Rifampicin-resistant tuberculosis in Iran: A systematic review and meta-analysis

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Abstract

Rifampicin (RIF)-resistant strain of Mycobacterium tuberculosis is an important barrier to effective tuberculosis (TB) treatment and prevention. The present study aimed to determine the frequency of RIF-resistant TB among patients with confirmed TB. Pubmed/Medline, Embase, Web of Science, and Scopus were searched for relevant articles published between January 1980 and January 2020. We pooled data with random-effects models when appropriate. After screening 1608 citations, 30 studies covering 8215 patients with TB were included. The pooled frequency of RIF-resistance among all patients with TB was 8.0% (95% CI 4.0–12.0). Our sub-group analysis showed that 4.0% of newly-diagnosed cases and 36.0% of previously-treated TB patients from different settings in Iran were RIF-resistant. Our study showed that the frequency of RIF-resistance among patients with TB was 8.0%. Programmatic implementation of rapid drug susceptibility testing (DST) such as the Xpert MTB/RIF assay as a primary diagnostic test for persons suspected of having a RIF-resistant TB would be helpful for the control of the drug resistance.

Introduction

Multidrug-resistant tuberculosis (MDR-TB), poses a global threat to TB control programs, especially in developing countries (1). In 2019, among the 81 million people in Iran, there was an estimated TB incidence of 13 per 100,000 population (1). Estimated Iran MDR/rifampicin (RIF)-resistant TB rates were 1.3% among new cases and 8.3% in retreatment cases (1). Patients with RIF-resistant TB, often seen as a proxy for MDR-TB, require treatment regimens that are longer, less effective, and less accessible than first-line regimens (2-8). The low numbers of well-equipped laboratories for drug susceptibility testing (DST) in Iran, make the diagnosis of RIF-resistance challenging in the country (6, 9, 10). As a result, RIF-resistant-TB, very often remains undetected, leading to further spread of drug-resistant TB and worse TB treatment outcomes (11-15). Given that RIF-resistant TB is among the major challenges for national TB control programs (NTP), identification of RIF-resistant TB resistance among Mycobacterium tuberculosis isolates could help us to better advance treatment achievement. Although some studies have investigated the prevalence of RIF-resistance in Iran, a comprehensive analysis has not yet been reported. In this study, we aimed to assess the frequency of RIF-resistance in M. tuberculosis isolates in Iran, using a systematic review and meta-analysis.

Materials and Methods

Search strategy

Pubmed/Medline, Embase, Web of Science, and Scopus from January 1, 1980, to January 1, 2020, were screened for English articles that contained the terms "tuberculosis", "rifampicin", and "Iran". Details of strategies used in Pubmed/Medline are given in Table S1 in the Appendix. Articles in Persian were also searched in the Iranian databases (SID [www.sid.ir] and Magiran [www.Magiran.com]) with similar strategies and related Persian keywords. We performed a systematic review and meta-analysis of the literature following PRISMA guidelines (16).

Study selection

All articles identified by the initial search were reviewed independently by two reviewers (FB and MJN) for relevance, with disagreements mediated by a third author (AAIF). The same reviewers also double reviewed all full-text articles. Studies were selected for inclusion if they met the following criteria: 1) presented original data; 2) provided the primary data on the total number of patients with TB, as well as the number of those with RIF-resistance; and 3) used the standard phenotypic DST method as recommended by WHO/CDC (17, 18). Data from studies evaluating molecular drug susceptibility tests were also included if the...
results were verified by DNA sequencing. Studies with unrepresentative samples of the general population of TB as well as insufficient information about patients’ characteristics were excluded.

**Data extraction**

Two reviewers (FB and MJN) performed double data extraction and entry using Microsoft Excel. A third reviewer (AAIF) judged any discrepancies between the two reviewers. From each study, study location, design, age, year, the total number of TB patients, number of RIF-resistance, as well as, when available, status of HIV, and history of the previous TB among participants were extracted. All data were extracted and compiled using the MS Excel software package (Microsoft, Redmond, WA, USA).

In the text, the term “new cases” refers to patients with TB who have never received anti-TB drugs. The term “previously treated cases” or “history of treatment” is used to refer to patients who had previously received anti-TB drugs. “RIF mono resistance” was used to define the resistance to only RIF. “RIF any resistance” referred to resistance to any kind of RIF resistance regardless of mono-resistance or multi-drug resistance (resistance to at least isoniazid and rifampicin).

**Quality assessment**

Two authors (FB and MJN) applied the Joanna Briggs Institute quality assessment tool for cross-sectional studies to assess the risk of bias for each study. They independently evaluated the components of the scale as “Yes”, “No”, “Unclear” or “Not Applicable”. This was used to guide the overall rating for the quality of each study as “Good”, or “Poor”. In case of disagreement, a consensus opinion was reached.

**Meta-analysis**

Statistical analyses were performed with STATA (version 14, IC; Stata Corporation, College Station, TX, USA). The pooled frequency of RIF-resistance among patients with confirmed TB was assessed by the random-effects model. Heterogeneity across studies was estimated by calculating the I² statistic. A P-value of less than 0.05 indicated that heterogeneity among the group of studies being analyzed was significant. To explore sources of studies’ heterogeneity, we did meta-regression and subgroup analysis. Publication bias was assessed statistically by using Begg’s tests (P<0.05 was considered indicative of statistically significant publication bias).

**Results**

The results of the literature search are displayed in Figure 1. Our initial search yielded 1608 studies. Of these, 67 were referred for full-text assessment, and 30 cross-sectional studies met the inclusion criteria and were selected for inclusion in the qualitative synthesis and meta-analysis (10, 19-47). Table 1 provides information on each of the included studies. Studies were conducted in different regions of Iran: Tehran was the most frequently represented city with 13 studies. In all included studies, conventional DST was performed by the standard method according to the WHO or CDC guidelines. The sample size ranged from 31 to 1242 individuals enrolled per study. A total of 8215 patients with TB were included in the meta-analysis. Five studies reported RIF mono-resistance for a total of 3205 TB cases. Although we sought to extract data on HIV infection and previous TB treatment, most studies did not provide sufficient information. Data on previous TB treatment was provided by only five of the 30 included studies and HIV infection by one.

**Quality assessment**

All included studies were rated as “Good” by both assessors, representing a low risk of bias.

**Frequency of RIF-resistance among patients with TB**

As shown in Figure 2, the overall frequency of RIF-resistance among all patients with TB was 8.0% (95% CI 4.0–12.0). We found a high degree of heterogeneity in the results across the included studies (I²=96%,...
Table 1. Characteristics of the included studies investigating the frequency of RIF-resistance among patients with confirmed TB

| First author          | Published time | Enrollment time | Location         | Mean age | Total No. of TB patients | Total No. of RIF-resistance | Type of patients | DST method     |
|-----------------------|----------------|-----------------|------------------|----------|--------------------------|----------------------------|------------------|----------------|
| Bahrami               | 2009-2010      | Adult           | Golestan         | 39       | 644                      | 24                         | New and retreatment case | WHO standard conventional DST |
| Mansoori              | 2010-2012      | Adult           | Tehran           | 44       | 286                      | 98                         | New and retreatment case | WHO standard conventional DST |
| Navazi                | 2011-2013      | Adult           | Tehran           | 45       | 142                      | 44                         | New and retreatment case | WHO standard conventional DST |
| Nasiri                | 2012-2014      | Adult           | Tehran           | 45       | 102                      | 40                         | New and retreatment case | WHO standard conventional DST |
| Velayati              | 2013-2015      | Adult           | Tehran           | 45       | 200                      | 80                         | New and retreatment case | WHO standard conventional DST |
| Bahrami               | 2014-2016      | Adult           | Tehran           | 45       | 200                      | 80                         | New and retreatment case | WHO standard conventional DST |
| Faraz                   | 2015-2017      | Adult           | Tehran           | 45       | 200                      | 80                         | New and retreatment case | WHO standard conventional DST |
| Marjani                | 2016-2018      | Adult           | Tehran           | 45       | 200                      | 80                         | New and retreatment case | WHO standard conventional DST |
| Yarei                 | 2017-2019      | Adult           | Tehran           | 45       | 200                      | 80                         | New and retreatment case | WHO standard conventional DST |
| Hadizadeh             | 2018-2020      | Adult           | Tehran           | 45       | 200                      | 80                         | New and retreatment case | WHO standard conventional DST |
| Livani                | 2019-2021      | Adult           | Tehran           | 45       | 200                      | 80                         | New and retreatment case | WHO standard conventional DST |
| Bahrami2              | 2020-2022      | Adult           | Tehran           | 45       | 200                      | 80                         | New and retreatment case | WHO standard conventional DST |
| Shaarmawi             | 2021-2023      | Adult           | Tehran           | 45       | 200                      | 80                         | New and retreatment case | WHO standard conventional DST |
| Javid                 | 2022-2024      | Adult           | Tehran           | 45       | 200                      | 80                         | New and retreatment case | WHO standard conventional DST |
| Maleki                | 2023-2025      | Adult           | Tehran           | 45       | 200                      | 80                         | New and retreatment case | WHO standard conventional DST |
| Farivar               | 2024-2026      | Adult           | Tehran           | 45       | 200                      | 80                         | New and retreatment case | WHO standard conventional DST |
| Khozamiri             | 2025-2027      | Adult           | Tehran           | 45       | 200                      | 80                         | New and retreatment case | WHO standard conventional DST |
| Naderi                | 2026-2028      | Adult           | Tehran           | 45       | 200                      | 80                         | New and retreatment case | WHO standard conventional DST |
| Mansoori              | 2027-2029      | Adult           | Tehran           | 45       | 200                      | 80                         | New and retreatment case | WHO standard conventional DST |
| Haidarnazad           | 2028-2030      | Adult           | Tehran           | 45       | 200                      | 80                         | New and retreatment case | WHO standard conventional DST |
| Bahrami3              | 2029-2031      | Adult           | Tehran           | 45       | 200                      | 80                         | New and retreatment case | WHO standard conventional DST |

RIF: Rifampicin; TB: tuberculosis

Subgroup analysis

Table 2 shows the subgroup analysis of the studies based on the type of RIF-resistance, and history of TB treatment. RIF-resistance was significantly higher among previously treated patients compared to new patients (4% vs 36%).

Table 2. Pooled frequency of RIF-resistance among subgroups of studies

| Subgroups                  | No. of study | Frequency (95 % CI) | Heterogeneity |
|----------------------------|--------------|---------------------|---------------|
| Type of RIF-resistance     |              |                     | P-Value       | I² (%) |
| Any resistance             | 28 (6879 TB cases) | 8.0 (4.0-12.0)     | 0.00          | 96    |
| Mono resistance            | 5 (1205 TB cases)  | 5.0 (0.0-12.0)     | 0.00          | 100   |
| History of treatment       |              |                     |               |       |
| New cases                  | 10 (1904 TB cases) | 4.0 (2.0-8.0)      | 0.00          | 79    |
| Previously treated cases   | 5 (383 TB cases)   | 36.0 (2.0-82.0)    | 0.00          | 100   |

RIF: Rifampicin; TB: tuberculosis

P=0.00). Based on meta-regression, the number of RIF-resistances per study resulted in a significant source of heterogeneity in the current study (P-value= 0.03). As per Begg’s (P=0.1) test, there was no evidence of publication bias.
Discussion

In the present study, the pooled frequency of RIF-resistant TB in all TB cases was found to be 8.0%. Our sub-group analysis also showed that 4.0% of newly diagnosed cases and 36.0% of previously-treated TB patients from different settings in Iran were RIF-resistant. The prevalence of RIF-resistant TB among new cases observed in this study is above the current WHO estimates of drug resistance for Iran (1). This suggests that the burden of RIF-resistance in new patients with TB may be underestimated and better programmatic strategies are needed.

Furthermore, several other studies reported quite a varied frequency of RIF-resistant TB in the different countries in the Middle East Region. The prevalence of RIF-resistant TB in this study compared to previous studies in Iraq (12.6%), Egypt (1.9%), Turkey (1%), Saudi Arabia (1%), and Kuwait (0.2%) (48). The variation of RIF-resistant TB across the country might be related to geographical variation, study setting, differences in patient selection, sample size, method of diagnosis, and TB control practice.

Several countries in the world have adopted an algorithm placing Xpert MTB/RIF as the initial and diagnostic test for RIF-resistance (49-55). The results from the early programmatic implementation of Xpert MTB/RIF testing in nine countries indicated that testing with Xpert MTB/RIF can detect a large number of people with TB that routine services failed to detect (56). As more cases are rapidly detected and treated, there will be a reduction in transmission of primary drug resistance in the community. In Iran, due to limited resources, only a few TB laboratories use Xpert MTB/RIF for rapid diagnosis of TB and detection of drug resistance. Accordingly, in the current systematic review, all studies used conventional DST for investigating the drug-resistant pattern in patients infected with M. tuberculosis.

We also indicated that near half of previously-treated TB patients in the current study were resistant to RIF (Table 3). This indicates that in Iran there may be high rates of acquired resistance to RIF. Failure of the appropriate treatment of TB patients is among the most common causes of the occurrence of drug resistance. This could be from the supply or quality of the drugs, possible inadequate drug intake by patients, and deficient infection control in hospitals (57, 58). Our results suggest that NTP needs to strengthen the management of drug-resistant TB, and patients previously treated for TB should be prioritized in case findings.

This review has some limitations. Not all regions in Iran had reported RIF-resistant TB, as such these were considered not fully representative. Another limitation was that not all necessary information, such as age, sex, ethnicity, and HIV, could be obtained from all included

Figure 2. Frequency of RIF-resistance among patients with confirmed TB

| Author      | Year | ES (95% CI) | % Weight |
|-------------|------|-------------|----------|
| Amiri       | 2019 | 0.04 (0.02, 0.08) | 3.70     |
| N Mansoori  | 2018 | 0.01 (0.00, 0.03) | 3.62     |
| Sirous      | 2018 | 0.02 (0.01, 0.04) | 3.73     |
| Sakhaee     | 2017 | 0.01 (0.00, 0.02) | 3.71     |
| Darban-Sarokhali | 2016 | 0.01 (0.00, 0.05) | 3.54     |
| Saheti      | 2016 | 0.12 (0.09, 0.16) | 3.68     |
| Zarei       | 2016 | 0.16 (0.11, 0.21) | 3.64     |
| Bagde       | 2015 | 0.00 (0.00, 0.06) | 3.37     |
| Tavanaee Sari | 2015 | 0.03 (0.01, 0.08) | 3.51     |
| Imam Fooladi | 2014 | 0.00 (0.00, 0.04) | 3.52     |
| Nasiri      | 2014 | 0.06 (0.04, 0.10) | 3.67     |
| Bahrami     | 2013 | 0.11 (0.07, 0.16) | 3.62     |
| Faraz        | 2012 | 0.02 (0.00, 0.06) | 3.54     |
| Marjani     | 2012 | 0.05 (0.03, 0.07) | 3.73     |
| Yazdi       | 2012 | 0.23 (0.11, 0.44) | 3.02     |
| Hadizeh     | 2011 | 0.11 (0.10, 0.14) | 3.76     |
| Livanis     | 2011 | 0.03 (0.01, 0.09) | 3.59     |
| Bahramani 2 | 2009 | 0.14 (0.11, 0.19) | 3.66     |
| Shamaei     | 2009 | 0.22 (0.19, 0.26) | 3.73     |
| Javid       | 2009 | 0.15 (0.06, 0.20) | 3.22     |
| Maleki      | 2009 | 0.00 (0.00, 0.04) | 3.52     |
| Farivar     | 2006 | 0.96 (0.45, 0.96) | 3.46     |
| Khorasani   | 2006 | 0.08 (0.03, 0.15) | 3.44     |
| Nomaee      | 2006 | 0.00 (0.00, 0.04) | 3.52     |
| Naderi      | 2004 | 0.96 (0.45, 0.96) | 3.46     |
| Mansoori    | 2003 | 0.41 (0.35, 0.47) | 3.68     |
| Heidajmoed  | 2001 | 0.01 (0.00, 0.04) | 3.60     |
| Bahramani 1 | 2000 | 0.04 (0.03, 0.06) | 3.73     |
| Overall     |     | 0.08 (0.04, 0.12) | 100.00   |

RIF: Rifampicin; TB: tuberculosis
studies. Therefore, relevant stratified analyses could not be performed to find out more details of the related risk factors.

**Conclusion**

Our study showed that the frequency of Rifampicin-resistance among patients with TB was 8.0%. Programmatic implementation of rapid DST such as the Xpert MTB/RIF assay as a primary diagnostic test for persons suspected of having a Rif-resistant TB would be helpful for control of the drug resistance.

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**Founding**

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**Conflicts of Interest**

None.

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