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Is rifampin resistance a reliable predictive marker of multidrug-resistant tuberculosis in China: A meta-analysis of findings

Zhengwei Liu[a,1], Huali Dong[b,1], BeiBei Wu[a], Mingwu Zhang[a], Yelei Zhu[a], Yu Pang[c,*], Xiaomeng Wang[a,*]

[a] The Institute of TB Control, Zhejiang Provincial Center for Disease Control and Prevention, No. 3399, Binsheng road, Binjiang District, Hangzhou 310005, China
[b] Department of Clinical Laboratory, Zhejiang Xiao Shan Hospital, Hangzhou, China
[c] National Clinical Laboratory on Tuberculosis, Beijing Key laboratory on Drug-resistant Tuberculosis Research, Beijing Chest Hospital, Capital Medical University, Beijing Tuberculosis and Thoracic Tumor Institute, No. 9, Beiguan Street, Tongzhou District, Beijing 101149, China

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SUMMARY

Objectives: Systematic review of multidrug-resistant tuberculosis (MDR-TB) prevalence among rifampicin (RIF)-resistant tuberculosis (RR-TB) patients in 34 provinces of China was conducted to correlate RIF resistance with concurrent isoniazid (INH) resistance.

Methods: Database searches (PubMed, Embase, China National Knowledge Infrastructure, Chinese Scientific Journal, Wanfang), identified drug resistance surveillance studies conducted between January 1, 2000 and June 30, 2018. Of 1554 records, random-effects meta-analysis of 34 studies of adequate methodological quality yielded 108,366 TB cases for MDR-TB prevalence analysis of RR-TB cases.

Results: MDR-TB prevalence among RR-TB cases varied from 57% (Xinjiang; 95% CI 47%, 67%) to 95% (Taiwan; 95% CI 92%, 98%), for a pooled national rate of 77% (95% CI 75%, 80%). Subgroup and meta-regression analyses revealed greater MDR-TB prevalence in previously treated versus new RR-TB cases ($P < 0.001$), with no significant differences of regional initial drug resistance rates or sampling methods. Regional MDR-TB prevalence among RR-TB cases was lowest (69%) in the Northeast Region (95% CI 65%, 73%) and highest (90%) in Hong Kong, Macao and Taiwan (95% CI 81%, 98%).

Conclusions: In China, ~77% of RR-TB cases are MDR-TB. Thus, RIF resistance cannot effectively predict MDR-TB. Highly variable RR-TB prevalence across China warrants improved TB management.

Introduction

Drug-resistant tuberculosis (TB), including rifampicin (RIF)-resistant TB (RR-TB) and multidrug-resistant tuberculosis (MDR-TB, with resistance to at least isoniazid and rifampicin), is becoming a threat to public health worldwide.[1,2] An estimated 558,000 MDR/RR-TB cases emerged in 2017, of which approximately half of MDR-TB cases were reported in India, China and Russia.[1] Due to limited availability of quality-assured laboratory resources in TB-endemic countries, confirmed cases of MDR-TB likely account for only a small proportion of actual cases.[3] Thus, early diagnosis of MDR-TB cases and prompt initiation of second-line TB drug therapy are crucial for reducing high mortality and MDR-TB transmission within the community.[4,5]

The accurate diagnosis of MDR-TB requires positive MTB culture and drug susceptibility test (DST) results.[6] However, conventional phenotypic methods take weeks or months to complete and therefore cannot satisfy MDR-TB patient needs for rapid treatment.[7] Fortunately, recently developed molecular DST diagnostic methods can identify drug-resistant tubercle bacilli in less time.[8] Consequently, the World Health Organization has endorsed the use of rapid molecular diagnostic testing for drug-resistant TB detection[9,10] that includes the Xpert MTB/RIF assay system (Cepheid, USA), a fully automated real-time assay. Xpert MTB/RIF has been widely used to diagnose patients infected with rifampicin (RIF)-susceptible MTB in resource-limited settings, since it is based on a simple procedure that can be completed without need for a specialized laboratory.[11] Meanwhile, various studies have reported results of Xpert MTB/RIF evaluations in persons with presumptive TB, demonstrating pooled sensitivity and specificity rates of 95% and 98%, respectively.[12] More importantly, the fact that more than 90% of RIF-resistant cases have been associated with isoniazid (INH) resistance has resulted in the use of RIF resistance as a

* Corresponding authors.
E-mail addresses: pangyupound@163.com (Y. Pang), xmwang@cdc.zj.cn (X. Wang).
[1] These authors contributed equally to the work.

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surrogate marker for MDR-TB.[13,14] However, in many countries the increasing threat of RIF-monoresistant MTB[15,16] suggests this practice may not always be sound, due to genetic diversity of MTB isolates among different geographic regions. As a consequence, epidemiological data regarding rates of RIF monoresistance are urgently needed to determine whether RIF resistance can serve as an adequate marker for MDR-TB in various settings.

China has the second highest burden of multidrug-resistant TB globally.[1] Results of a recent national survey of drug-resistant TB in China indicates that 5.7% of new cases and 25.6% of previously treated cases were infected with MDR-TB.[2] Of an estimated 58,000 incident MDR-TB cases in 2017, only 17% were detected using appropriate laboratory tests, thus highlighting the urgent need to improve accessibility of DST services in China.[1] To meet this need, the Global Fund has provided support to equip nearly one third of county-level TB laboratories with Xpert MTB/RIF detection systems in China.[17] Consequently, the availability of this widely used molecular diagnostic system for detecting RIF resistance of MTB now permits studies to be conducted to determine if RIF resistance can serve as a reliable marker for predicting concurrent INH resistance in China. In this work we conducted a systematic review to evaluate the proportion of multidrug-resistant MTB cases among patients with RIF-resistant MTB using drug-resistant TB surveillance data collected from 34 provinces. In addition, we analyzed prevalence rates of drug-resistant TB across regions of China.

Methods

Identification of studies

We searched the following databases: PUBMED (2000–2018), EMBASE (2000–2018), the China National Knowledge Infrastructure Database (CNKI, Chinese, 2000–2018), the Chinese Scientific Journal Database (VIP database, Chinese, 2000–2018) and the Wanfang database (Chinese, 2000–2018). All searches were up to date as of June 2018. Search terms used included “tuberculosis,” “mycobacterium tuberculosis,” “drug resistance,” “surveillance,” and “China.” Reference lists from primary studies and review articles were searched and articles written in English and Chinese were selected for full-text review.

Inclusion criteria

Studies included in the meta-analysis were required to meet predetermined criteria as follows: (i) include a cross-sectional study of drug-resistant TB, with enrollment of as large a number of TB cases as reported for each province of China; (ii) provide sufficient information on drug-resistant profiles of TB patients, including RIF resistance and MDR-TB; (iii) provide enough information on sampling method and enrollment of TB patients for evaluation of methodological quality.

Studies were excluded from the review if they met the following criteria: (i) conference abstracts or reviews; (ii) studies conducted at the prefectural and county level; (iii) small studies conducted within the same province rather than studies with larger sample sizes across provinces.

Data extraction

The final analyses included one representative study focused on prevalence of drug-resistant TB from each province. Two independent reviewers determined the eligibility of studies enrolled in this meta-analysis. If any disagreement arose between reviewers, it was resolved by a third reviewer. Data extracted included author(s), year of publication, year of study conducted, sampling method, number of surveillance sites, methodology of drug susceptibility testing and drug susceptibility testing results. Data were recorded and compiled using Microsoft Excel (Microsoft, Redmond, WA, USA).

Statistical analysis

We used RevMan 5.3 (Cochrane Collaboration, Oxford, United Kingdom) for conducting meta-analysis of drug susceptibility testing results pertaining to MTB strains, with calculation of summary estimates based on 95% confidence intervals (CIs). A random effect model was generated to obtain the pooled effect size for calculating the proportion of drug-resistant TB cases within regions across studies.[18] Next, differences in prevalence of MDR-TB among RR-TB cases between subgroups were calculated using the U test, with a P value of less than 0.05 considered statistically significant. Heterogeneity of studies was estimated using the Higgins I^2 test, with significant heterogeneity declared if the I^2 value was greater than 60%.[18] A prevalence rate of MDR-TB among RR-TB cases of greater than 90% was considered the cut-off threshold for warranting use of RIF resistance as a proxy marker for detection of MDR-TB.

Results

We initially identified 1554 records. After elimination of duplicates, 1166 records remained. We screened the titles and abstracts of the remaining records and 1033 irrelevant records were excluded. Finally, 34 studies were included in the final analysis based on inclusion criteria (Fig. 1). The reference list of all included studies is summarized in Table 1. Of the 34 included studies, 31 were written in Chinese and 3 were in English. Most of these studies were published between 2011 and 2018 and employed drug surveillance methods endorsed by WHO. Sample sizes ranged from 217 to 52,781 and represented a combined total of 108,366 TB cases. In 33 studies, patients were classified according to anti-TB treatment history.

The MDR-TB prevalence rate among the RR-TB population varied widely across regions, from 57% (95% CI 47%, 67%) in Xinjiang to 95% (95% CI 92%, 98%) in Taiwan. Combining the results generated a pooled prevalence rate of MDR-TB among RR-TB cases of 77% (95% CI 75%, 80%) that masked the substantial heterogeneity among regions. Table 2 presents subgroup analyses of MDR-TB prevalence. Prevalence rates of MDR-TB within RR-TB cases were higher in previously treated patient populations than in new cases ($P < 0.001$), with prevalence rates statistically no different between the Northern Region and Southern Region of China ($P = 0.124$). Similarly, prevalence rate differences between regions with different initial drug resistant rates ($P = 0.309$) were not due to different sampling methods used across studies ($P = 0.074$) (Fig. 2).

We further analyzed pooled data of drug-resistant TB among various regional subgroups. As shown in Fig. 3, geographic variability in prevalence of drug-resistant TB was observed; of the nine economic regions of China, two regions exhibited a pooled RR-TB prevalence rate greater than 15%, including the Northwest Region (24%, 95% CI 14%, 33%) and Northeast Region (17%, 95% CI 16%, 18%), the latter of which exhibited a rate approximately 2-fold greater than that obtained in Hong Kong, Macao, and Taiwan (8%, 95% CI 3%, 12%). With regard to new cases, the highest pooled RR-TB prevalence rate was noted in the Northeast Region (11%, 95% CI 10%, 12%), while the Northwest Region had the highest prevalence (44%) of RR-TB in previously treated patients (95% CI 14%, 74%).

Notably, we observed a significant difference in prevalence rates of MDR-TB among RR-TB cases across regions. Overall, 6 of 9 regions had prevalence rates below 80%, while the remaining three regions had prevalence rates ranging from 80% to 90%. The lowest prevalence rate (69%) was found in the Northeast Region (95%

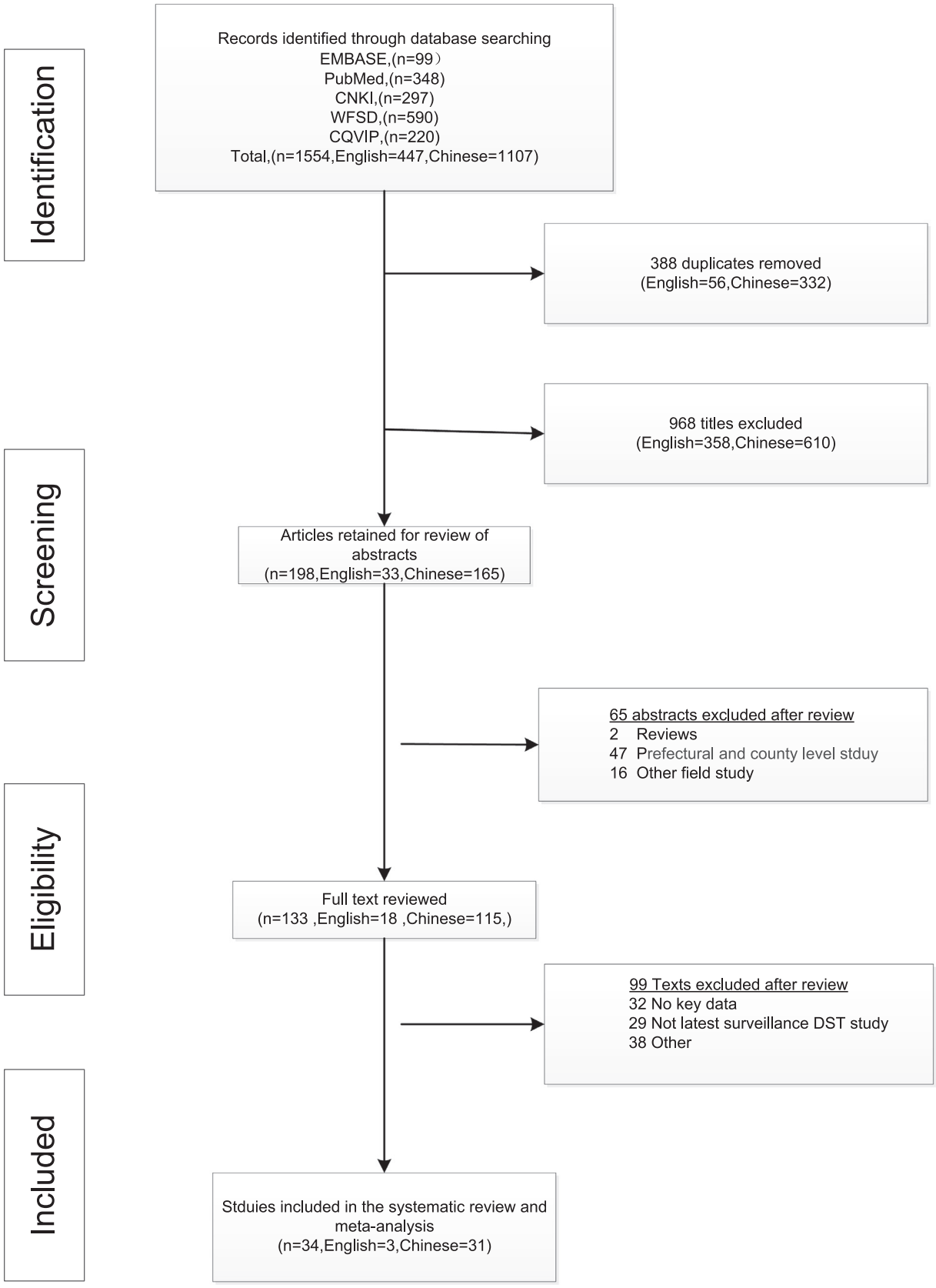

Fig. 1. Summary of literature search and study selection.

Table 1
Features of included studies.

	Province	Region	TB incidence rate per population[a]	Data resource	Sample size included for analysis	Method used for DST	Prevalence of DR-TB (%)	Prevalence of MDR-TB (%)	Prevalence of RR-TB (%)	Prevalence of MDR-TB out of RR-TB (%)	Reference
Wang et al. (2018)	Anhui	MRYTR	56.77	WHO surveillance	2530	L-J proportion	26.4	7.6	11.4	66.8	19
An et al. (2007)	Beijing	NC	31.01	WHO surveillance	1197	L-J proportion	20.1	3.5	5.6	62.7	20
Liu et al. (2009)	Chongqing	SW	73.34	WHO surveillance	1119	L-J proportion	14.9	4.6	6.2	75.4	21
Chen et al. (2013)	Fujian	SC	42.74	WHO surveillance	1452	L-J proportion	22.9	5.4	8.2	66.4	22
Si et al. (2009)	Gansu	NW	58.13	WHO surveillance	909	L-J absolute concentration	26.0	10.1	14.5	69.7	23
Zhong et al. (2001)	Guangdong	SC	71.82	WHO surveillance	1648	L-J proportion	19.6	6.4	8.4	76.1	24
Luo et al. (2013)	Guangxi	SW	86.27	CDC-based data	1611	L-J proportion	16.4	5.9	7.9	74.8	25
Chen et al. (2016)	Guizhou	SW	130.66	CDC-based data	2635	L-J proportion	17.7	5.9	8.3	71.2	26
Huang et al. (2017)	Hainan	SC	84.18	CDC-based data	1339	L-J proportion	20.9	6.9	9.5	72.4	27
Li et al. (2016)	Hebei	NC	45.34	Hospital-based data	974	L-J proportion	34.1	13.2	17.8	74.6	28
Xie et al. (2008)	Heilongjiang	NE	80.16	WHO surveillance	1995	L-J proportion	42.8	12.1	16.9	71.3	29
Du et al. (2006)	Henan	MRYR	60.13	WHO Surveillance	1487	L-J proportion	35.3	12.9	15.5	83.5	30
Kam et al. (2001)	Hongkong	HMT	69.0	CDC-based data	52,781	L-J absolute concentration	15.6	2.6	3.0	84.0	31
Li et al. (2002)	Hubei	MRYTR	74.70	WHO surveillance	1097	L-J proportion	23.3	6.4	8.8	72.2	32
Yang et al. (2018)	Hunan	MRYTR	75.50	Hospital-based data	11,486	L-J proportion	30.6	16.4	20.8	79.2	33
Wang et al. (2007)	Inner Mongolia	MRYR	48.30	WHO surveillance	1262	L-J proportion	44.8	16.1	20.5	78.4	34
Yang et al. (2011)	Jiangsu	EC	35.93	WHO surveillance	1824	L-J proportion	41.0	16.6	19.4	85.6	35
Zhao et al. (2016)	Jiangxi	MRYTR	71.99	CDC-based data	283	L-J proportion	27.2	3.9	5.3	73.3	36
Yuan et al. (2015)	Jilin	NE	49.76	WHO surveillance	1771	L-J proportion	40.1	11.9	16.8	70.7	37
Zhong et al. (2017)	Liaoning	NE	51.40	CDC-based data	912	L-J proportion	38.2	11.8	18.9	62.8	38
Zhang et al. (2007)	Macao	HMT	67.0	CDC-based data	1460	MGIT	16.2	3.2	3.6	90.4	39
Wang et al. (2015)	Ningxia	NW	40.04	CDC-based data	665	L-J proportion	26.6	7.8	9.9	78.8	40
Shen et al. (2017)	Qinghai	NW	128.70	CDC-based data	236	L-J proportion	55.9	30.9	37.3	83.0	41
Zhang et al. (2017)	Shaanxi	MRYR	56.30	WHO Surveillance	1516	L-J proportion	29.5	5.9	7.8	76.3	42
Li et al. (2013)	Shandong	NC	30.78	CDC-based data	5542	L-J proportion	19.4	3.7	4.4	83.9	43
Mei et al. (2007)	Shanghai	EC	27.28	WHO surveillance	964	L-J proportion	17.9	5.7	7.0	82.1	44
Guan et al. (2015)	Shanxi	MRYR	38.65	Hospital-based data	1258	L-J absolute concentration	35.2	10.8	13.3	81.4	45
Long et al. (2014)	Sichuan	SW	65.66	CDC-based data	1293	L-J proportion	23.0	8.1	10.8	75.0	46
Jou et al. (2006)	Taiwan	HMT	41.0	CDC-based data	935	MGIT	27.7	15.8	16.6	95.5	47
Li et al. (2010)	Tianjin	NC	21.14	CDC-based data	656	L-J proportion	27.0	6.3	7.9	78.9	48
Shi et al. (2011)	Tibet	NW	154.37	Hospital-based data	217	L-J proportion	65.9	45.6	51.6	88.4	49
Jia et al. (2008)	Xinjiang	NW	185.66	WHO surveillance	1083	L-J proportion	26.4	4.6	8.0	57.5	50
Xu et al. (2015)	Yunnan	SW	55.47	CDC-based data	1274	L-J proportion	37.9	7.5	8.7	85.6	51
Chen et al. (2016)	Zhejiang	EC	48.78	WHO surveillance	955	L-J proportion	25.1	6.4	7.7	82.4	52

EC: Eastern coastal; MRYTR: Middle Reaches of Yangtze River; MRYR: Middle Reaches of Yangtze River; NE: Northeast; NC: Northern coastal; NW: Northwest; SC: Southern coastal; SW: Southwest; HMT: Hongkong, Macao and Taiwan; RR-TB: rifampin-resistant tuberculosis; MDR-TB: multidrug-resistant tuberculosis; DR-TB: drug-resistant tuberculosis; DST: drug susceptibility testing; WHO: World Health Organization; L-J: Löwenstein-Jensen.

[a] Data for TB incidence rate from the National Active Tuberculosis Case Report System, 2017 (except for Hongkong, Macao and Taiwan).

Table 2
Meta-analysis for prevalence of MDR-TB among RR-TB by treatment history, region and prevalence of drug resistance.

Subgroup	Studies (*N*)	Sample size included for analysis	Median (Range)	RR-TB (*N*)	MDR-TB (*N*)	Pooled prevalence of MDR-TB among RR-TB		I^2	*P*
						%	95% CI		
Treatment history									
New case	33	92,693	1058(108–48,924)	4462	3304	72%	69%–75%	74%	<0.001
Previously treated cases	33	15,437	234(46–3857)	4191	3486	82%	79%–85%	82%	
Region									
Northern	15	21,463	1197(236–5542)	2488	1862	75%	71%–78%	79%	0.124
Southern	19	86,903	1339(217–52,781)	6253	5001	79%	76%–83%	89%	
Regions with various prevalence of DR-TB									
<30%	22	83,670	1268(283–52,781)	4056	3186	76%	72%–80%	88%	0.309
>30%	12	24,696	1260(217–11,486)	4685	3677	80%	74%–86%	95%	
Regions with various prevalence of MDR-TB									
<5%	7	63,465	1197(283~52,781)	2136	1752	77%	70%–83%	87%	0.591
>5%	27	44,901	1274(217~11,486)	6605	5111	78%	73%–82%	95%	
Method used for drug surveillance									
WHO guideline	20	33,871	1469.5(909–5542)	3434	2587	75%	72%–78%	82%	0.074
Others	14	74,495	954.5(217–52,781)	5307	4276	80%	77%–84%	90%	

RR-TB: rifampin-resistant tuberculosis; MDR-TB: multidrug-resistant tuberculosis; DR-TB: drug-resistant tuberculosis; CI: confidence interval; WHO: World Health Organisation.

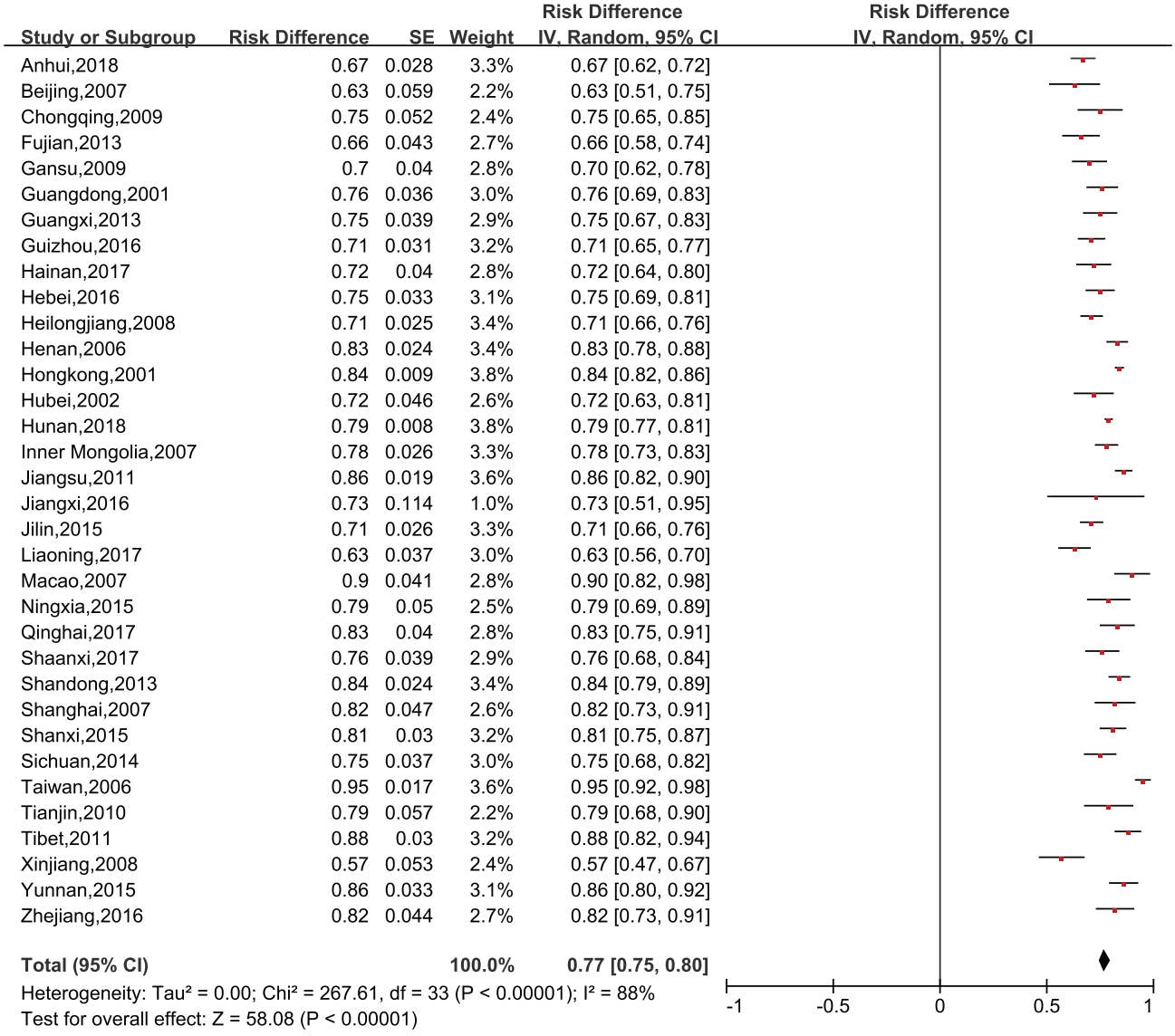

Fig. 2. Prevalence of MDR-TB among RR-TB among various provinces in China.

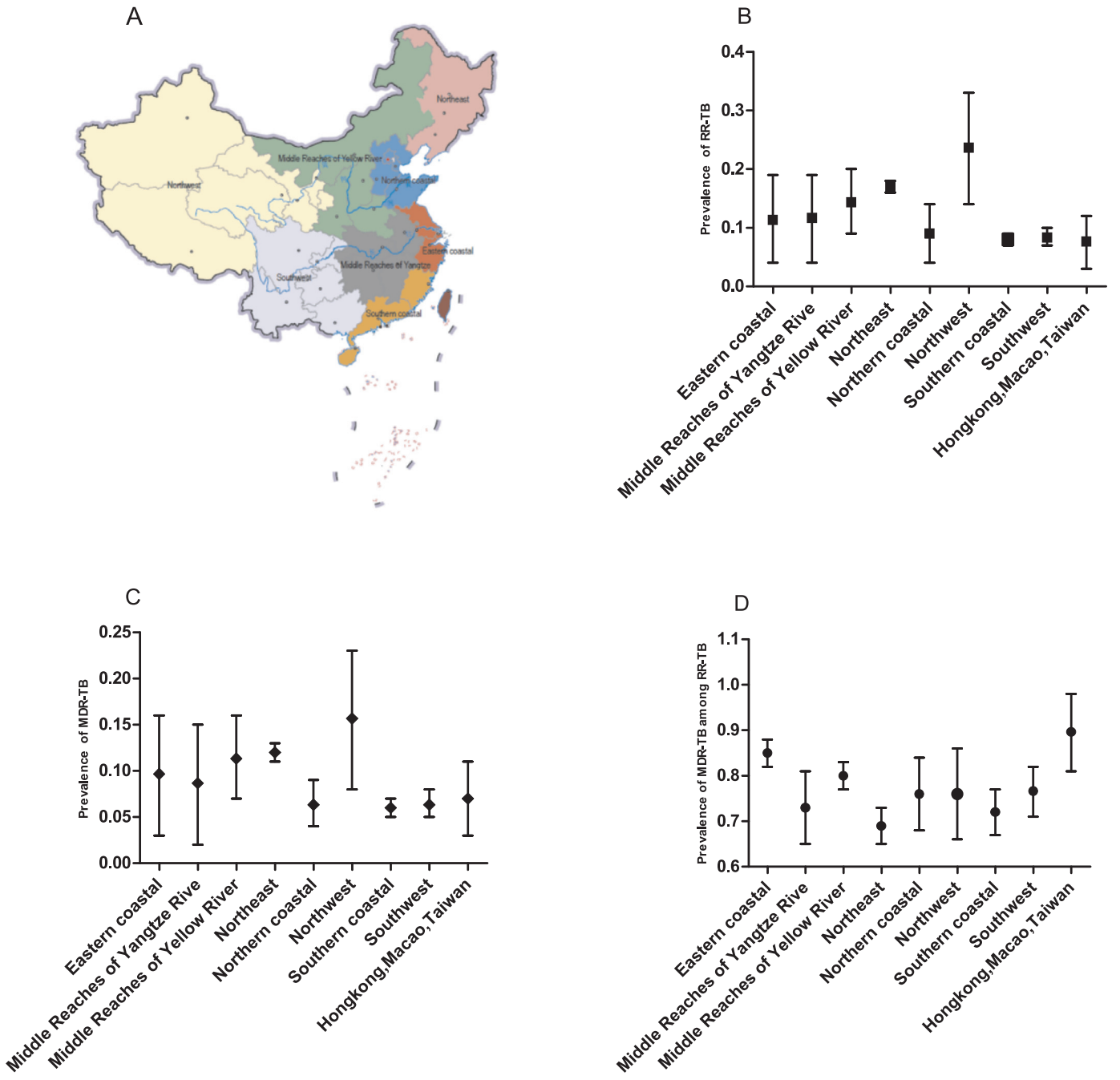

Fig. 3. Pooled prevalence of MDR-TB among RR-TB stratified across various regions in China. (A) Distribution of the nine economic regions of China; (B) pooled prevalence of RR-TB across nine economic regions; (C) pooled prevalence of MDR-TB across nine economic regions; (D) pooled prevalence of MDR-TB among RR-TB cases across nine economic regions.

CI 65%, 73%), while the highest rate of 90% (95% CI 81%, 98%) was found in Hong Kong, Macao, and Taiwan.

Discussion

China has the second largest MDR-TB burden globally.[2] Early diagnosis of this severe form of TB is essential to prevent its transmission within the community.[4] New diagnostic tests, such as GeneXpert MTB/RIF, are now available that could improve our ability to accurately and rapidly diagnose MTB, especially of RIF-resistant MTB.[11] These resources permit the question to be answered regarding whether RIF resistance can serve as an effective marker for MDR-TB. In this study, we compiled representative data from ~0.11 million TB patients with active disease in China and estimated the prevalence of MDR-TB among RR-TB patients to be 77% (95% CI 75%, 80%). In a previous report of MTB isolates collected from various countries (excluding China), the use of RIF resistance as a surrogate resistance marker could detect 95% of MDR strains.[13] Moreover, Ahmad and colleagues found that 91% of RIF-resistant samples among MTB isolates from Western Asia were also INH-resistant.[14] Notably, these results were not replicated in China, since a nationwide survey there of drug-resistant TB revealed that only 86% of RIF-resistant MTB were also MDR-TB.[2] Likewise, results of another study corroborated these results by demonstrating that approximately 77% of patients with RIF-resistant TB in the four prefectures in China were resistant to INH.[7] Indeed, of all of the

regions included in this meta-analysis, only Taiwan and Macao exhibited a prevalence rate of MDR-TB among RR-TB exceeding 90%. Therefore, these conflicting results suggest that the prevalence of RIF-monoresistant TB varies geographically and that RIF resistance would not serve as a reliable surrogate marker of MDR-TB in every local setting.

The high prevalence of RIF monoresistance has important implications for the design of strategies to diagnose and clinically manage RR-TB cases in China. On the one hand, frequent RIF monoresistance has made it essential to separately verify INH resistance before making a final diagnosis of MDR-TB. However, due to the 24-h doubling time of MTB, several weeks are required before reliable standard phenotypic DST results can be obtained.[53] By contrast, molecular diagnostics is available as a promising alternative method for rapid detection of drug-resistant TB, but unfortunately current China Food and Drug Administration (CFDA)-approved assays are only recommended for diagnosing smear-positive TB patients, as no commercial alternative is available for diagnosing patients with negative smear results. Therefore, appropriate laboratory methods are urgently needed to evaluate patients with low bacterial load. On the other hand, INH used together with RIF is the cornerstone of short-course chemotherapy for non-MDR-TB patients.[54] Although treatment of RR-TB cases using this standard MDR-TB regimen would result in substantially favorable treatment outcomes, RIF treatment is unnecessary. In fact, such patients would likely benefit from sole treatment with INH, a more efficacious and less toxic agent than RIF. Therefore, the high incidence of RIF monoresistance highlights the critical need to determine INH susceptibility before initiating treatment of RR-TB patients in China.

Notably, the prevalence of RR-TB exhibited great diversity across various regions of China, with Northeast and Northwest Regions appearing as “hotspots” of RIF resistance. The most important finding of this analysis is that more than one-tenth of new TB cases exhibited resistance to RIF in the Northeast Region, with such a high incidence of RIF resistance in this population likely reflecting greater transmission of RR-TB within this community. Therefore, in view of the epidemic of RR-TB in this region, the use of feasible molecular DST-based diagnostic testing in this region would shorten laboratory turnaround time. Another notable finding is that previously treated cases living in the Northwest Region had the highest proportion of RR-resistant cases in China, suggesting a high degree of improper management of TB patients at the time of initial diagnosis as a cause of increased drug resistance.[55] Although the Directly Observed Treatment Strategy (DOTS) has been implemented in China since 2000s to improve TB patient treatment adherence,[56] the Northwest Region, a vast territory with sparse population, has become a major barrier to effective implementation of the DOT strategy. Thus, additional strategies to improve patient treatment adherence should be employed in this region, such as maintaining mobile phone communication, providing education for patients and family and providing nutritional support.[55,57] Taken together, the geographic diversity of drug-resistant TB highlights the need for alternative TB screening and management strategies tailored to different regions.

There were several obvious limitations to this study. First, we included 34 studies of which 3 (8.8%) had a high risk of bias that may affect the precision of our estimates. Second, 14 studies recruited patients based on consecutive hospital readmissions rather than on patient discovery via WHO-endorsed drug-resistant TB surveillance, possibly resulting in the overestimation of drug-resistant TB prevalence estimates. Third, as observed previously for meta-analyses of this type, we observed huge heterogeneity among studies included in the final analysis. Most of this heterogeneity may reflect variability in sample collection methods and/or surveillance period duration. Fourth, various regions were unequally represented, with some regions represented by only a single study of small sample size, which may introduce bias into our findings.

To conclude, our results demonstrate that only ~77% of RR-TB patients in China are infected with MDR-TB, indicating that RIF resistance is an unsatisfactory indicator of MDR-TB in this country. In addition, the prevalence of RR-TB exhibits great diversity across regions, highlighting the urgent need for alternative strategies for TB screening and management throughout China.

Declaration of Competing Interest

The authors declare that they have no competing interests.

CRediT authorship contribution statement

Zhengwei Liu: Conceptualization, Data curation, Formal analysis, Methodology, Resources, Software, Writing - original draft, Writing - review & editing. **Huali Dong:** Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **BeiBei Wu:** Data curation, Writing - review & editing. **Mingwu Zhang:** Data curation, Writing - review & editing. **Yelei Zhu:** Data curation, Writing - review & editing. **Yu Pang:** Data curation, Formal analysis, Investigation, Project administration, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **Xiaomeng Wang:** Formal analysis, Funding acquisition, Supervision, Writing - original draft, Writing - review & editing.

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Availability of data and materials

The datasets generated and analysed from the current study are not publicly available at this time as further analyses are ongoing, but are available from the corresponding author on reasonable request.

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