Decreased mortality seen in rifampicin/multidrug-resistant tuberculosis meningitis treated with linezolid in Shenzhen, China

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Abstract
Background: The morbidity of rifampicin/multidrug-resistant tuberculosis meningitis (RR/MDR-TBM) has shown an increasing trend globally. Its mortality rate is significantly higher than that of non-rifampicin/multidrug-resistant tuberculosis meningitis (NRR/MDR-TBM). This article aimed to explore risk factors related to RR/MDR-TBM, and compare therapeutic effects of linezolid (LZD)- and non-linezolid-containing regimen for RR/MDR-TB patients in Shenzhen city. Furthermore, we aimed to find a better therapy for pathogen-negative TBM with RR/MDR-TBM related risk factors.

Methods: We conducted a retrospective study enrolling 137 hospitalized cases with confirmed TBM from June 2014 to March 2020. All patients were divided into RR/MDR-TBM group (12 cases) and NRR/MDR-TBM group (125 cases) based on GeneXpert MTB/RIF and (or) phenotypic drug susceptibility test results using cerebral spinal fluid (CSF). The risk factors related to RR/MDR-TBM were investigated through comparing clinical and examination features between the two groups. The mortality rate of RR/MDR-TBM patients treated with different regimens was analyzed to compare their respective therapeutic effects. A difference of \( P < 0.05 \) was considered statistically significant.

Results: Most patients (111/137, 81%) were from southern or southwestern China, and a large proportion (72/137, 52.55%) belonged to migrant workers. 12 cases were RR/MDR-TBM (12/137, 8.8%) while 125 cases were NRR/MDR-TBM (125/137, 91.2%). The proportion of patients having prior TB treatment history in the RR/MDR-TBM group was significantly higher than that of the NRR/MDR-TBM group (6/12 vs. 12/125, 50% vs. 10.5%, \( P < 0.01 \)). No significant difference was observed on other clinical and examination features between the two groups. Mortality was significantly lower in RR/MDR-TBM patients on linezolid-containing treatment regimen than those who were not (0/7 versus 3/5, 0% versus 60%, \( P = 0.045 \)).

Conclusions: The main related risk factor of RR/MDR-TBM is the history of anti-tuberculosis treatment. Linezolid-containing regimen appears to lower mortality rate of RR/MDR-TBM significantly in our study. We think Linezolid should be evaluated prospectively in the treatment of RR/MDR-TBM.

Keywords: Tuberculous meningitis, Linezolid, Blood–brain barrier, Rifampicin/multidrug-resistant TBM
serious central nervous system sequelae [1, 2]. In recent years, an increase in the number of drug-resistant tuberculosis meningitis cases has been reported. Compared to non-drug-resistant tuberculosis meningitis, drug-resistant tuberculosis meningitis, especially rifampicin/multidrug-resistant tuberculosis meningitis (RR/MDR-TBM) is more lethal with increased medical cost for the patient [3, 4]. China is the world’s second largest country with a high burden of RR/MDR-TB, the estimated number of people infected with RR/MDR-TB in 2019 was about 65,000 (about 14% of the world total). RR/MDR-TB accounted for 7.1% and 23% in newly diagnosed and previously treated tuberculosis patients respectively [5]. As the most lethal form of tuberculosis, the incidence of TBM constituted about 1% of all tuberculosis cases worldwide [6], and about 7.23% of extrapulmonary tuberculosis cases in China [7]. However, the incidence of RR/MDR-TBM and its related risk factors remains unclear. Herein, we conducted a retrospective study in which 137 confirmed TBM patients were enrolled. These patients were hospitalized in the Third People’s Hospital of Shenzhen from June 2014 to March 2020. The hospital is the only designated hospital for the treatment of TBM patients in Shenzhen city. Shenzhen is a megacity with a long-term lived population of more than 13 million, with a large floating population of migrant workers from other cities, especially the southern and southwestern provinces of China. Thus TBM cases being treated in our hospital can reflect the general situation of the disease in south and southwest China to some extent. We compared the related characteristics (including demographic, clinical and examination characteristics) between RR/MDR-TBM and non-rifampicin/multidrug-resistant tuberculosis meningitis (NRR/MDR-TBM) patients to explore risk factors associated with RR/MDR-TBM. Furthermore, we compared the effects of linezolid- (LZD) and non-linezolid-containing (non-LZD) regimens on the prognosis of RR/MDR-TBM. On this basis, we discussed the empirical treatment regimen for pathogen-negative TBM with RR/MDR-TBM related risk factors. We hope it will help improve the prognosis of RR/MDR-TBM and pathogen-negative TBM in China.

**Method**

**Patients’ enrollment and data collection:**

1) Enrollment process: This study adopted a retrospective method. We collected the data of 151 tuberculous meningitis patients who were hospitalized and met the diagnostic criteria for confirmed tuberculous meningitis from June 2014 to March 2020. Among them, 14 patients who did not perform GeneXpert MTB/RIF and drug susceptibility test (DST) were excluded. Finally, 137 patients were enrolled in the study (Fig. 1), including 98 males and 39 females, age ranged from 2 to 76 years, with a median age of 29 years. We collected the demographicclinical and examination characteristics of these patients from the medical record through the hospital information system (HIS) and the hospital laboratory information system (LIS), and confirmed the survival status of discharged patients through phone and medical follow-up.

2) Entry criteria: Met the diagnostic criteria for definite tuberculous meningitis [8], that is, in addition to the clinical manifestations of TBM and abnormality of cerebrospinal fluid (CSF), the patient’s CSF examination met at least one of the following two criteria: 1. GeneXpert MTB/RIF (GeneXpert) positive nucleic acid test for *Mycobacterium tuberculosis* (MTB). 2. BACTEC MGIT 960 positive culture identifying as MTB, with a phenotypic drug sensitivity test (DST) performed simultaneously. Only one pathogen-positive CSF result was analyzed for each patient.

3) Diagnostic criteria for RR/MDR TBM cases: Met the diagnostic criteria for definite tuberculous meningitis case and fulfilled at least one of the following two criteria: 1. Positive GeneXpert test indicating resistance to rifampicin (RIF) 2. CSF MTB positive culture, and DST showing resistance to rifampicin and resistance or sensitivity to isoniazid.

4) We described the demographic features of TBM patients according to the results of GeneXpert and/or DST in CSF. All patients were divided into RR/MDR group and NRR/MDR group, then we compared the differences of the main clinical and examination characteristics between the two groups. On this basis, we explored the associated risk factors of RR/MDR TBM. Finally, we compared the differences in mortality between the two groups and the impact of different regimen on the prognosis of RR/MDR-TBM.

**Laboratory examination**

1) Method of obtaining CSF specimen: Lumbar puncture was performed within 24 h from admission. For patients whose CSF was acquired through lateral ventricle drainage, the pressure of CSF was measured. The CSF specimen was submitted at once after collection for tests such as white blood cell count and classification, biochemistry, acid-fast bacillus (AFB), GeneXpert, MTB culture and species identification, *Candida* membrane polysaccharide antigen, bacte-
ria and fungi smears and culture. The volume of CSF used for GeneXpert and MTB culture was 1–2 ml.

(2). Laboratory examination method:

1). GeneXpert MTB/RIF: According to literature and instrument operating instructions [9, 10].

2). BACTEC MGIT 960 Mycobacterium Culture Identification System for cerebrospinal fluid MTB: according to literature [11].

3). The phenotypic drug susceptibility test (DST) of MTB: absolute concentration method was adopted [12]. The test covered a minimum of 4 drugs (isoniazid, rifampin, ethambutol, streptomycin), including low and high concentration.

4). Acid-fast staining, white blood cell count and classification, biochemistry of CSF and blood routine, blood biochemistry, blood tuberculosis interferon release assay (IGRA) and HIV antibody were operated in accordance with the instruction of the instrument and kit.

(3). Anti-tuberculosis treatment regimen: Non-RR/MDR-TBM group: Anti-tuberculosis treatment regimen included: Isoniazid (10–15 mg/Kg/day, the maximum dose was 0.9 g/day, administered intravenously during hospitalization, then changed to oral administration after discharge); Rifampicin (10-15 mg/Kg/day, maximum 0.6 g/day, administered intravenously during hospitalization, and changed to oral administration after discharge); Pyrazinamide (25–30 mg/Kg/day, 1.5–2.0 g for adults, oral or nasal administration); ethambutal (15 mg/kg/day, 0.75–1.0 g for adults, oral or nasal administration). Some patients were supplemented with streptomycin injection or levofloxacin (or moxifloxacin) on top of the above. Full course of treatment for
NRR/MDR-TBM is 12–18 months except in the patient’s death. RR/MDR-TBM group: 7 patients were treated with LZD-containing regimen (LZD 1200 mg/day, intravenously or orally in the first 2 weeks of hospitalization, then changed to oral administration 600 mg/day, for a course of 3 to 18 months). The regimen also included levofloxacin (or moxifloxacin) and 2–4 of the following drugs: cycloserine, pyrazinamide, high-dose isoniazid, amikacin, protonamide, in dosage in accordance with the nation’s management guideline for RR/MDR-TB). Five patients received the non-LZD-containing regimen in the early stage which included the following 4–6 drugs: levofloxacin (moxifloxacin), pyrazinamide, high-dose isoniazid, rifampicin, amikacin, protonamide, cycloserine and ethambutol. The scheduled course of treatment for RR/MDR-TBM was a minimum of 24 months except for the patient’s death. In addition to anti-tuberculosis therapy, all patients were treated with glucocorticoids for up to 3 months and other adjuvant treatments deemed necessary such as mannitol for lowering intracranial pressure. Several were performed with lateral ventricle drainage.

(4). Treatment outcome: expressed as survival status at the end of the treatment course [13]. In the case the course of treatment had not been finished, the survival status at 6 months of treatment was taken as treatment outcome. Treatment outcome was expressed as death or survival.

(5). Statistical methods: qualitative data were expressed as percentages; quantitative data were expressed as mean or median± standard deviation. Rates were compared using chi-square test or Fisher’s exact probability method, and quantitative data were compared using t-test or rank-sum test. The difference was considered statistically significant when P < 0.05. The statistical software used is Prism 5.0 software package.

Results

1. Birthplace and occupational distribution of the TBM patients: most of the patients came from southern and southwestern provinces of China, such as Guangdong province (18.3%) and Guangxi Zhuang Autonomous Region (9.5%). Migrant workers (72 cases, 52.55%) were the most common occupation for these patients (Table 1).

| Native place                     | Cases number | Ratio |
|----------------------------------|--------------|-------|
| Shenzhen city                    | 10           | 7.3%  |
| Guangdong province (except Shenzhen) | 25           | 18.3% |
| Guangxi Zhuang Autonomous Region | 13           | 9.5%  |
| Hunan province                   | 12           | 8.8%  |
| Jiangxi province                 | 11           | 8.0%  |
| Hubei province                   | 8            | 5.8%  |
| Sichuan province                 | 13           | 9.5%  |
| Guizhou province                 | 10           | 7.3%  |
| Chongqing city                   | 9            | 6.6%  |
| Unknown place                    | 7            | 5.1%  |
| Other 11 province or city        | 19           | 13.9% |

| Occupation                      | Cases number | Ratio |
|----------------------------------|--------------|-------|
| Migrant worker                   | 72           | 52.6% |
| Staff (white collar)             | 15           | 11.0% |
| Unemployment or housework        | 12           | 8.8%  |
| Retirement                       | 10           | 7.3%  |
| Self-employed people             | 8            | 5.8%  |
| Homeless people                  | 8            | 5.8%  |
| Students                         | 6            | 4.4%  |
| Imprisoned                       | 3            | 2.2%  |
| Farmer                           | 3            | 2.2%  |

2. Drug resistance profile of the TBM patients: the difference of drug resistance between new cases and previously treated cases was (6/119, 5.0%) and (6/18, 33.3%) for rifampicin and (3/119, 2.5%) and (4/18, 22.2%) for multidrug respectively. Both were shown to be significant statistically (P < 0.01) (Table 2).

3. Comparison of clinical features and CSF examination features between RR/MDR-TBM group and NRR/MDR-TBM groups: 50% of the patients in the RR/MDR-TBM group had a history of anti-tuberculosis treatment (6/12), while only 10.5% were reported in
the NRR/MDR-TBM group (6/125). The difference between the two groups was statistically significant (P < 0.01). Difference in other factors showed no statistical significance (Table 3).

4. Comparison of mortality between RR/MDR-TBM group and NRR/MDR-TBM group: the difference of mortality between RR/MDR-TBM group and NRR/MDR-TBM group showed no statistical significance, regardless of treatment completion and follow-up status. See Table 4.

5. Comparison of mortality between RR/MDR-TBM patients groups treated with different regimens: among RR/MDR-TBM patients, the mortality of patients treated with LZD-containing regimen at early treatment stage was significantly lower compared with those without (P = 0.045), see Table 5–6.

### Table 3 The comparison of the features between RR/MDR-TBM and NRR/MDR-TBM groups

|                | TBM     | RR/MDR-TBM | NRR/MDR-TBM | P value |
|----------------|---------|------------|-------------|---------|
| Total          | 137     | 12         | 125         |         |
| Male           | 98      | 11         | 87          | 0.178   |
| Age(year)      | 29      | 29±18      | 29±12.25    | 0.927   |
| TB history     | 18      | 6          | 12          | <0.001  |
| Miliary PTB    | 71      | 6          | 65          | 0.895   |
| Active PTB     | 55      | 6          | 49          | 0.466   |
| Extrapulmonary TB | 44  | 4          | 40          | 0.819   |
| HIV co-infection | 17  | 2          | 15          | 0.992   |
| Type-II diabetes | 7   | 1          | 6           | 0.595   |
| Course of disease (days from onset to admission) | 10±10 | 3±12 | 10±10 | 0.314 |
| Headache       | 85      | 5          | 80          | 0.128   |
| Fever          | 93      | 8          | 85          | 0.433   |
| Vomiting       | 40      | 2          | 38          | 0.505   |
| Convulsions    | 12      | 3          | 9           | 0.123   |
| Consciousness disorder | 56  | 7          | 49          | 0.198   |
| Neck stiff     | 114     | 10         | 105         | 0.725   |
| Cranial nerve impairment | 23  | 2          | 21          | 0.695   |
| Pathological sign | 33  | 6          | 33          | 0.084   |
| Paralysis      | 9       | 1          | 8           | 0.725   |
| GCS score      | 13.13±2.57 | 12.25±2.83 | 13.22±2.54 | 0.215   |
| BMRC gradel    | 76      | 4          | 72          | 0.190   |
| BMRC gradell   | 33      | 4          | 29          | 0.667   |
| BMRC grade III | 28    | 4          | 24          | 0.432   |
| Death/total    | 24/87   | 3/12       | 21/75       | 0.895   |
| Hyponatremia   | 35      | 5          | 30          | 0.180   |
| IGRA (positive/total) | 98/128 | 8/11       | 90/117      | 0.954   |
| CD4 T cell count | 221±189 | 213±188    | 280±196     | 0.156   |
| CSF examination|         |            |             |         |
| Elevated CSF pressure | 72  | 7          | 65          | 0.675   |
| WBC (10⁹/L)    | 231±87.5 | 104±442.3 | 287±389    | 0.060   |
| NEUT%          | 56.8±24.8 | 57.5±24.9 | 56.8±24.9 | 0.961   |
| PRO (mg/L)     | 1843±1201 | 1885±1222 | 1407±714   | 0.167   |
| CL (mmol/L)    | 110±12.3 | 110.6±12.5 | 112.7±10.96 | 0.385   |
| GLU (mmol/L)   | 1.9±1.2 | 1.9±1.2    | 2.0±1.0    | 0.522   |
| ADA (U/L)      | 8.7±15.6 | 5.4±4.2    | 9.0±16.3   | 0.172   |

(N)RR/MDR-TBM, (non) rifampicin/multidrug-resistant tuberculous meningitis

PTB, pulmonary tuberculosis; HIV, human immunodeficiency virus; GCS, Glasgow Coma Scale; BMRC, the modified British Medical Research Council; Grade I (GCS 15; no focal neurological signs); grade II (GCS 11–14, or 15 with focal neurological signs), and grade III (GCS ≤ 10) disease. IGRA, interferon gamma release assay; CSF, cerebrospinal fluid; WBC, white blood cell; NEUT, neutrophilic granulocyte; PRO, total protein; CL, chloride; GLU, glucose; ADA, adenosine deaminase
The study showed that most of the TBM patients being treated in our hospital were from the south and southwest of China, with a large proportion of them being migrant workers. RR/MDR-TBM accounted for a relatively high proportion among them. The history of anti-tuberculosis treatment was found to be one of the related risk factors for RR/MDR-TBM. Treatment regimen comprising linezolid seemed to be decreasing the mortality of RR/MDR-TBM significantly.

The incidence of TB in the south and southwest of China has been reported to be higher than other regions of the country. This was found to be consistent with the findings in our study based on patient’s demographic data. More than half of the patients in our study were migrant workers. The high incidence of TBM among them may be attributed to poor nutrition and deprivation of rest resulted from a low income and long working hours. A weak or impaired immune system fails to provide proper defense against Mycobacteria tuberculosis.

More and more RR/MDR-TBM had been reported in recent years. Some small sample size studies had shown that RR/MDR-TBM accounted for 12%–39.29% of TBM patients in western China, and the ratio of isoniazid-resistant TBM even reached as high as 64.29% [14, 15]. Even in children with first-time TB infection, MDR and XDR accounted for 7.2% [16]. Although the sample size of these studies was small, it still indicated that RR/MDR-TBM is not a rare disease in China. Reports from other countries also suggested that RR/MDR-TBM constituted a relatively high proportion of TBM patients [3, 4, 17, 18]. Our study showed the proportion of RR/MDR-TBM patients in Shenzhen is also high (12/137, 8.8%). In terms of proportion, RR/MDR-TBM in previously treated cases is significantly higher than that of primary infection cases (33.3% vs. 5.0%, P < 0.01), which is in line with the situation of RR/MDR-PTB. This can be explained by the fact that TBM is developed from PTB. Therefore, the history of anti-tuberculosis treatment should be considered as the main risk factor for RR/MDR-TBM.

### Table 4

|                  | Total | RR/MDR-TMB | nRR/MDR-TBM | P value |
|------------------|-------|------------|-------------|---------|
| Deaths           | 24    | 3          | 21          |         |
| Survivors        | 63    | 9          | 54          |         |
| Loss to follow-up| 50    | 0          | 50          |         |
| Mortality1       | 27.6% | 25.0%      | 28.0%       | 0.895   |
| Mortality2       | 17.5% | 25.0%      | 16.8%       | 0.752   |
| Mortality3       | 54.0% | 25.0%      | 56.8%       | 0.071   |

Mortality 1: excluding those lost to follow-up. Mortality 2: including those lost to follow-up and assuming all of them survived. Mortality 3: including those lost to follow-up and assuming all of them demised.

### Table 5

| Linezolid containing regimen | Non-linezolid regimen | P value |
|------------------------------|-----------------------|---------|
| Total cases                  | 7                     | 5       |         |
| Death                        | 0                     | 3       |         |
| Mortality                    | 0%                    | 60%     | 0.045   |

### Table 6

| Group | Case | Age range (y) | Length of disease(d) | BMRC | HIV | Mi-TB | Regimen | Length of Lzd(m) | Outcomes |
|-------|------|---------------|----------------------|------|-----|-------|---------|------------------|----------|
| LZD   | Case1| 15–24         | 3                    | III  | –   | +     | LZD-INH-PZA-Mfx-Cs | 3        | Survival          |
| Case2 | 25–34 | 7             | II                   | –    | –   | –     | LZD-Mfx-CS-PZA-INH-Pto | 6        | Survival          |
| Case3 | 25–34 | 14            | III                  | –    | –   | –     | LZD-Mfx-Pro-PZA-Am  | 6        | Survival          |
| Case4 | 25–34 | 1             | II                   | –    | +   | +     | LZD-INH-PAZ-EMB-Lfx-Am | 6        | Survival          |
| Case5 | 25–34 | 3             | I                    | +    | +   | +     | LZD-Mfx-Pro-PZA-Am  | 8        | Survival          |
| Case6 | 15–24 | 1             | I                    | +    | +   | +     | LZD-Mfx-Pza-Pro-Am  | 9        | Survival          |
| Case7 | 35–44 | 15            | I                    | –    | –   | –     | LZD-INH-PZA-Mfx-CS | 10       | Survival          |
| Non-LZD | Case8 | 24–34       | 77                   | II   | –   | –     | INH-RIF-PZA-EMB-Lfx  | Death    | Death              |
| Case9 | 15–24 | 3             | II                   | –    | –   | –     | INH-RIF-PZA-Moxifloxacin | Death   | Death              |
| Case10| 25–34 | 21            | III                  | –    | +   | +     | INH-PZA-Moxifloxacin-Pro-Am | Survival | Survival          |
| Case11| 45–54 | 1             | I                    | –    | +   | +     | INH-RIF-PZA-EMB  | Death    | Death              |
| Case12| 45–54 | 3             | III                  | –    | –   | –     | INH-PZA-EMB-Lfx-Am | death   | death              |

F, female; m, male; y, year; d, day; m, month; HIV, human immunodeficiency virus; mi-TB, military tuberculosis; BMRC, the modified British Medical Research Council. Grade I (GCS 15; no focal neurological sign), grade II (GCS 11–14, or 15 with focal neurological sign), and grade III (GCS ≤ 10) disease. INH, isoniazid; RIF, rifampicin; PZA, pyrazinamide; EMB, ethambutol; Lfx, levofloxacin; Mfx, moxifloxacin; Am, amikacin; Cs, cycloserine; LZD, linezolid; Pto, prothionamide.
According to the previous report, 13 mg/kg of IV RIF can achieve an equivalent of AUC0-24 h which drives rifampicin effect and a higher Cmax compared to 20 mg/kg of orally administered RIF [20].

Many patients in the NRR/MDR-TBM group were lost to follow-up. Reasons behind may include: an invalid contact number due to an expired calling card or the patient leaving the city to return to his/her birthplace due to loss of job. Secondly, we cannot rule out that possibility of the telephone number being cancelled was due to the patients’ death. So we assume two extreme situations, that is, patients who were lost to follow-up in this study either survived or died (the real situation should locate between these two extremes). And the results showed that in any case, the difference of mortality between the RR/MDR-TBM group and NRR/MDR-TBM group remained insignificant, indicating that after timely and proper anti-TB treatment, the mortality of RR/MDR-TBM patients was not higher than that of NRR/MDR-TBM.

Among RR/MDR-TBM patients, mortality rate in patients on treatment regimen with LZD was significantly lower than those without (see Tables 5–6). This showed that LZD may improve treatment outcome due to its strong early bactericidal activity (EBA) and excellent permeability through the blood–brain barrier (BBB). Its CSF-to-serum ratio of the areas under the curves nearly reached 1.0 [23]. Some retrospective studies had indicated that LZD was able to manifest satisfactory effect to life-threatening TBM and improved their early outcomes for both children and adult TBM patients. In Li’s research involving 86 children with TBM, 32 (88.9%) in 36 LZD-treated hospitalized cases and 35 (70%) of 50 control group had favorable outcomes (p = 0.037). In addition, there was no significant difference in the frequency of adverse effect between the 2 groups [24]. In another research conducted by Sun et al. 16 LZD-treated TBM patients (BMRC grade II or III) achieved a faster and higher percentage of Glasgow coma scale and temperature recovery, a higher CSF/blood glucose ratio, and lower CSF white blood cell counts than the control group did (p < 0.05) [25]. But in these two studies, DST or fast detection of MTB nucleic acid such as Genexpert MTB/RIF had not been performed, so the proportion of RR/MDR-TBM was unclear. The addition of a single drug to a failing regimen is perilous, as it may induce further resistance. Meanwhile, the case number in Sun et al.’s study is too small to reach a good representation of evidence-based conclusion and the study only evaluated interim outcome, long term outcome was not known. Only some case reports observed favorable long term outcomes of RR/MDR-TBM patients who received LZD treatment.
To our knowledge, our cohort study appears to be the first one to evaluate the long term outcomes of LZD-containing regimen on RR/MDR-TBM patients. For pathogen-positive TBM cases, anti-tuberculosis treatment regimen can be formulated based on the results of drug sensitivity test. Unfortunately, only less than 40% of total non-HIV TBM cases in this study were tested pathogen-positive even with the use of assays with high sensitivity and specificity like GeneXpert RIF/MTB or GeneXpert Ultra [28]. For pathogen-negative cases, it is advisable to initiate empirical anti-tuberculosis treatment as early as possible. The regimen consists of first-line drugs (isoniazid, rifampicin, pyrazinamide, ethambutol), which, however, has yielded unsatisfactory outcome on drug-resistant TBM, especially RR/MDR-TBM. Even when fluoroquinolones is added to the regimen and the dose of rifampicin is increased, it can only lower the mortality of isoniazid-resistant TBM but not that of RR/MDR-TBM [3, 18]. Previous literatures and our study showed that the proportion of RR/MDR-TBM in pathogen-positive TBM patients with prior TB treatment history is very high in China. We believe the same also exists in pathogen-negative TBM patients with previous TB treatment history. Treatment regimen composes of first-line anti-tuberculosis drugs alone will obviously worsen their outcome. So for pathogen-negative TBM cases treated previously, linezolid may be beneficial when it is added to an empirical treatment regimen. But this should be evaluated by large scale and prospective study. Meanwhile the regimen should contain other effective second-line drugs, such as levofloxacin (moxifloxacin) or cycloserine [29]. The challenge, however, is whether RIF should be included in the regimen, since more than 60% of the previously treated TBM patients in our study showed sensitivity to RIF, and a large proportion of them complicated with PTB, so RIF and other first-line drugs should also be included.

There are some limitations in this study. First of all, it is unclear whether the drug resistance profile of pathogen-negative TBM patients is exactly the same as that of pathogen-positive TBM patient. Meanwhile, DST did not test sensitivity to some second line drugs such as linezolid, fluoroquinolones and cycloserine. Secondly, the number of RR/MDR-TBM cases was very small, so the lower mortality was not necessarily due to LZD but maybe by chance. It is necessary to further increase case number for a prospective multicenter cohort study to evaluate the efficacy and adverse effects of LZD-containing regimens. Finally, the high proportion of lost to follow-up patients in the NRR/MDR-TBM group also made it difficult to analyze the results, although we had made appropriate assumptions.

Conclusions
The history of anti-tuberculosis treatment is considered to be the main related risk factor of RR/MDR-TBM. Notwithstanding our small sample size retrospective study, LZD-containing regimen seemed to lower the mortality of RR/MDR-TBM significantly. We think LZD should be evaluated prospectively in the treatment of RR/MDR-TBM.

Abbreviations
ADA: Adenosine deaminase; AFB: Acid fast bacilli; BBB: Blood brain barrier; BMRC: The modified British Medical Research Council; CL: Chloride; CSF: Cerebrospinal fluid; DST: Drug susceptibility test; EBA: Early bactericidal activity; GLU: Glucose; GSC: Glasgow Coma Scale; HIS: Hospital information system; HIV: Human Immunodeficiency Virus; INH: Isoniazid; IS: Laboratory information system; LZD: Linezolid; MTB: Mycobacterium tuberculosis; NRR/MDR-TBM: Non-rifampicin/multidrug-resistant tuberculosis meningitis; PRO: Protein; PTB: Pulmonary tuberculosis; RIF: Rifampicin; RR/MDR-TBM: Rifampicin/multidrug-resistant tuberculosis meningitis; TB: Tuberculosis; WHO: World Health Organization.

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Authors’ contributions
MTF designed the research and contributed to the writing of the article and the addition of the references. MTF, YFS, ZM and JFZ were responsible for data collection, patients’ clinic visiting and telephone contact. HRA made contribution to the revision of the manuscript. PZZ was responsible for data analysis. HM L performed the main examination including GeneXpert MTB/RIF and DST, etc. ZYW, QTY, GFD and GBL provided critical comments and revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
Some of them have been provided in the manuscript, the rest was available from the corresponding author on reasonable request.

Declarations
Ethic approval and consent to participant
This study was approved by the ethics committee of The Third People’s Hospital of Shenzhen as part of the National Key Project for Infectious Disease and complied with the Declaration of Helsinki. Informed consent was not obtained as it is a retrospective study.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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