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MAJOR ARTICLE

# New All-Oral Short-term Regimen for Multidrug-Resistant Tuberculosis: A Semi-randomized Controlled Trial Conducted in China

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***Background.*** This study aimed to evaluate the efficacy and safety of an all-oral short-term regimen for treating multidrug-resistant tuberculosis (MDR-TB).

***Methods.*** In this semirandomized, controlled, multicenter clinical study, patients with MDR-TB who were sensitive to fluoroquinolones were assigned to treatment groups at enrollment. Patients were assigned to group C (4–6 months: bedaquiline + linezolid + clofazimine + moxifloxacin + cycloserine; 5 months: clofazimine + moxifloxacin + cycloserine) unless this protocol was unsuitable or unacceptable, in which case they were randomly assigned to group A (4–6 months: isoniazid + ethambutol + pyrazinamide + protionamide + amikacin + clofazimine + moxifloxacin; 5 months: ethambutol + pyrazinamide + clofazimine + moxifloxacin) or group B (4–6 months: isoniazid + ethambutol + pyrazinamide + protionamide + linezolid + clofazimine + moxifloxacin; 5 months: ethambutol + pyrazinamide + clofazimine + moxifloxacin). The primary outcome was the proportion of patients achieving successful outcomes.

***Results.*** From September 2020 to June 2023, 397 patients with MDR-TB were screened and 360 were enrolled. Among them, 90.3% of group C achieved good treatment outcomes, as compared with 57.1% in group A (control) and 75.0% in group B. Group C demonstrated higher sputum culture conversion and pulmonary cavity closure rates than group B, with group A showing the lowest rates. The most common adverse events were skin blackening (29.3%) and hyperuricemia (20.6%). Prolonged QT intervals were observed in 39 participants, predominantly in group C (24.3%).

***Conclusions.*** The all-oral 9- to 11-month short-term regimen shows promise as a new treatment option for MDR-TB. Incorporating bedaquiline into an orally administered regimen may improve treatment outcomes and reduce relapse rates. Despite certain limitations, these findings provide valuable insights for developing improved treatments for MDR-TB in China.

**Keywords.** bedaquiline; multidrug resistant; outcome; safety; tuberculosis.

Tuberculosis (TB) remains a global health challenge, with rifampicin-resistant TB (RR-TB) posing a significant threat to disease control efforts. According to the World Health Organization (WHO) *Global Tuberculosis Report 2022* [1], an estimated 410 000 individuals worldwide were affected by RR-TB in 2022, caused by *Mycobacterium tuberculosis* strains resistant to rifampicin. Despite the WHO's recommendation that all confirmed RR-TB cases receive treatment regimens for multidrug-resistant TB (MDR-TB), defined as resistance to at least isoniazid (INH) and rifampicin, the global treatment success rate for RR-TB remains at only 60% [2].

Traditionally, MDR-TB treatment regimens have been lengthy, toxic, and resource intensive, often relying on injectable second-line drugs. In 2018, the WHO categorized second-line anti-TB drugs into 3 groups (A, B, and C) based on their safety and efficacy profiles [3, 4]. In 2019, the WHO introduced new treatment guidelines for MDR/RR-TB and extensively drug-resistant TB, which fundamentally changed the approach to managing these cases [2–4]. These guidelines recommend short-course regimens (9–11 months) for 2 groups of patients: those who have not previously received second-line MDR-TB treatment for >1 month and those without resistance to fluoroquinolones (FQs) or second-line injectable drugs. Following completion of the international randomized controlled

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STREAM stage 1 trial, the WHO recommended the 9- to 11-month standardized short-course Bangladesh regimen, comprising 7 anti-TB drugs, as an alternative to long-term regimens under certain conditions [5]. However, this regimen includes injectable drugs associated with significant adverse reactions, such as ototoxicity and nephrotoxicity, and injection-based drug delivery is often viewed as inconvenient [6, 7]. To address these challenges, a modified Bangladesh regimen was developed, replacing second-line injectables with linezolid (LZD), significantly improving patient adherence. Nonetheless, prolonged LZD use has been linked to a high incidence of adverse reactions.

In 2020 the WHO recommended a 9- to 12-month all-oral regimen incorporating bedaquiline (BDQ) in place of injectable drugs for eligible patients [8]. Further updates to WHO guidelines in 2022 [9] included recommendations for a 9-month all-oral treatment regimen for patients with MDR/RR-TB and FQ sensitivity. These updates spurred the adoption of all-oral short-term treatment programs in countries such as South Africa, Niger, Vietnam, and South Korea, where superior outcomes have been reported as compared with regimens incorporating injectable drugs [10–13].

Despite these advancements, such programs have yet to be implemented in China. Additionally, many Chinese patients face barriers to BDQ access due to cardiac concerns or financial constraints, underscoring the urgent need for alternative treatment strategies. This study aims to address these gaps by evaluating the efficacy and safety of a novel all-oral short-term regimen as compared with regimens containing high-dose INH and/or second-line injectable drugs. The ultimate goal is to shorten treatment duration while enhancing treatment effectiveness and patient compliance in MDR/RR-TB cases in China.

## MATERIALS AND METHODS

### Patient Enrollment

This semirandomized, controlled, multicenter clinical study was conducted from September 2020 to June 2023 at 40 research centers in 36 cities across China, including Beijing Chest Hospital (affiliated with Capital Medical University), Jilin Tuberculosis Hospital, Xi'an Chest Hospital, and others. Study participants were continuously enrolled and included patients with TB and confirmed diagnoses of MDR/RR-TB. Each diagnosis was verified with rapid molecular drug sensitivity testing performed via Xpert, line probe assay, or other assays prior to enrollment. Participating hospitals were instructed to screen for FQ-resistant TB cases using molecular and phenotypic drug sensitivity tests.

***Inclusion Criteria*:** Inclusion criteria were as follows:

- Volunteers who signed informed consent forms and received follow-up care
- Male or female patients aged 18 to 65 years, including inpatients and outpatients
- No history of anti-TB drug treatment or only a brief history of such treatment (<1 month)
- MDR/RR-TB diagnosis confirmed via molecular drug sensitivity test results
- Chest computed tomography scan findings indicative of TB, with pulmonary lesions detected with or without cavities
- Nonpregnant premenopausal women (with negative urine pregnancy test results) who agreed to use effective contraceptive measures during the study

***Exclusion Criteria*:** Exclusion criteria were as follows:

- Molecular and phenotypic drug sensitivity test results indicating FQ-resistant TB, history of allergies to anti-TB drugs used in this study, or current treatment with contraindicated drugs related to the study regimens
- Severe renal insufficiency, defined as a creatinine clearance rate <30 mL/min
- Liver function impairment, with alanine aminotransferase and/or aspartate aminotransferase levels exceeding 3 times the upper limits of the laboratory reference range, unless temporarily elevated (such participants could be enrolled after regaining normal liver function)
- Inability to receive treatment or follow-up care
- Presence of severe comorbidities
- Pregnant or lactating women
- Inability to take oral medications
- Current participation in other clinical trials
- Positive HIV or active viral hepatitis infection status

### Trial Design

This semirandomized, controlled, nonblinded clinical trial allocated patients to treatment groups based on suitability for the group C protocol. Patients were initially assigned to group C unless the protocol was deemed unsuitable or unacceptable for their treatment. In such cases, patients were randomly assigned to group A or group B via computer-generated random number tables, with statisticians managing the randomization process. Group C participants received an all-oral regimen comprising BDQ, moxifloxacin (MFX), LZD, cycloserine (Cs), and clofazimine (CFZ) during the 4- to 6-month intensive phase, followed by MFX, CFZ, and Cs during the 5-month consolidation phase. The duration of the intensive phase depended on sputum culture results: participants with negative sputum culture results at 3 months underwent a 4-month intensive phase, while those with positive culture results continued the intensive phase for up to 6 months.

Group A (control group) received a regimen containing high-dose INH, MFX, amikacin (administered intravenously or intramuscularly), CFZ, prothionamide, pyrazinamide

(PZA), and ethambutol (EMB) during the 4- to 6-month intensive phase, followed by MFX, CFZ, PZA, and EMB during the 5-month consolidation phase.

Group B participants received an all-oral regimen consisting of high-dose INH, MFX, LZD, CFZ, prothionamide, PZA, and EMB during a 4- to 6-month intensive phase, followed by MFX, CFZ, PZA, and EMB during a 5-month consolidation phase (Figure 1).

Drug dosages for all participants were administered according to body weight, as outlined in Table 1.

#### Study Assessments

Participants meeting the inclusion criteria underwent regular physical examinations during treatment to monitor for adverse events. Sputum cultures were collected to confirm the presence of *M tuberculosis* before treatment initiation, and the process was repeated monthly during treatment for participants who could produce sputum. Body weight was assessed before treatment and monitored monthly throughout the treatment period.

Participants underwent routine monthly testing to monitor blood, liver, and kidney function, as well as electrolyte levels. Electrocardiography was performed prior to treatment and monthly thereafter until treatment completion. All patients were screened for HIV and viral hepatitis before treatment. Chest computed tomography scans were conducted at baseline, every 3 months during treatment, and during follow-up visits at 6 and 11 months posttreatment. Patients requiring LZD treatment were instructed to undergo vision assessments and monthly Ishihara tests (for color blindness) starting before treatment and continuing through the treatment duration.

Adverse events were defined and graded according to an adaptation of the AIDS Clinical Trials Group table for grading adverse experiences [14]. Serious adverse events were classified as grade 3 events. All patients were monitored by trained physicians experienced in diagnosing and managing adverse drug reactions, following guidelines outlined in the "Peer Handbook" provided in the WHO guidelines for the planning and management of drug-resistant tuberculosis [3].

Treatment outcomes for patients with MDR/RR-TB were determined in accordance with WHO guidelines [15]. A cure was defined as treatment completion with ≥3 consecutive negative culture results taken at least 30 days apart after the intensive phase or after 8 months if no intensive phase was used. Patients who did not meet the criteria for cure but showed no evidence of treatment failure were classified as having completed treatment.

Treatment failure was defined as treatment termination or a permanent change in ≥2 anti-TB drugs due to any of the following: (1) lack of culture conversion by the end of the intensive phase, (2) bacteriologic reversion during the continuation phase, (3) detection of acquired resistance to FQs or second-line injectable drugs, or (4) adverse drug reactions.

Death was defined as death from any cause during treatment. Loss to follow-up was recorded if a participant experienced a treatment interruption of 2 consecutive months. Treatment outcomes were subsequently classified as either favorable (cure or treatment completion) or adverse (treatment failure or death) [15].

#### Sample Size Calculation

This study was designed as a superiority trial to evaluate the efficacy and safety of a novel all-oral short-term regimen as compared with a regimen containing injectable drugs for treating MDR-TB cases in China. Based on previous studies [12, 16–18], favorable outcome rates were estimated at 63% for group A (control), 77% for group B, and 85% for group C. With PASS 15 software, a total sample size of 288 cases across 3 groups was calculated to provide 90% power to detect differences between group A and group B, assuming a 1-sided type I error of 0.05. Loss to follow-up was defined per the WHO TB reporting framework as 20%; this includes patients who did not start treatment after diagnosis or had treatment interruptions ≥2 consecutive months. Thus, the required total sample size was increased to 360 participants, with a minimum of 120 per group.

#### Ethical Approval

This study was approved by the Ethics Committee of Beijing Chest Hospital, affiliated with Capital Medical University (2022; Scientific Research, Provisional Examination, No. 17). Written informed consent was obtained from all study participants prior to enrollment. This clinical trial is registered on the ClinicalTrials.gov website (NCT04545788).

#### Data Analysis

All original data were entered into a computer database and analyzed with SPSS software 29.0 (IBM). Intergroup differences in demographic data were treated as continuous variables and tested for significance by the *t* test. Clinical results and incidence rates of adverse events among participants (randomly assigned to control and experimental groups) were compared by the $\chi^2$ test. Univariate and multivariate analyses were performed to identify risk factors associated with adverse clinical outcomes. Kaplan-Meier curves were generated to visualize the cumulative percentages of cases achieving culture conversion and pulmonary cavity closure during treatment. Intergroup differences with *P* values <.05 were considered statistically significant.

## RESULTS

#### Study Population

Between September 2020 and June 2023, a total of 397 patients with MDR-TB were screened for enrollment in the study. Of these, 10 patients did not meet the inclusion criteria, 18 refused to participate, and 9 were excluded for other reasons (eg,

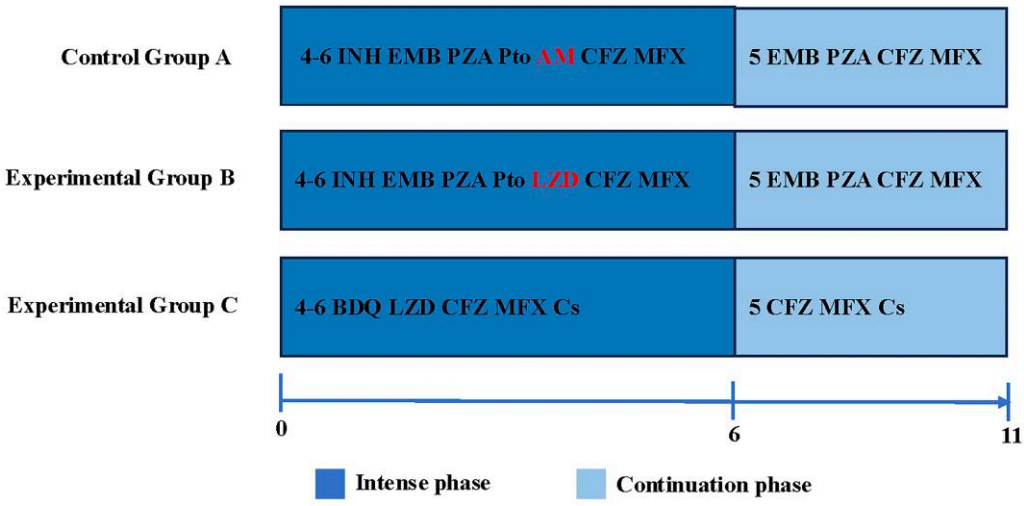


**Figure 1.** Enrollment of participants in this study. Drug regimens included isoniazid (INH), ethambutol (EMB), pyrazinamide (PZA), protionamide (Pto), amikacin (AMK), clofazimine (CFZ), moxifloxacin (MFX), linezolid (LZD), bedaquiline (BDQ), and cycloserine (Cs). Group A: 4–6 months, INH + EMB + PZA + Pto + AMK + CFZ + MFX; 5 months, EMB + PZA + CFZ + MFX. Group B: 4–6 months, INH + EMB + PZA + Pto + LZD + CFZ + MFX; 5 months, EMB + PZA + CFZ + MFX. Group C: 4–6 months, BDQ + LZD + CFZ + MFX + Cs; 5 months, CFZ + MFX + Cs.

**Table 1. Dosages and Usage of Drugs Administered to the 3 Groups**

| | Weight | |
|---|---|---|
| Drug | 30–50 kg/d | ≥50 kg/d |
| LZD, 600 mg/pill | 600 mg[a] | |
| BDQ, 100 mg/pill | 400 mg[b] | |
| MFX, 400 mg/pill | 400 mg | |
| CFZ, 100 mg/capsule | 100 mg | |
| EMB, 250 mg/pill | 750 mg | |
| PZA, 500 mg/pill | 1500 mg | |
| High-dose INH, 100 mg/pill | 400 mg | 600 mg |
| Pto, 200 mg/pill | 600 mg | |
| AMK, 200 mg/injection | 400 mg | |
| Cs, 250 mg/pill | 500 mg | 750 mg |

Group A: 4–6 months, INH + EMB + PZA + Pto + AMK + CFZ + MFX; 5 months, EMB + PZA + CFZ + MFX. Group B: 4–6 months, INH + EMB + PZA + Pto + LZD + CFZ + MFX; 5 months, EMB + PZA + CFZ + MFX. Group C: 4–6 months, BDQ + LZD + CFZ + MFX + Cs; 5 months, CFZ + MFX + Cs.

Abbreviations: AMK amikacin; BDQ, bedaquiline; CFZ, clofazimine; Cs, cycloserine; EMB, ethambutol; INH, isoniazid; LZD, linezolid; MFX, moxifloxacin; Pto, protionamide; PZA, pyrazinamide.

[a]For patients with peripheral neuropathy caused by LZD, the dosage can be reduced to 600 mg, 3 times per week, or 300 mg per day.

[b]Once per day for 2 weeks, then 200 mg, 3 times a week, for 34 weeks.

positive HIV status or serious comorbidities). Ultimately, 360 patients were enrolled and assigned to 3 groups: 260 cases to the experimental groups (group C, 120 participants; group B, 120 participants) and 120 patients to the control group (group A). A total of 84 patients in group A, 100 in group B, and 103 in group C completed the study (Figure 2).

The final cohort consisted of 287 patients, including 191 males (66.6%) with an average age of 41.9 years and 96 females (33.5%) with an average age of 36.8 years. The distribution of males across groups A, B, and C was 59, 70, and 62, respectively. Pulmonary cavities were detected in 109 patients (38.0%), while 45 (15.7%) had comorbid diabetes.

Key baseline characteristics—including median body mass index, the proportion of participants with pulmonary cavities, the average number of cavities per participant, the proportion with comorbid diabetes, and albumin levels—did not differ significantly between group C and either group A or group B (Table 2).

### Treatment Outcomes

Analysis of treatment outcomes among the 287 participants revealed that 216 (75.3%) achieved good treatment outcomes, while 27 (9.4%) were lost to follow-up and 3 (1.1%) died (Table 3). Intergroup comparisons showed that the good treatment outcome rate was significantly higher in group C vs group B ($P = .015$) and group A ($P < .001$). Additionally, the treatment outcome rate in group B was significantly higher than that in group A rate ($P < .001$). Significant intergroup differences in good treatment outcomes were also observed when all 3 groups (A, B, and C) were analyzed together ($P < .001$). Comparison of loss to follow-up revealed that group A had a significantly higher rate than groups B and C during the treatment process.

Intergroup comparisons of demographic risk factors associated with poor treatment outcomes indicated that patients with pulmonary cavities had a 3.111-fold higher risk of experiencing poor outcomes as compared with those without pulmonary cavities (Table 4). Other parameters, including gender, age, body mass index, and diabetes, were not significantly associated with treatment outcomes. Although univariate analysis

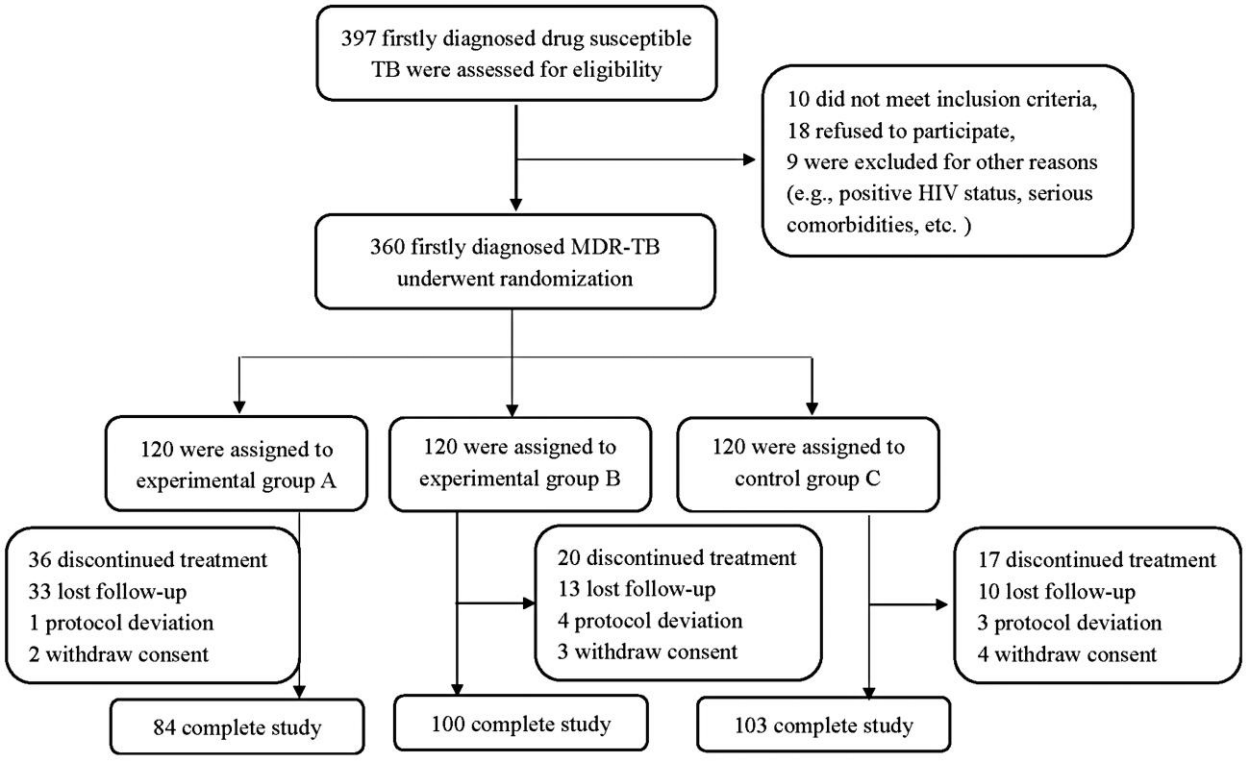


**Figure 2.** From September 2020 to June 2023, 397 patients with MDR-TB were initially evaluated for enrollment in the study. Of these, 10 did not meet the inclusion criteria, 18 refused to participate, and 9 were excluded for other reasons (eg, positive HIV status, serious comorbidities). A total of 360 patients were included in the study and assigned equally to 3 groups: group A (120 cases), group B (120 cases), and group C (120 cases). Ultimately, 84 patients in group A, 100 in group B, and 103 in group C completed the study. MDR-TB, multidrug-resistant tuberculosis.

identified significant differences in albumin levels among groups, no significant intergroup differences were detected in multivariate analysis.

Sputum culture conversion rates among the 3 groups were visualized by Kaplan-Meier curves (Figure 3), showing cumulative proportions of sputum samples converting from positive to negative over time. Group C demonstrated the highest sputum culture conversion rate, followed by group B, with group A having the lowest rate ($P < .05$). Similarly, group C had the highest pulmonary cavity closure rate, while no significant difference was observed between groups A and B for cavity closure (Figure 4).

### Safety

Table 5 lists the adverse events reported in the 3 groups. Among the 287 study participants, the most common adverse events were blackened skin (n = 84), hyperuricemia (n = 59), and liver damage (n = 51). For group C participants, skin darkening was the most common adverse reaction (44/103, 42.7%). For group B participants, hyperuricemia (27/100, 27.0%), adverse gastrointestinal reactions (22/83, 26.5%), and liver damage (22/83, 26.5%) were the most frequent adverse reactions, while hyperuricemia (22/84, 26.2%) was the main adverse reaction observed in group A participants.

Adverse reactions of concern, such as cardiotoxicity and peripheral neuropathy, were also observed. Among 39 patients who exhibited prolonged QT intervals, most (24.3%) were in group C, 10.0% were in group B, and 6.0% were in group A (24.3% vs 10.0%, $P = .004$; 24.3% vs 6.0%, $P < .001$). Peripheral neuropathy was reported in 36 participants, the majority of whom were in group C (25.2%), as opposed to 10.0% in group B, with no cases observed in group A (25.2% vs 10.0%, $P = .004$; 25.2% vs 0.0%, $P < .001$).

Adverse reactions related to blood system abnormalities were observed in all 3 groups, with half of the cases occurring in group B (13/26, 50.0%). No serious adverse events were reported during the study.

## DISCUSSION

Patients with MDR/RR-TB treated with short-course regimens that include newer oral drugs are expected to experience a better quality of life than patients undergoing standard RR-TB regimens. First, patient adherence improves with the availability of injectable-free anti-TB regimens, which facilitate community program implementation by reducing travel costs for injections and minimizing lost wages and hospitalization expenses during

**Table 2. Demographic and Clinical Characteristics of the Study Participants in the 3 Groups**

| Characteristic | Median (Range) or No. (%) | | | *P* Value |
|---|---|---|---|---|
| | Group A (n = 84) | Group B (n = 100) | Group C (n = 103) | |
| Age, y | 46.5 (21–64) | 42.5 (23–74) | 37.5 (20–68) | .074 |
| Male | 59 (70.2) | 70 (70.0) | 62 (60.2) | .233 |
| Body mass index, kg/m$^2$ | 20.2 (14.1–31.2) | 20.2 (14.7–48.1) | 20.1 (15.1–40.1) | .143 |
| Combined with pulmonary cavity | | | | .341 |
| Yes | 32 (38.1) | 43 (43.0) | 34 (33.01) | |
| No | 52 (61.9) | 57 (57.0) | 69 (67.0) | |
| No. of cavities per patient | 0.90 | 0.98 | 0.62 | .125 |
| Combined with diabetes | | | | .891 |
| Yes | 13 (15.50 | 17 (17.0) | 15 (14.6) | |
| No | 71 (84.5) | 83 (83.0) | 88 (85.4) | |
| Albumin level, g/L | 38.78 (26.0–53.2) | 40 (18.0–52.2) | 40 (20.5–63.4) | .063 |

See Table 1 for regimen per group.

Abbreviation: BMI, body mass index.

**Table 3. Treatment Outcome of Patients in the 3 Groups**

| Treatment Outcome | Patients, No. (%) | | | *P* Value |
|---|---|---|---|---|
| | Group A (n = 84) | Group B (n = 100) | Group C (n = 103) | |
| Good outcome | 48 (57.1) | 75 (75.0) | 93 (90.3) | <.001 |
| Cure | 37 (44.1) | 52 (52.0) | 89 (86.4) | |
| Treatment completed | 11 (13.1) | 23 (23.0) | 4 (3.9) | |
| Failure outcome | 15 (17.9) | 21 (21.0) | 8 (7.8) | <.001 |
| Treatment failure | 15 (17.9) | 19 (19.0) | 7 (6.8) | |
| Death | 0 (0.0) | 2 (2.0) | 1 (1.0) | |
| Lost to follow-up | 21 (25.0) | 4 (4.0) | 2 (1.9) | |

See Table 1 for regimen per group.

the intensive phase of standard anti-TB treatment. Second, faster recovery from the illness and its treatment reduces discomfort and enhances patients' overall quality of life.

Currently, the WHO recommends 2 orally administered short-course regimens: the 6-month BPaLM (comprising BDQ, Pa-824, and LZD, with or without MFX) and the 9- to 11-month BDLLfxC regimen (comprising BDQ, delamanid, LZD, levofloxacin [Lfx], and CFZ), along with PZA, prothionamide, EMB, and high-dose INH depending on the patient's specific needs and drug susceptibility profiles. Additionally, three 9-month regimens have been introduced following the 6-month regimens. For patients with extensively drug-resistant TB, those ineligible for shorter regimens, or those whose shorter regimens have failed, longer treatment durations exceeding 18 months remain an option.

Consistent with WHO recommendations, countries such as South Africa and South Korea have reported superior outcomes with short-term all-oral regimens as compared with traditional injectable-based regimens [13, 14, 19]. For instance, Nguyen et al [11] demonstrated a 90% cure rate for a new short-term all-oral regimen in Vietnamese patients with MDR/RR-TB that included BDQ, Lfx, CFZ, LZD, and PZA, prompting the replacement of the WHO-recommended 7-drug regimen in that context. Similarly, a 24-week study of the BPaLM regimen reported an 89% favorable outcome rate [20]. Our study aligns with these findings, achieving high cure rates in the experimental group C (90.3%). Additionally, a meta-analysis of the 9- to 11-month all-oral regimen recommended by the WHO revealed successful outcomes in 73% of patients [8], consistent with our results for group B (75%). Nevertheless, larger clinical studies with diverse and extensive patient populations are required to comprehensively evaluate the safety and efficacy of these regimens in Chinese patients with MDR/RR-TB.

The limited number of available anti-TB drugs suitable for short-term all-oral regimens for patients with MDR/RR-TB highlights the need for optimized treatment approaches. In our study, BDQ, Lfx, CFZ, LZD, and Cs (WHO-designated group A and B drugs) were included in the experimental group C regimen. To expedite the evaluation of effectiveness and safety, our study adopted a design similar to the Nix-TB prospective single-arm clinical study, which prioritized nonrandomized enrollment into the experimental group. Early results of the Nix-TB study, published in September 2022, demonstrated the efficacy of replacing injectable drugs with oral BDQ, which reduced adverse reaction rates and improved compliance. This has led to the development of short-course regimens incorporating BDQ, which the WHO now recommends for MDR/RR-TB treatment.

In a different approach, our study administered an all-oral anti-TB regimen to experimental group B participants, replacing injectable drugs in the Bangladesh regimen with oral LZD. Ultimately, group C demonstrated the highest treatment success rate (90.3%), followed by group B (75.0%) and group A (57.1%). Group C also achieved the highest rates of sputum culture conversion and pulmonary cavity closure. Additionally, results presented here revealed that group B and group C

**Table 4. Analysis of Risk Factors of Treatment Outcome Related to Demographic Characteristics**

| | Good Outcome (n = 216) | | Failure Outcome (n = 44) | | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|---|---|---|---|
| Risk Factor | Cure (n = 178) | Treatment Completed (n = 38) | Treatment Failure (n = 41) | Death (n = 3) | Odds Ratio (95% CI) | *P* Value | Odds Ratio (95% CI) | *P* Value |
| Sex | | | | | 1.429 (.739–2.762) | .289 | 1.333 (.644–2.757) | .439 |
| Male | 113 | 28 | 24 | 1 | | | | |
| Female | 65 | 10 | 17 | 2 | | | | |
| Age, y | | | | | | .826 | | .941 |
| 18–24 | 25 | 6 | 5 | 0 | | | | |
| 25–44 | 82 | 16 | 19 | 2 | | | | |
| 45–65 | 70 | 16 | 17 | 1 | | | | |
| Body mass index | | | | | | .112 | | .156 |
| <18.5 | 45 | 8 | 10 | 1 | | | | |
| 18.5–23.9 | 108 | 28 | 24 | 1 | | | | |
| ≥24 | 25 | 2 | 7 | 1 | | | | |
| Albumin level, g/L | | | | | 0.307 (.105–.896) | .031 | 0.374 (.119–1.173) | .092 |
| <30 | 11 | 2 | 2 | 1 | | | | |
| ≥30 | 167 | 36 | 39 | 2 | | | | |
| Combined with diabetes | | | | | 0.701 (.309–1.594) | .397 | 1.342 (.541–3.325) | .526 |
| Yes | 23 | 10 | 9 | 0 | | | | |
| No | 155 | 28 | 32 | 3 | | | | |
| Combined with pulmonary cavity | | | | | 3.111 (1.593–6.075) | .001 | 2.639 (1.287–5.409) | .008 |
| Yes | 61 | 12 | 26 | 1 | | | | |
| No | 117 | 26 | 15 | 2 | | | | |
| No. of cavities | | | | | | .189 | | |
| ≤2 | 163 | 36 | 36 | 3 | | | | |
| 3–5 | 12 | 1 | 5 | 0 | | | | |
| ≥6 | 3 | 1 | 0 | 0 | | | | |

Abbreviation: BMI, body mass index.

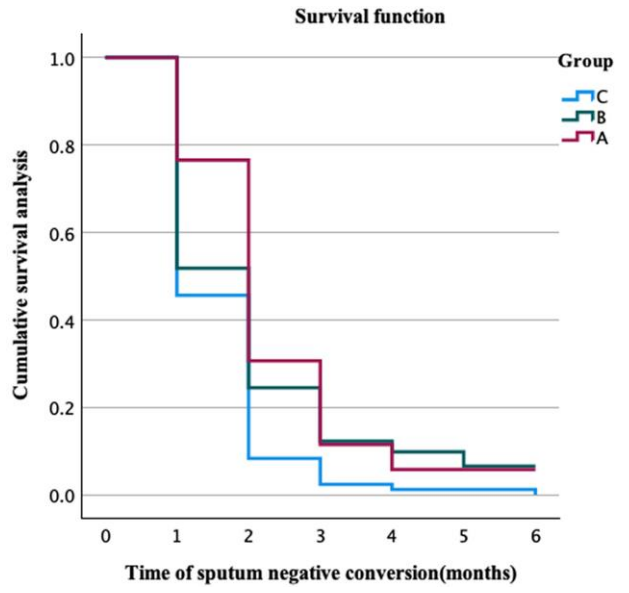


**Figure 3.** Comparison of the time to sputum culture conversion to negative among groups A, B, and C.

missed visits at rates that were lower than the corresponding rate for control group A. These results suggest that the novel all-oral regimens evaluated in groups B and C may reduce missed visit rates, thereby improving treatment adherence and outcomes as compared with injectable-based regimens.

Adverse reaction rates varied significantly among groups, with hyperuricemia incidence rates lower in groups B and C than in group A. However, group C experienced relatively higher rates of peripheral neuropathy and blood system abnormalities, primarily linked to LZD use. A systematic review reported that 35% of patients discontinued LZD due to adverse effects, including peripheral neuropathy (31%) and anemia (25%) [21]. Additionally, group C had the highest QTcF interval prolongation rate, likely caused by the combined effects of BDQ, MFX, and CFZ. A prior study indicated that CFZ is a primary contributor to QTcF prolongation in BDQ-containing regimens, with QTcF intervals in the BPaLM group more closely resembling those in the BPaL group than the standard 9- to 20-month regimens [20]. These findings underscore the importance of closely monitoring patients for cardiotoxicity and other adverse events during treatment.

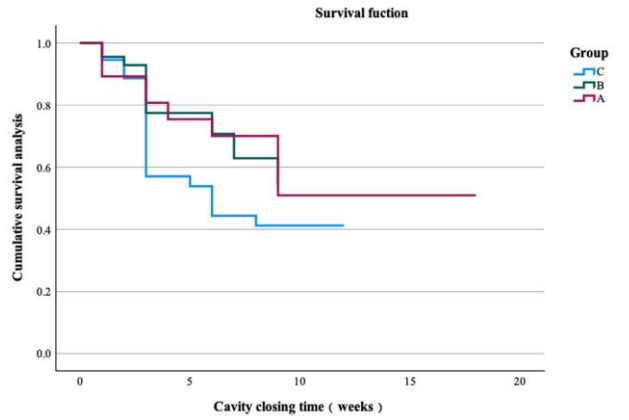


**Figure 4.** Comparison of pulmonary cavity closure time among groups A, B, and C.

**Table 5. Adverse Events of Included Patients During Treatment in the 3 Groups**

| Adverse Event | Group A (n = 84) | Group B (n = 100) | Group C (n = 103) | *P* Value |
|---|---|---|---|---|
| Liver damage | 17 (20.2) | 22 (22.0) | 12 (11.7) | .122 |
| Renal injury | 0 (0.0) | 0 (0.0) | 1 (1.0) | … |
| Hyperuricemia | 22 (26.2) | 27 (27.0) | 10 (9.7) | .003 |
| Gastrointestinal disorders | 15 (17.9) | 22 (22.0) | 13 (12.6) | .210 |
| Peripheral neuropathy | 0 (0.0) | 10 (10.0) | 26 (25.2) | <.001 |
| Fever | 0 (0.0) | 0 (0.0) | 0 (0.0) | … |
| Rash | 1 (1.2) | 2 (2.0) | 1 (1.0) | … |
| Blood system abnormalities | 2 (2.4) | 13 (13.0) | 11 (10.7) | .034 |
| Arrhythmia | 0 (0.0) | 1 (1.0) | 4 (3.9) | … |
| Visual disturbances | 0 (0.0) | 0 (0.0) | 2 (1.9) | … |
| Mental and psychological disorders | 3 (3.6) | 3 (3.0) | 4 (3.9) | … |
| Cardiotoxic QTcF interval prolongation | 5 (6.0) | 9 (10.0) | 25 (24.3) | <.001 |
| Skin blackening | 18 (21.4) | 22 (22.0) | 44 (42.7) | <.001 |
| Ototoxicity | 1 (1.2) | 2 (2.0) | 2 (1.9) | … |
| Adverse reactions involving joints or soft tissues | 0 (0.0) | 1 (1.0) | 2 (1.9) | … |
| Hypothyroidism | 0 (0.0) | 0 (0.0) | 0 (0.0) | … |
| Electrolyte abnormalities | 1 (1.2) | 3 (3.0) | 0 (0.0) | … |

See Table 1 for regimen per group.

This study had several limitations. First, group C was not randomized due to the high cost of BDQ and the inability of some patients to accept BDQ-containing regimens. This nonrandomized design was implemented to expedite the evaluation of the effectiveness and safety of the group C regimen and was modeled after the Nix-TB prospective single-arm clinical study, in which participants were first enrolled in the experimental group, followed by the other experimental and control groups. Second, clinical outcomes were evaluated only up to the completion of therapy, without posttreatment follow-up to assess relapse rates. Future studies should address this limitation by analyzing recurrence rates across all 3 groups. Third, while further analysis of factors associated with increased adverse reaction risk would have been valuable, limited data precluded such an investigation in this study. Fourth, regular resistance testing was not conducted during treatment, resulting in missed opportunities to detect acquired FQ resistance, which may have contributed to suboptimal outcomes in some patients. Future research should include continuous resistance monitoring throughout the treatment period to enable timely regimen adjustments. Finally, the relatively small sample size and the exclusion of patients who were HIV positive and those who were receiving antiretroviral therapy may limit the generalizability of these findings. Larger studies with more diverse patient populations are necessary to improve the robustness and applicability of the conclusions.

In conclusion, a new short-term all-oral regimen containing BDQ, MFX, LZD, CFZ, and Cs shows promise as an effective treatment for patients with MDR/RR-TB. The findings from this study provide valuable insights to inform the development of improved therapies for MDR/RR-TB in China. Further research is urgently needed to optimize regimens incorporating BDQ and other novel agents to simplify and shorten MDR/RR-TB treatment protocols.

## Notes

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***Author contributions.*** N. C. and W. N. designed this study. W. J., W. S., and Q. L. participated in the data analysis. W. J., W. N., Q. W., and Jun W. wrote the manuscript. L. M., M.H., Jing W., Y. D., B. C., and X. L. participated in the data collection and patient follow-up. All authors approved the final version of the article.

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