Linezolid-Containing Regimen Lowers Mortality of Rifampicin/Multidrug-Resistant Tuberculous Meningitis in Shenzhen, China

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Abstract

Background: The morbidity of rifampicin/multidrug-resistant tuberculous meningitis (RR/MDR-TBM) is increasing in many countries and regions in the world. Its mortality is significantly higher than non rifampicin/multidrug-resistant ones (NRR/MDR-TBM). This article aims to explore the RR/MDR-TBM related risk factors, and compare the different therapeutic effects to the RR/MDR-TBM patients between linezolid-containing anti-tuberculosis regimen and non linezolid regimen in Shenzhen city. Furthermore, we want to find a better therapy for pathogen negative TBM with RR/MDR-TBM related risk factors.

Methods: 137 cases with confirmed TBM (pathogen positive), who were hospitalized in the Third People's Hospital of Shenzhen from June 2014 to March 2020, were enrolled in this study, all patients were divided into RR/MDR-TBM group (12 cases) and NRR/MDR-TBM group (125 cases) according to the GeneXpert MTB/RIF and (or) phenotypic drug susceptibility test of CSF (cerebral spinal fluid). The risk factors related to RR/MDR-TBM were investigated through comparing the clinical and examination features between the two groups. The mortality of RR/MDR-TBM patients treated with different regimens was analyzed to compare their respective therapeutic effects to the RR/MDR-TBM. $P < 0.05$ differences is considered statistically significant.

Results: Most of the patients (111/137, 81%) were from southern or southwestern China, and a large proportion (72/137, 52.55%) is migrant workers. 12 cases were RR/MDR-TBM (12/137, 8.8%) in all TBM patients while 125 cases were NRR/MDR-TBM (125/137, 91.2%). The proportion of previously treated cases in RR/MDR-TBM group was significantly higher than that in NRR/MDR-TBM group (6/12 vs 12/125, 50% vs 10.5%, $P < 0.01$), while there was no significant difference in other clinical and examination features between the two groups. The mortality of RR/MDR-TBM treated with the linezolid-containing regimen was significantly lower than that treated with non linezolid regimen ($P = 0.045$).

Conclusions: The main related high-risk factor of RR/MDR-TBM is the history of anti-tuberculosis treatment. Linezolid-containing regimen appears to lower the mortality of RR/MDR-TBM significantly. Therefore, it is recommended that linezolid-containing regimen can be used as a better empirical anti-tuberculosis therapy for pathogen negative TBM previously treated in China.

Background:

Tuberculous meningitis (TBM) is the most fatal type of tuberculosis, especially in children or adults co-infected with HIV. Even after standardized anti-tuberculosis treatment, the mortality can still reach as high as 20%-50%, and nearly half of the survivors will develop serious central nervous system sequelae [1, 2]. In recent years, reports of drug-resistant tuberculosis meningitis have been increasing. Compared with non-drug-resistant tuberculosis meningitis, drug-resistant tuberculosis meningitis, especially rifampicin/multidrug-resistant tuberculous meningitis (RR/MDR-TBM) is more lethal and means more medical cost for the patient, so more and more attention has been paid to it [3, 4]. China is one of the 30 high burden RR/MDR-TB countries of the world, the estimated number of people with RR/MDR

tuberculosis in 2018 is about 66,000 (14% of the world). RR/MDR-TB accounts for 7.1% among the newly diagnosed tuberculosis patients, while among pulmonary tuberculosis patients treated previously ,RR/MDR-TB accounts for 21% [5]. As the most lethal tuberculosis type, the incidence of TBM accounts for about 1% of all tuberculosis [6], and it accounts for about 7.23% of extrapulmonary tuberculosis in China[7], however, the incidence of RR/MDR-TBM and its related risk factors are unknown. In this study, we describe the onset and drug resistance profile of 137 confirmed TBM patients who were hospitalized in the Third People's Hospital of Shenzhen city from June 2014 to March 2020, as the hospital is the only designated hospital for the treatment of TBM patients in Shenzhen city, its data for TBM can represent the general situation of the TBM onset in Shenzhen. We compared the related characteristics(including demographic, clinical and examination characteristics) between RR/MDR-TBM patients and non-rifampicin/multidrug-resistant tuberculous meningitis (NRR/MDR-TBM) patients to explore the RR/MDR-TBM related risk factors,furthermore, we compared the effects of linezolid-containing and non linezolid regimens on the prognosis of RR/MDR-TBM. On this basis, we discuss the empirical treatment regimen for pathogen-negative TBM with RR/MDR-TBM related risk factors—we hope it can improve the prognosis of RR/MDR-TBM and pathogen-negative TBM in China.

Method:

1: patients enrollment and data collection:

(1):Case enrollment process: This study adopts a retrospective method, we collect the data of 151 tuberculous meningitis patients who were hospitalized and met the diagnostic criteria for tuberculous meningitis from June 2014 to March 2020, among them, 14 patients who did not perform GeneXpert MTB/RIF and Mycobacterium tuberculosis phenotype drug susceptibility test(DST) were excluded. Finally, 137 patients were enrolled in the study, including 98 males and 39 females, the youngest was 2 years old, and the oldest was 76 years old, with a median of 29 years old. We collect the demographic/clinical and examination characteristics of patients through the HIS and LIS system of the hospital, and confirm the survival status of discharged patients through telephone contact or outpatient visit.

(2)Case entry criteria: meet the diagnostic criteria for definite tuberculous meningitis[8], that is, in addition to the clinical manifestations of tuberculous meningitis and abnormal cerebrospinal cytology and biochemical examinations, the patient's cerebrospinal fluid examination meets at least one of the following two criteria: 1. GeneXpert MTB/RIF (GeneXpert) indicates a positive nucleic acid test for Mycobacterium tuberculosis. 2. The BACTER MGIT960 liquid culture method for mycobacteria culture was positive and was identified as Mycobacterium tuberculosis (MTB), at the same time, a phenotypic drug sensitivity test was performed. Only one pathogen-positive CSF result was analyzed for each patient.

(3) Diagnostic criteria for RR/MDR TBM cases: meet the diagnostic criteria for definite tuberculous meningitis case and meet at least one of the following two criteria: 1.GeneXpert test is positive and

indicates resistant to rifampicin(RIF). 2. The cerebrospinal fluid MTB culture is positive, and the DST shows that it is resistant to rifampicin ,meanwhile, isoniazid is also resistant or sensitive.

(4) We described the demographic features of the TBM patients ,according to the results of CSF GeneXpert and/or DST, all patients were divided into RR/MDR group and NRR/MDR group,then we compare the differences of the main clinical and examination characteristics between the two groups, on this basis, we explore the main related risk factors of RR/MDR tuberculous meningitis, and compare the differences in mortality between the two groups and the impact of different regimen on the prognosis of RR/MDR-TBM.

2. Laboratory examination:

(1). Method of obtaining cerebrospinal fluid specimen: Lumbar puncture is performed within 24 hours after admission to obtain cerebrospinal fluid. Some patients' cerebrospinal fluid are acquired through lateral ventricle drainage, the pressure of cerebrospinal fluid is measured, and the CSF specimen is submitted at once after acquirement for tests such as routine cytology, biochemistry, acid-fast bacillus (AFB), GeneXpert, MTB culture and species identification, Cryptococcus membrane polysaccharide antigen, bacteria and fungi smears and culture, etc. the volume of CSF used for GeneXpert and MTB culture is 1–2 ml.

(2) Laboratory examination method:

1. GeneXpert MTB/RIF: According to the literature and instrument operating instructions [9, 10].
2. MGIT 960 Mycobacterium Culture Identification System for cerebrospinal fluid Mycobacterium tuberculosis: follow the literature and operating instructions [11].
3. The phenotypic drug susceptibility test(DST) of Mycobacterium tuberculosis adopts the absolute concentration method method: according to the literature and operating instructions [12].
4. Acid-fast staining, cytology, biochemistry of CSF and blood routine, blood biochemistry, blood tuberculosis interferon release assay, HIV antibody detection, etc. are operated in accordance with the instruction of the instrument and kit.

3. Anti-tuberculosis treatment regimen: Non-RR/MDR-TBM group: The anti-tuberculosis treatment regimen includes: Isoniazid (10–15 mg/Kg/day, the maximum dose is 0.9 g/day, intravenous administration is used during hospitalization, and it is changed into oral administration after discharge), Rifampicin (10–15 mg/Kg/day, the maximum amount is 0.6 g/day, intravenously administered during hospitalization, and changed into oral administration after discharge), Pyrazinamide (25–30 mg/Kg/day,1.5-2.0 g for adults, oral administration or nasal feeding), ethambutal(15 mg/kg/day,0.75-1.0 g for adults, oral administration or nasal feeding), some patients were plus streptomycin injection or levofloxacin (or moxifloxacin), the scheduled total course of treatment for NRR/MDR TBM is 12–18 months except for the patient's death. RR/MDR-TBM group: 7 patients were treated with linezolid-containing regimen (linezolid 0.6 g/day, intravenously or orally

administration during hospitalization, and changed into oral administration after discharge. The course of linezolid administration was 3 months to 18 months), the regimen include levofloxacin (or moxifloxacin) and the following 2–4 drugs: cycloserine, pyrazinamide, high-dose isoniazid, amikacin, protionamide, etc(the dose is in accordance with the nation's guideline of China for RR/MDR TB). Five patients receive the non-linezolid-containing regimen in the early stage. The regimen included the following 4–6 drugs: levofloxacin (moxifloxacin), pyrazinamide, high-dose isoniazid, rifampicin, amikacin, and protionamide, cycloserine, ethambutol, etc.the scheduled total course of treatment for RR/MDR TBM is 24 months at least except for the patient's death. In addition to anti-tuberculosis therapy, all patients were treated with glucocorticoids(the treatment course was up to 3 months) and other necessary adjuvant treatments such as mannitol for depressing intracranial pressure. several of them are performed with lateral ventricle drainage.

4. main outcome of the patients: survival status at the end of the course of treatment. If the the course of treatment has not been finished, the survival status at 6 months of treatment is considered as the main outcome, it is divided into death and survival.

(4)The enrollment of the patients, see figure 1.

5.Statistical methods: qualitative data are expressed as percentages, quantitative data are expressed as mean or median $\pm$ standard deviation, rates are compared using chi-square test or Fisher's exact probability method, and quantitative data are compared using t-test or rank-sum test, the difference was statistically significant when $P < 0.05$, and the statistical software used Prism 5.0 software package.

Results:

1. Native place and occupational distribution of the TBM patients: Most of the patients came from southern and southwestern provinces of China. The southern provinces mainly include: Guangdong Province (except Shenzhen, 25 cases, 18.25%), Guangxi Zhuang Autonomous Region (13 cases, 9.49%)), Hunan Province (12 cases, 8.76%), Jiangxi Province (11 cases, 8.03%), Hubei Province (8 cases, 5.84%), Shenzhen has only 10 native cases(7.3%). Southwestern provinces mainly include: Sichuan Province (13 cases, 9.49%), Guizhou Province (10 cases, 7.3%), Chongqing City (9 cases, 6.57%), and the other 11 provinces (19 cases,13.87%). The occupations are migrant workers (72 cases, 52.55%), staff (15 cases, 10.95%), unemployment or housework (12 cases, 8.76%), retirement (10 cases, 7.30%), self-employed (8 cases, 5.84%), Homeless people (8 cases, 5.84%), students (6 cases, 4.38%), prisoners (3 cases, 2.19%), farmers (3 cases, 2.19%), see Table 1.

2. Drug resistance profile of the TBM patients: Among all 137 patients, the resistance rate of rifampicin was 8.8% (12/137), the resistance rate of isoniazid was 3.4% (3/89), and the rate of multidrug resistance was 5.1% (7/137). Among new cases, the rifampicin resistance rate was 5.0% (6/119), the isoniazid resistance rate was 2.6% (2/78), and the multidrug resistance rate was 2.5% (3/119). Among the

previously treated cases, the resistance rate of rifampicin was 33.3% (6/18), the resistance rate of isoniazid was 3.4% (1/18), and the rate of multidrug resistance was 22.2% (4/18). The difference of rifampicin/multidrug resistance rate between the two groups are statistically significant, See Table 2.

3. Comparison of clinical features and cerebrospinal fluid examination features between the RR/MDR-TBM group and the NRR/MDR-TBM group: 50% of the patients in the RR/MDR-TBM group had a history of anti-tuberculosis treatment (6/ 12), while only 10.5% of the patients in the NRR/MDR-TBM group had a history of anti-tuberculosis treatment(6/125), the difference between the two groups was statistically significant, other factors including age, gender, type of pulmonary tuberculosis, and HIV infection, diabetes prevalence and clinical manifestations, cerebrospinal fluid tests, T lymphocyte subsets, T-SPOT, etc. had no significant difference between the two groups, see Table 3.

4.The 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 are not statistically significant, no matter whether the loss to follow-up are alive or not, see Table 4.

5. The comparison of mortality between RR/MDR-TBM patients groups treated with different regimens: Among RR/MDR-TBM patients, the mortality of these patients treated with linezolid -containing regimen in the early stage was significantly lower compared with the patients treated without linezolid regimen($P = 0.045$), see Table 5.

Table 1
the native place and occupational distribution of the patients

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%
criminal	3	2.2%
farmer	3	2.2%

Table 2
the drug resistant type of the TBM patients

Drug-Resistant type	total(137)	new cases(119)	previously treated cases(18)	P value
INH resistant	3/90(3.3%)	2/79(2.5%)	1/11(9.1%)	0.330
RFP resistant	12/137(8.8%)	6/119(5.0%)	6/18(33.3%)	< 0.01
multidrug resistant	7/137(5.1%)	3/119(2.5%)	4/18(22.2%)	< 0.01
<p>multidrug resistant: INH resistant plus RFP resistant. new cases: a newly registered episode of TB in a patient who has never been treated for TB or has taken anti-TB medicines for less than 1 month. previously treated cases: patients who have received 1 month or more of anti-TB medicines in the past.</p>				

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	<0.01
miliary PTB	71	6	65	0.895
secondary PTB	55	6	49	0.466
extrapulmonary TB	44	4	40	0.819
HIV co-infection	17	2	15	0.992
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
convulsion	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
GSC score	13.13 ± 2.57	12.25 ± 2.83	13.22 ± 2.54	0.215
BMRC stageⅡ	76	4	72	0.190
BMRC stageⅢ	33	4	29	0.667
BMRC stage Ⅳ	28	4	24	0.432
death/total	24/87	3/12	21/75	0.895
hyponatremia	35	5	30	0.180

	TBM	RR/MDR-TBM	NRR/MDR-TBM	P value
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	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	1843 ± 1201	1885 ± 1222	1407 ± 71.4	0.167
CL	110 ± 12.3	110.6 ± 12.5	112.7 ± 10.96	0.385
GLU	1.9 ± 1.2	1.9 ± 1.2	2.0 ± 1.0	0.522
ADA	8.7 ± 15.6	5.4 ± 4.2	9.0 ± 16.3	0.172

Table 4
the comparison of the mortality between RR/MDR-TBM and NRR/MDR-TBM groups

	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
the mortality of the RR/MDR-TBM patients treated with different regimens

	linezolid containing regimen	Non-linezolid regimen	P value
total cases	7	5	
death	0	3	
mortality	0%	60%	0.045

Discussion

The Third People's Hospital of Shenzhen is the only designated hospital for treatment of TBM patients in Shenzhen, Shenzhen is a megacity with a long-term lived population of more than 13 million, while the registered population account for less than 40%, and the native population just account for even far smaller proportion, most of the population are immigrant from other cities, this is also paralleled with the proportion of TB patients in their composition of domicile and population. Among the patients included in this study, only 10 patients belonged to registered Shenzhen population (7.3%), and 25 were from other cities of Guangdong province (18.3%). Others were mainly from southern province of China including 13 from Guangxi (9.5%) and 12 from Hunan (8.8%), 11 from Jiangxi (8.0%), 8 from Hubei (5.8%), and 13 from Sichuan (9.5%), 10 from Guizhou (7.3%), 9 from Chongqing (6.6%), etc., 7 people (5.1%) with unknown household registration, the number of cases from other 11 provinces is only 19 people (13.9%). More than half of the patients are migrant workers, and they are relatively young, with a median age of only 29. Therefore, our data can represent the incidence of TBM among the population in southern and southwestern provinces of China better than other researches, especially in the migrant workers in Shenzhen, the reason that the incidence of TBM is higher in the migrant workers in Shenzhen may be due to the migrant worker's low income and hard work, which lead to their poor nutrition condition and lack of break, these finally lower their immunity to resist to *Mycobacteria tuberculosis*.

China is the world's second largest country with a high burden of RR/ MDR-TB after India, the estimated number of people with RR/MDR tuberculosis in 2018 is about 66,000 (14% of the world). RR/MDR-TB accounts for 7.1% among the newly diagnosed tuberculosis patients, while Among pulmonary tuberculosis patients treated previously, RR/MDR-TB accounts for 21% [5]. As the most lethal tuberculosis type, there have been more and more reports of RR/MDR-TBM in China and abroad in recent years. Some small sample of studies have shown that RR/MDR-TBM accounts for 12%-39.29% of TBM patients in western China, isoniazid resistant TBM reached 64.29%[13, 14], even in children (untreated previously for tuberculosis) MDR and XDR accounted for 7.2%[15]. Although the sample size of the above studies is small, it also indicates that RR/MDR-TBM was not rare in China. Many foreign reports also suggest that RR/MDR-TBM accounts for a relatively high proportion of TBM patients [3, 4, 16, 17]. Our research shows that among all patients with positive pathogens and detected for rifampicin resistance, rifampicin resistance rate reached 8.8%, isoniazid resistance (rifampicin sensitive) rate 3.4%, multidrug-resistant rate is 5.1%, and because some patients have not been detected for isoniazid resistance, the ratio of isoniazid resistance and multidrug resistance should be higher. Among previously treated cases, the ratio of RR/MDR-TBM patients is as high as 33.3%, and among new cases, the ratio of RR/MDR-TBM patients is only 5.0%, the difference between them is statistically significant. The above results indicate that among the patients with tuberculous meningitis in Shenzhen, the proportion of RR/MDR-TBM patients is higher, and the proportion of RR/MDR-TBM previously treated cases is significantly higher than that of new cases, hence, the previous history of anti-tuberculosis treatment should be taken as the main risk factor for RR/MDR-TBM, which is similar to RR/MDR pulmonary tuberculosis.

A series of studies have suggested that the high-risk factors associated with RR/MDR pulmonary tuberculosis include previous history of anti-tuberculosis treatment, HIV infection, diabetes and other factors[4, 5, 18]. In our study, the proportion of previously treated cases in the meningitis group was up to 50%, while the proportion of previously treated cases in the NRR/MDR-TBM group was only 10.5%. The difference between the two was statistically significant, however, the difference in other factors (including HIV infection rate, diabetes prevalence and various clinical manifestations, cerebrospinal fluid cytology and biochemical test indicators, etc.) between the two groups was not statistically significant, indicating that the previous anti-tuberculosis treatment history is the most important related risk factor for RR/MDR-TBM. Therefore, TBM patients who have a history of anti-tuberculosis treatment must be alert to the possibility of RR/MDR-TBM.

TBM is the most severe type of tuberculosis with the highest mortality, According to different reports, its mortality ranges from 20–50%[1, 2, 19], worst still, up to 25% of the survivors will develop various central nervous system sequelae, which will seriously lower their life quality and increase long-term mortality[20]. Compared with drug-sensitive TBM, the mortality of various drug-resistant TBM is even higher, for example, the mortality of isoniazid-resistant meningitis is 56%, and the mortality of RR/MDR-TBM treated with first-line anti-tuberculosis drugs is even as high as 100% [4, 21]. Therefore, the early diagnosis of tuberculous meningitis and the evaluation of its drug resistance are essential for formulating the correct regimen and reducing the mortality of patients. In this study, there was no significant difference in mortality between the RR/MDR-TBM group and the non RR/MDR-TBM (excluding those who were lost to follow-up), there are many patients in the NRR/MDR-TBM group who were lost to follow-up in this study, The reason may be included: firstly, the contact telephone number has expired or been cancelled because the patient had to return to his(her) native place due to loss of labor, secondly, it cannot be ruled out that the telephone number was cancelled due to the patients' death, Therefore, we assumed two extreme situations, that is, all patients who were lost to follow-up survived or died (the real situation should locate between these two extreme cases), and the results showed that in any cases, There was no significant difference in the mortality between RR/MDR groups and NRR/MDR-TBM group, indicating that after timely and correct anti-tuberculosis treatment, the mortality of RR/MDR-TBM patients was not higher than that of NRR/MDR-TBM.

Among RR/MDR-TBM patients, the mortality rate of the group treated with linezolid containing regimen was significantly lower than that of the group treated with non-linezolid regimen, this is consistent with the results of many domestic and foreign related studies, so our research further supports that linezolid has a good therapeutic effect on RR/MDR-TB, the reasons that linezolid has a good curative effect is, on the one hand related to its strong early bactericidal activity against RR/MDR Mycobacterium tuberculosis, on the other hand, linezolid exhibits excellent permeability of the blood-brain barrier, so it can keep the higher drug concentration in the cerebrospinal fluid and brain tissue [22, 23]

For confirmed TBM cases, the anti-tuberculosis treatment regimen can be formulated based on the results of the drug sensitivity test, unfortunately, despite the application of various new detection methods such as GeneXpert RIF/MTB, GeneXpert Ultra, less than 40% of the clinically diagnosed TBM

cases (including definite, probable, and possible cases) without HIV co-infection are pathogen-positive cases (definite cases) by the above methods, and more than 60% of the cases are pathogen negative (probable or possible cases) [24]. For probable or possible cases, it is generally advised to give empirical anti-tuberculosis treatment as soon as possible, and the empirical anti-tuberculosis treatment usually uses regimen for drug-sensitive TBM (isoniazid, rifampicin, pyrazinamide, ethambutol) [25], but this regimen has very poor effect on drug-resistant TBM, especially RR/MDR-TBM. Even if fluoroquinolones are added to the regimen and the dose of rifampicin is increased, it can only decrease the mortality of isoniazid-resistant TBM but cannot reduce the mortality of RR/MDR-TBM [3, 17]. On the contrary, if drug-sensitive TBM patients are treated with RR/MDR-TBM regimen, it may increase drug adverse effects and the economic burden of patients. Therefore, for pathogen negative TBM cases, the risk of drug resistance should be assessed before the initiation of empirical anti-tuberculosis treatment. Both our and other authors' studies have shown that the proportion of RR/MDR-TBM in the pathogen-positive TBM patients in China is relatively high, especially in the previously treated cases, our data shows it can reach as high as 33%. And we assume that the similar situation should occur in the pathogen-negative TBM patient population, that is, the ratio of RR/MDR-TBM will be significantly higher in previously treated cases, and the regimen composed of first-line anti-tuberculosis drugs will obviously increase the mortality. Therefore, we recommend that for pathogen-negative TBM cases with a history of anti-tuberculosis, an empirical treatment regimen for RR/MDR-TBM comprised of linezolid and other second-line anti-tuberculosis drugs should be administered from the initiation of treatment, while for pathogen-negative TBM new cases, a regimen comprised of first-line anti-tuberculosis drugs can be administered. Once the therapeutic effect is not good, it should be changed into the regimen for RR/MDR-TBM, because it has been proven that no matter the drug sensitivity, the linezolid containing regimen manifests good therapeutic effect to life-threatening TBM. In the group of drugs recommended by WHO for the treatment of multidrug-resistant tuberculosis, drugs that are known to easily penetrate the blood-brain barrier and achieve effective inhibitory concentration include linezolid, fluoroquinolones (levofloxacin, moxifloxacin), cycloserine, and pyrazinamide, ethionamide/prothionamide, high-dose isoniazid, imipenem, meropenem, etc. (amikacin easily penetrates the blood-brain barrier only when the meninges are inflamed, bedaquiline, delamanid, clofazimine still lack relevant data on the permeability of the blood-brain barrier). Therefore, it is necessary to choose the above drugs to constitute an effective anti-tuberculosis regimen [26–28]. Recent studies have shown that linezolid has a strong early bactericidal activity and easily penetrates the blood-brain barrier. Its cerebrospinal fluid drug concentration/blood drug concentration can reach as high as 80–100% [30], so it should be used as an essential component drug for RR/MDR-TBM treatment regimen. It shows that the use of linezolid-containing regimens can significantly reduce the mortality and improve the prognosis of RR/MDR-TBM patients, and the use of linezolid for drug-sensitive patients with severe TBM can also significantly improve the prognosis [22, 23, 27]

The limitations of this study: first of all, it is not clear whether the drug resistance profile of the pathogen-negative TBM patient population is exactly the same as that of the pathogen-positive TBM patient population. However, the prerequisite for clarifying drug resistance is pathogen positive, so maybe there is

no very good solution for this question ,it's only a convinced deduction but not a confirmed conclusion. Secondly, the number of RR/MDR-TBM cases in this study is small, and it is necessary to further increase the number of cases for a prospective multicenter cohort study to evaluate the efficacy and adverse effects of linezolid-containing regimens, finally, the high ratio of loss to follow-up of NRR/MDR-TBM patients in this study also makes it difficult to analyze the results, although we have made appropriate assumptions.

Conclusions

In summary, our results shows for the first time that in recent years, the population of TBM patients in Shenzhen is mainly migrant workers from southern and southwestern China, RR/MDR-TBM accounts for a relatively high proportion among them. The main related high-risk factor of RR/MDR-TBM is the history of anti-tuberculosis treatment. Linezolid containing regimen can decrease the mortality of RR/MDR-TBM significantly, therefore, we recommended linezolid-containing regimen as the empiric anti-tuberculosis treatment for pathogen negative TBM with a history of anti-tuberculosis in China.

Abbreviations

RR/MDR-TBM: rifampicin/multidrug-resistant tuberculous meningitis

NRR/MDR-TBM: non rifampicin/multidrug-resistant tuberculous meningitis

RR/MDR-TB: rifampicin/multidrug-resistant tuberculosis.

DST: drug susceptibility test.

CSF: cerebrospinal fluid.

WHO: World Health Organization.

PTB: pulmonary tuberculosis.

TB: tuberculosis.

HIV: Human Immunodeficiency Virus.

PRO: protein

CL: chloride

ADA: adenosine deaminase

GLU: glucose

GSC: Glasgow Coma Scale

Declarations

Ethic approval and and consent to participant

This study was approved by the ethics committee of The Third People's Hospital Of Shenzhen for the National Key Project for Infectious Disease and complied with the Declaration of Helsinki, the informed consent was not obtained as it is a retrospective study.

Consent for publication

Not applicable.

Availability of supporting data

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions:

Mu-tong Fang designed the research and contributed to the writing of the article and the addition of the references. Mu-tong Fang, You-feng Su , Zhi Mao , Jian-feng Zeng were responsible for data collection, patient clinic visiting and telephone contact, Pei-ze Zhang was responsible for data cleaning and analysis, Hou-ming Liu performed the main examination including GeneXpert MTB/RIF and DST. etc.Zhong-yuan Wang, Qian-ting Yang, Guo-fang Deng,Guobao Li provided critical comments and revised the manuscript. All authors read and approved the final manuscript.

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Figures

Figure 1

the enrollment of the patients Unperformed with DST: it means that DST is not performed when MTB culture is positive(as the patient had died or abandoned treatment and discharged before the lab informed a positive culture)