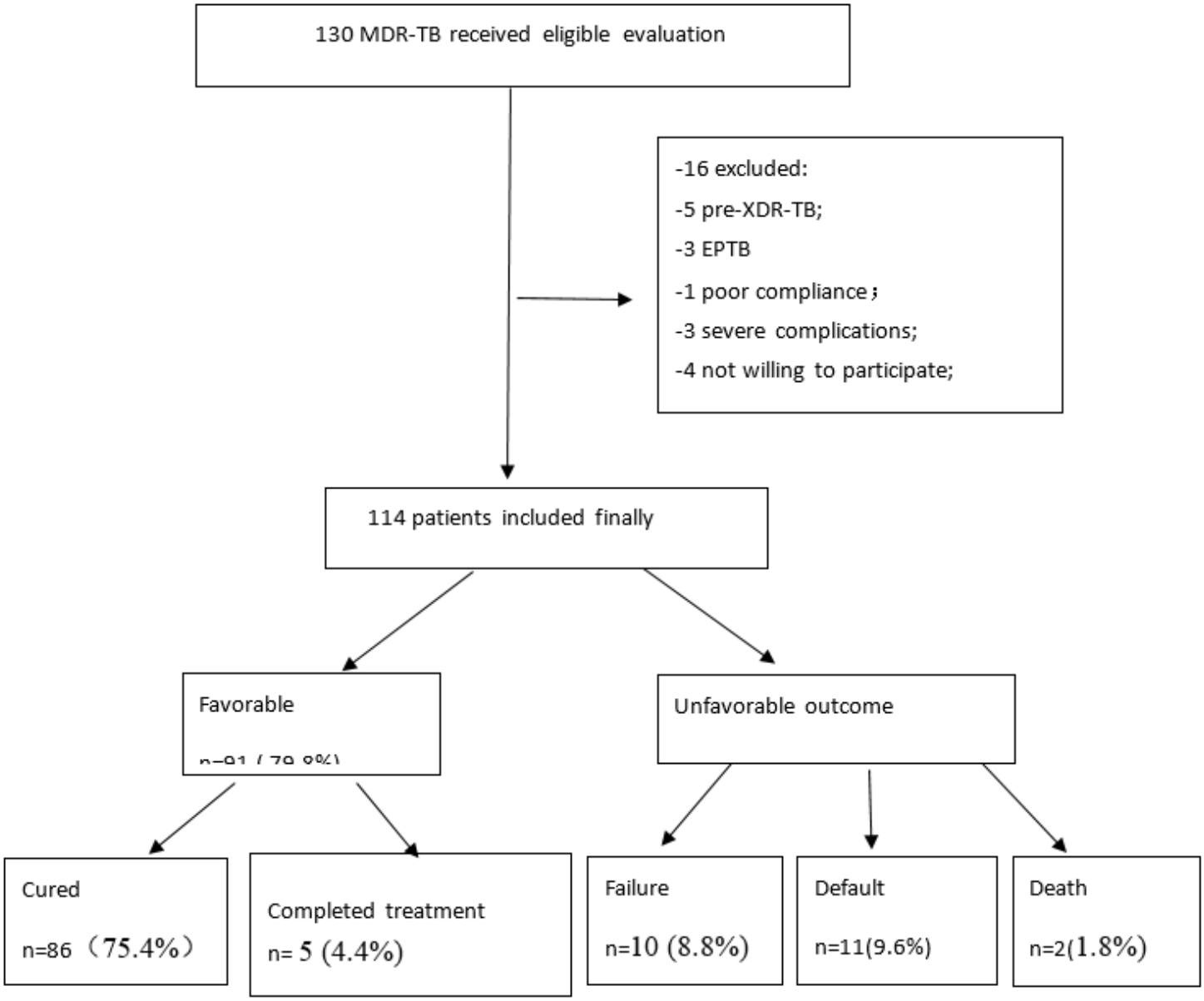

Figure 1

Flow diagram

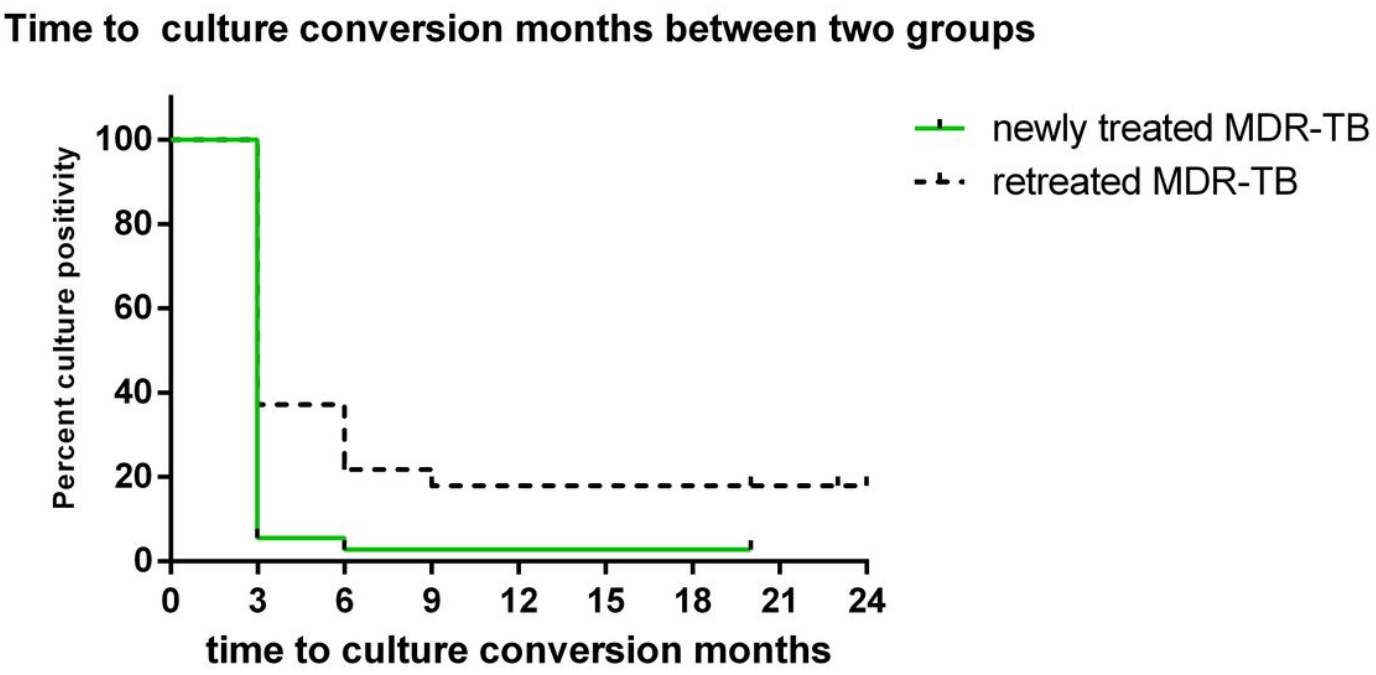

Figure 2

The differences of time to culture conversion between two groups

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CONSORT2010Checklist.doc