

## Pattern of drug resistant *Mycobacterium tuberculosis* in the west and northwest of Iran: a meta-analysis

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### ABSTRACT

**Background and Objectives:** Drug-resistant tuberculosis (Tb) is a major public health issue across the world. Therefore, it is crucial to determine its pattern in different regions of the world. The aim of this study was to review the prevalence of drug resistant TB in the west and northwest of Iran.

**Materials and Methods:** A systematic literature search was performed to identify studies (2010 to 2021) in Google Scholar, PubMed, Thomson Reuters, Scientific Information Database (SID), Cochrane Library, and Medical Library (MedLib) databases. The patterns of any drug-resistant *Mycobacterium tuberculosis* (MTB); resistance to isoniazid (INH), rifampicin (RMP), streptomycin (SMP), ethambutol (EMB), and multiple drug resistance (MDR) were reviewed in tuberculosis in the west and northwest of Iran.

**Results:** In this review, 7 studies met the eligibility criteria for a meta-analysis. The pooled proportion of any drug resistant TB was 13% (CI 95%: 9.0, 17.0) (43.0% in re-treatment group). The pooled prevalence of any drug resistant TB was more than 1.5 times higher in men compared to women (15% vs. 9.0%). The pooled prevalence (%) of resistance to INH, RMP, SMP, EMB and MDR-TB was 11.0%, 12.0%, 13.0%, 6.0%, and 6.0%, respectively. Kermanshah Province (a province in the west of Iran) showed a high prevalence of any type of drug resistance and MDR-TB (15.9% and 20.0%, respectively).

**Conclusion:** It seems that the western provinces of Iran have a different pattern of drug resistance compared to the northwestern provinces. Considering the extent of Iran and the neighboring countries, it is recommended that the pattern of tuberculosis drug resistance be reviewed separately in different provinces or regions of Iran. Drug resistance in the re-treatment group was more than three times that of all patients with TB drug resistance. The burden of drug resistance reduces significantly with better control and management of TB drug treatment and preventing re-infection.

**Keywords:** Drug resistance; Tuberculosis; Meta-analysis

### INTRODUCTION

Drug-resistant tuberculosis (TB) has a major contribution to antimicrobial resistance worldwide as a public health threat. About half a million people are

infected with drug-resistant TB globally every year (1). Although TB is a preventable and curable disease, 1.5 million patients die from TB annually (1).

According to the World Health Organization (WHO), the proportion of multiple drug resis-

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tant (MDR) TB among new patients and previously treated cases is 1.3% and 8.3% in Iran, respectively (2019) (2). MDR-TB is caused by *Mycobacterium tuberculosis* (MTB) strains that are resistant to at least isoniazid (INH) and rifampicin (RMP) (3).

Iran shares borders with high prevalence countries such as Azerbaijan, Armenia, Pakistan, and Iraq, and the emergence of drug resistant TB has become a serious clinical problem in border cities of Iran (4). It is, therefore, crucial to determine the burden of drug resistant TB across these borders. This review and meta-analysis study was conducted to determine the prevalence of drug resistant TB in the west and northwest of Iran.

## MATERIALS AND METHODS

**Eligibility criteria and information source.** Articles published in English or Persian between January 2010 and December 2021, that evaluated drug-resistant MTB in the west and northwest of Iran were eligible for inclusion. A web-based citation index was used for citing documents.

**Search.** The Medical Subject Heading (MeSH) database was used for keywords. The relevant studies published in Persian and English were retrieved from Cochrane Library, Google Scholar, PubMed, Thomson Reuters, Scientific Information Database (SID), and Medical Library (MedLib). The search strategy developed by the authors was as follows: ("Drug Resistance"[Mesh]) AND "Tuberculosis" [Mesh] AND "Iran"[Mesh].

**Study selection.** Studies were selected if they (1) were published in Persian or English, (2) included information on TB drug resistance among MTB patients, (3) were performed in the west or northwest of Iran, and (4) were conducted using the reference proportion method for detection of drug resistance. Studies that (1) lacked randomization in patient selection, (2) lacked a cross-sectional design, (3) used the same sample of patients in more than one study, and (4) were conducted in special sub-populations (for example studies that used patients with specific characteristics) were excluded.

**Data collection process.** Two authors (KhA, LS)

selected the data based on the Cochrane Consumers and Communication Review Group's data extraction template. One of the authors (LS) extracted the data and the other author (KhA) rechecked the data.

**Data items.** The primary outcome was the proportion (95% CI) of drug-resistant MTB based on any resistance to Tb drugs; resistance to INH, RMP, streptomycin (SMP), ethambutol (EMB), and multiple drug resistance (MDR).

**Analysis.** The pooled proportion of drug-resistant MTB was calculated using random-effects models. The I<sup>2</sup> statistic was applied to evaluate heterogeneity among studies.

## RESULTS

A literature search was performed to find cross-sectional studies published between 2010 and 2021. The electronic search yielded 32 studies in six databases. After the exclusion of duplicate studies, 21 articles remained for further assessment (Fig. 1).

Following full-text evaluation, only 3 articles met the eligibility criteria (5-7). The findings of one of the studies (conducted by the author of the present article) in which 5 border provinces in the west and northwest of Iran were studied were reported separately, and in more detail for each province in this review (6). Finally, 7 studies were available for analysis. All studies were done on MTB patients except for one study (6), that was conducted on patients with pulmonary tuberculosis. A summary of the results of TB drug resistances according to the province is shown in Table 1.

The pooled proportion of any drug resistance (for 5 studies) was 13.0% (95% CI: 9.0, 17.0;  $I^2_{\text{Heterogenit y}} = 0.0\%$ ,  $p = 0.76$ ,) (Fig. 2) (6). The proportion of any drug resistance was 15% (95% CI: 8.0, 21.0) in male and 9.0% (95% CI: 4.0, 13.0) in female patients.

The pooled proportion of any drug resistance (6) in retreatment groups was 43% (95% CI: 24.0, 62.0) and the output was homogeneous ( $I^2_{\text{Heterogenit y}} = 0.0\%$ ,  $P=0.64$ ).

The frequency of any drug resistance in the re-treatment groups was: 2 in East Azerbaijan (of 6 retreatment cases), 0 in West Azerbaijan (of 2 cases), 1 in Ardebil (of 4 cases), 4 in Kermanshah (of 7 cases),

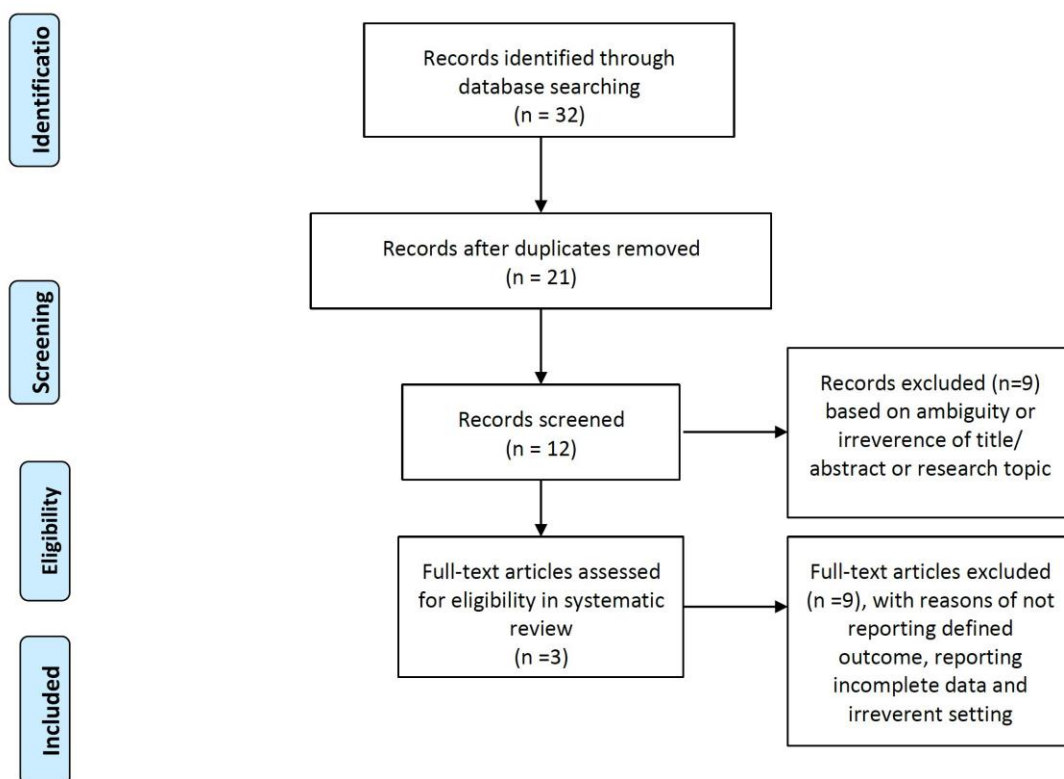


Fig. 1. Flow chart of included studies.

Table 1. Summary of results of Tuberculosis drug resistance according to province

Authors, year	Provinces	Sample size	Type	INH (%)	RMP (%)	EMB (%)	SMP (%)
Nasiri (2014) (5)	Kermanshah	15	MTB	4 (27)	3 (20)	3 (20)	3 (220)
Mohajeri (2014) (7)	Kermanshah	112	MTB	18 (16.07)	16 (14.29)	15 (13.39)	25 (22.32)
Sahebi (2016) (6)	West Azerbaijan	45	MTB	4 (8.89)	7 (15.56)	0 (0.0)	5 (11.11)
Sahebi (2016) (6)	Ardebil	30	MTB	4 (13.33)	4 (13.33)	2 (6.67)	3 (10.0)
Sahebi (2016) (6)	Kermanshah	53	MTB	5 (9.43)	9 (16.98)	2 (3.77)	7 (13.21)
Sahebi (2016) (6)	Kurdistan	56	MTB	7 (12.5)	7 (12.5)	3 (5.36)	6 (10.71)
Sahebi (2016) (6)	East Azerbaijan	96	Pulmonary MTB	8 (8.33)	6 (6.25)	2 (2.08)	9 (9.38)

and 4 in Kurdistan (of 8 cases).

The prevalence of resistance to INH, RMP, SMP and EMB was 11.0% (95% CI: 8.0, 14.0), 12.0% (95% CI: 8.0,16.0) , 13.0% (95% CI: 9.0,17.0), and 6.0% (95% CI: 2.0, 10.0), respectively (Table 2) (5-7).

A Forrest plot of the MDR proportion according to provinces is shown in Fig. 3. The pooled prevalence of MDR TB was 6% (95% CI: 3.0, 9.0) (5-7). The highest and lowest prevalence belonged to Kermanshah province (5, 7) (11%; CI95%: 4-19) and East Azerbaijan (6) (3%; CI 95%: 1-9%), respectively.

## DISCUSSION

This review study was conducted to evaluate the pattern of drug resistant MTB in the west and north-west of Iran. The sample size in these studies ranged between 15 and 112 subjects (5-7). The prevalence of any drug resistant TB was 13.0 (95% CI: 9.0, 17.0). This proportion was obtained from 5 studies (5-7).

The proportion of MDR TB was 6% (95% CI: 3.0, 9.0) (5-7). The highest prevalence of MDR TB was seen in Kermanshah Province ((20.0%, 95% CI: 7.0, 45.0) (5) and 13.40%, CI 95%: 9.0, 22.0) (7)).

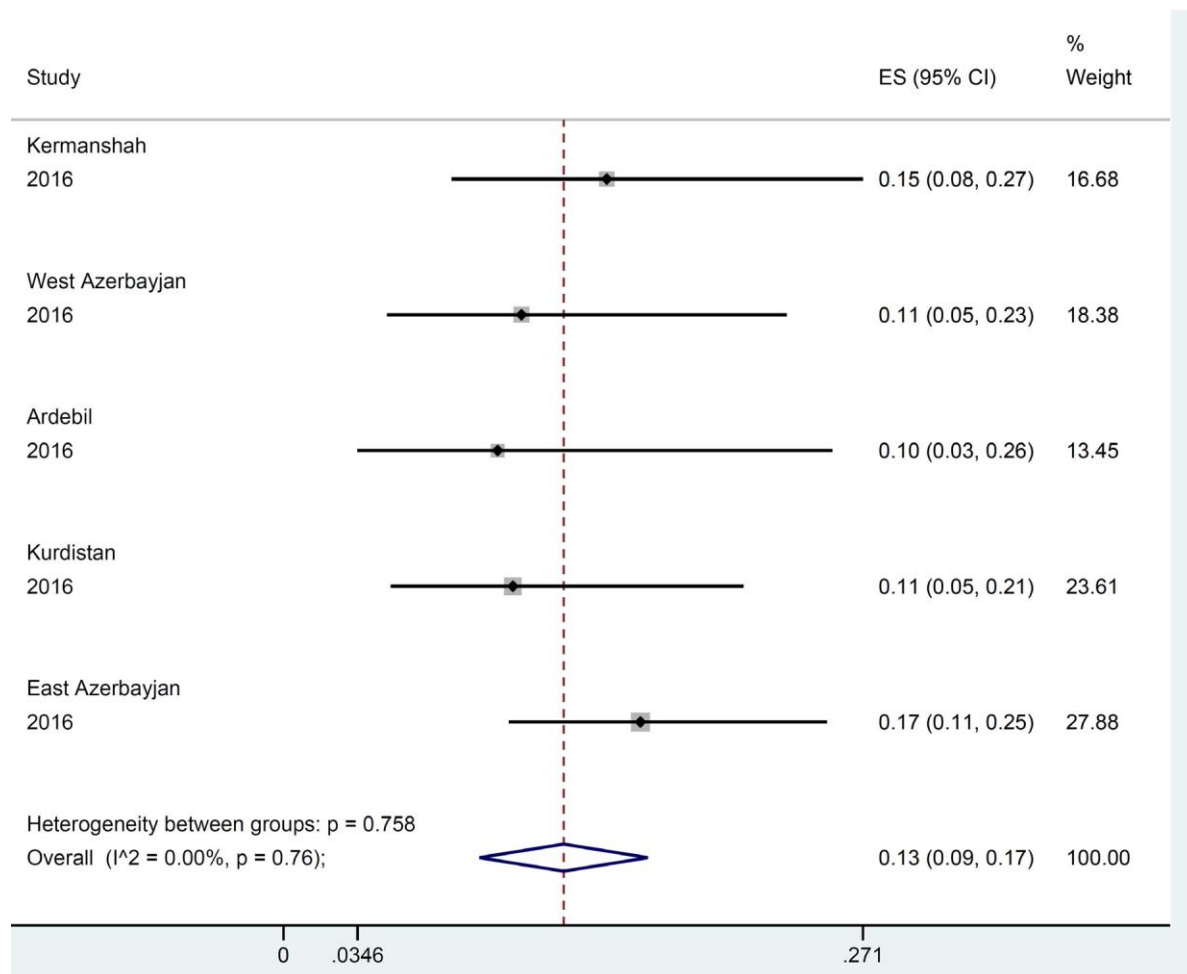


Fig. 2. Forest plot of proportion of any drug resistant *Mycobacterium tuberculosis*

Table 2. Pooled proportion of INH, RMP, EMB, and SMP drug resistance pattern in west and northwest of Iran

Province	INH	RMP	EMB	SMP
	Prevalence (CI 95%)	Prevalence (CI 95%)	Prevalence (CI 95%)	Prevalence (CI 95%)
East Azerbaijan	8.0 (4.0,16.0)	6.0 (3.0,13.0)	2.0 (1.0,7.0)	9.0 (5.0,17.0)
Kermanshah	14.0 (8.0,21.0)	15.0 (10.0,21.0)	10.0 (1.0,19.0)	19.0 (12.0,25.0)
West Azerbaijan	9.0 (4.0,21.0)	16.0 (8.0,29.0)	-	11.0 (5.0,23.0)
Ardebil	13.0 (5.0,30.0)	13.0 (5.0,30.0)	7.0 (2.0,21.0)	10.0 (3.0,26.0)
Kurdistan	13.0 (6.0,24.0)	13.0 (6.0,24.0)	5.0 (2.0,15.0)	11.0 (5.0,21.0)
Total	11.0 (8.0,14.0)	12.0 (8.0,16.0)	6.0 (2.0,10.0)	13.0 (9.0,17.0)
I <sup>2</sup> (P-Value)	0.0% (0.48)	22.26% (0.26)	61.06% (0.02)	27.88% (0.22)

The lowest prevalence was seen in East Azerbaijan (3.0%), which was similar to 2001 (8).

The present study found that 43.0% of the previous treatment and 11.0% of new treatment groups were at least resistant to a first-line TB drug. One of the most important causes of re-infection is treatment failure, which occurs due to poor management of treatment

(9). Prevention of TB re-infection prevents drug resistance in addition to reducing the economic and social burden of the disease (10).

The highest and lowest prevalence of any drug resistant TB in the re-infection group was observed in Kermanshah Province (57%, 95% CI: 25.0, 84.0) and West Azerbaijan (0.0%) (6), respectively. This

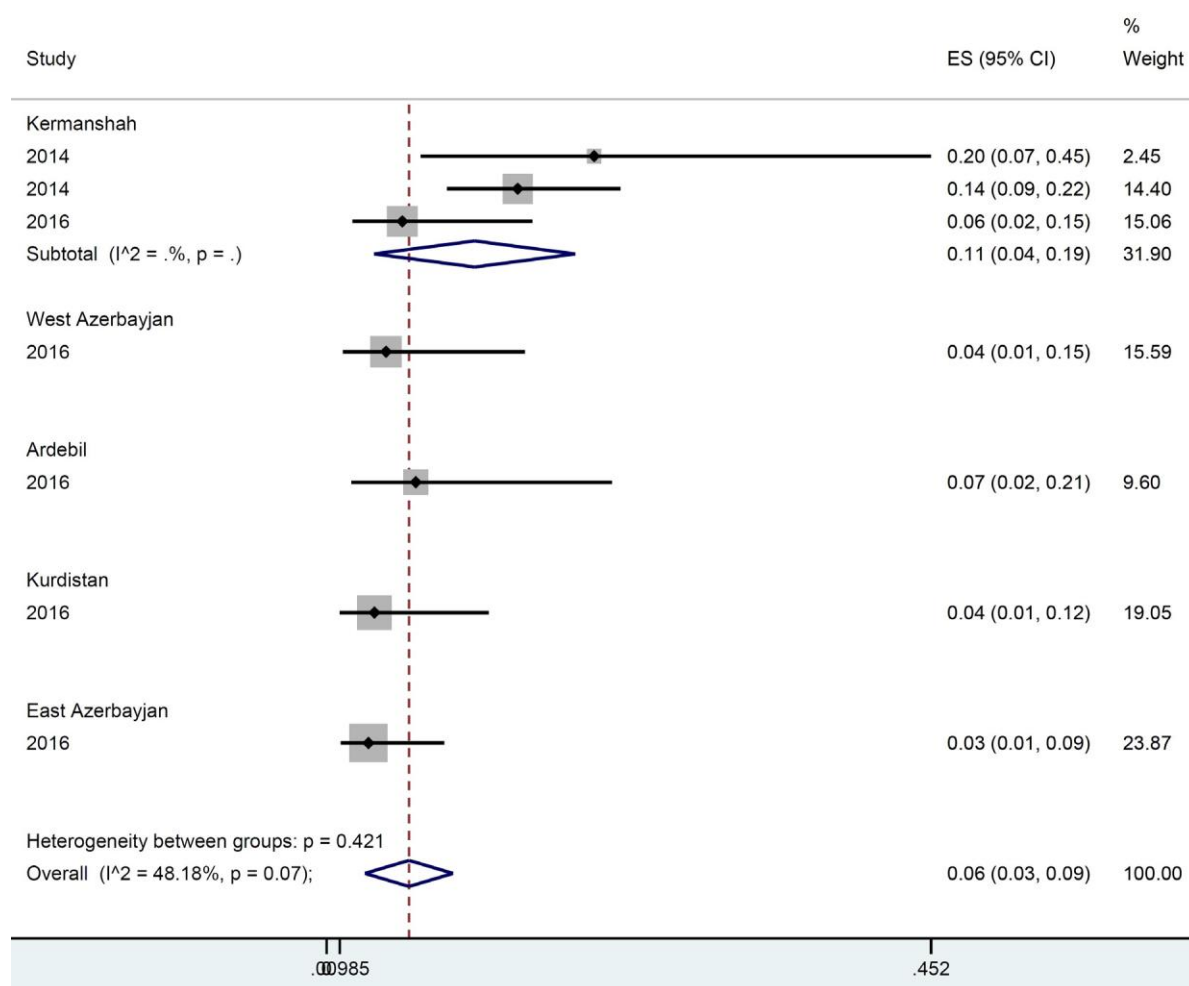


Fig. 3. Forest plot of proportion of MDR pattern in west and northwest of Iran

finding was not consistent with a systematic review of the prevalence of drug resistance among patients conducted in Tehran, capital of Iran (5 studies) and Golestan Province, north of Iran (1 study) (3). Our subjects were geographically different from the previous review; moreover, the patients in the present study were purely Iranian while more than 10% of the patients were not Iranian in the above review study.

Kermanshah Province (western border province) consistently showed a high prevalence of MDR-TB. Since Iran has borders with seven countries with different patterns of tuberculosis prevalence and drug resistance, and also since Iran has more than 30 provinces with different environmental, ecological, and demographic characteristics, regional and provincial studies of tuberculosis drug resistance will produce more reliable results.

One of the strengths of this study was its strict inclusion criteria since studies were included in the

analysis that was homogeneous in terms of study design and determination technique. In addition, immigrants were not included in this review study.

This review has a major limitation that needs to be addressed. Although many articles were found initially, the number of eligible studies was quite small after screening, which could affect the power of the study.

**CONCLUSION**

The pooled proportion of any drug resistant TB was 13%, and this proportion was significantly high in re-treatment groups (43%). Moreover, the prevalence of drug resistance was higher in men compared to women. It seems that the western provinces of Iran have a different pattern of drug resistance compared to the northwestern provinces.

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