

Multidrug-resistant tuberculosis in Iran: a multicenter study

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Abstract

The worldwide incidence of multidrug-resistant tuberculosis (MDR-TB) is rapidly increasing, and it has emerged as a pressing public health issue in Iran. Nevertheless, there is a scarcity of up-to-

date research on the prevalence of MDR-TB in individuals with pulmonary TB in the country. In this cross-sectional study, we gathered a total of 1216 respiratory samples, each corresponding to a unique patient, from five distinct regional TB laboratories in Iran. We identified clinical isolates as *Mycobacterium tuberculosis* using the IS6110-based polymerase chain reaction assay and Xpert MTB/RIF. Drug susceptibility testing (DST) was conducted using the conventional proportion method. Out of the collected specimens, 448 tested positive for *M. tuberculosis*. Among these isolates, 445 (99.4%) exhibited susceptibility to the tested drugs, while 3 (0.6%) were found to be MDR. The findings from this recent study indicate that the prevalence of MDR in Iran stands at 0.6%. The absence of recently approved treatment protocols in various regions of Iran, along with inadequately equipped laboratories lacking DST capabilities, could contribute significantly to the rise in TB/MDR-TB prevalence in Iran. Therefore, the implementation of enhanced treatment management strategies and the adoption of innovative technologies are essential steps toward improving the current situation.

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Introduction

Tuberculosis (TB) remains a persistent global public health challenge, demanding continuous investigation, particularly regarding its multidrug-resistant TB (MDR-TB) form [1-4].

Iran, geographically situated at the nexus of Asia and the Middle East, merits focused scrutiny. Despite reporting a relatively lower TB incidence compared to neighboring high-burden nations, Iran's extensive borders with countries where TB and drug-resistant TB are prevalent make it susceptible to the infiltration and dissemination of drug-resistant TB strains [5,6].

To address this dynamic landscape, a contemporary nationwide assessment of MDR-TB prevalence within Iran is crucial. Previous studies have offered valuable localized insights but failed to provide a comprehensive national overview [7-11]. This study not only enhances the scientific understanding of MDR-TB within Iran but also informs evidence-based policy decisions and bolsters national TB control programs. By contributing to the global effort against MDR-TB, this research recognizes Iran's pivotal role in safeguarding public health, both domestically and internationally.

Materials and Methods

Study population

In this cross-sectional study, a comprehensive collection of 1216 respiratory samples, derived from the same number of patients, was undertaken across five distinct regional TB laboratories in Iran. These locations include Tehran, Mashhad, Ahvaz,

Shiraz, and Isfahan. The duration of data collection spanned from May 1, 2021, to Jun 15, 2022. It is noteworthy that all samples underwent identification and drug susceptibility testing (DST) within the advanced confines of the Tehran Regional TB reference laboratory. This state-of-the-art facility, overseen by the Swedish Institute for Infectious Disease Control, possesses the requisite capabilities for conducting accurate DST. The sampled individuals encompassed both newly diagnosed TB cases and those facing treatment failure or relapse. The study was approved by the Ethics Committee of the Shahid Beheshti University of Medical Sciences, Tehran, Iran (IR.SBMU.MSP.REC.1400. 677).

Identification of *Mycobacteria*

Each sample underwent fluorochrome staining and confirmation through Ziehl-Neelsen methods. Subsequently, slope cultures on Lowenstein-Jensen medium were incubated at 37°C, and weekly growth assessments were conducted for up to 8 weeks. Bacterial isolates were identified as *M. tuberculosis* using established biochemical tests, which encompassed niacin production, nitrate reduction, and catalase activity [8].

Molecular identification of *Mycobacterium tuberculosis*

The molecular identification of *Mycobacterium tuberculosis* was achieved through the utilization of IS6110-based polymerase chain reaction (PCR) assay and Xpert MTB/RIF. Genomic DNA extraction for IS6110-based PCR assay employed the QIAamp DNA Mini Kit (QIAGEN, Germantown, MD, USA) in adherence to the provided instructions. The targeted amplification of a 123 bp fragment of insertion element IS6110, a distinctive element of the *M. tuberculosis* complex, was executed employing previously described PCR primers. Positive and negative controls constituted genomic DNA from *M. tuberculosis* H37Rv (ATCC27294) and *M. fortuitum* (ATCC 49404), respectively. Xpert MTB/RIF was executed on clinical specimens in accordance with established protocols [6].

Drug susceptibility testing

Confirmed *M. tuberculosis* isolates underwent DST for isoniazid (INH) and rifampicin (RIF) through the proportion method on LJ

medium. The evaluation of resistance manifested as the percentage of colonies attaining growth on critical drug concentrations: 0.2 µg/mL for INH and 40 µg/mL for RIF. The interpretation adhered to standard resistance criteria (*i.e.*, 1% for all drugs). To ensure quality control, the *M. tuberculosis* H37Rv strain (ATCC 27294) was employed in DST testing [6].

Statistical analysis

Data underwent analysis using MedCalc 14 statistical software. To assess the disparities between categorical variables, the Chi-square statistical test was employed.

Results

Mycobacterial isolates

Of the 1216 respiratory samples analyzed, 448 (36%) were identified as positive for *M. tuberculosis*. Patient history variables, encompassing age, gender, and HIV status, are delineated in Table 1.

Drug susceptibility testing

Within the pool of *M. tuberculosis* isolates, a staggering 445 (99.4%) exhibited pan-susceptibility, while a discrete subset of 3 (0.6%) displayed MDR, as depicted in Table 2. Out of these MDR cases, 2 were identified in retreatment patients, with the remaining case emerging from a new TB case. Notably, no statistical discrepancies surfaced between basic characteristics and the occurrence of MDR isolates.

Discussion

Our investigation reveals a concerning yet informative insight into the prevalence of MDR-TB within the examined population, with a documented frequency of 0.6%. This finding underscores the ongoing challenges and complexities entailed in managing TB in Iran.

Addressing the incidence and mortality of TB is imperative for global public health, particularly in nations with intermediate or

Table 1. Basic characteristics.

Variable	No. of <i>Mycobacterium tuberculosis</i> (%)	No. of multidrug resistant tuberculosis	p
Sex			
Male	320 (71.0)	2 (67.0)	>0.05
Female	128 (27.0)	1 (33.0)	
Age			
18-35	75 (16.0)	0 (0.0)	>0.05
35-80	373 (84.0)	3 (100)	
HIV			
Positive	2 (0.4)	1 (33.0)	>0.05
Negative	446 (99.6)	2 (67.0)	

Table 2. Drug-resistant patterns.

Type of resistance	No. of <i>Mycobacterium tuberculosis</i> (%)
Pan-susceptible	445 (99.4)
Multidrug resistance	3 (0.6)

high TB rates. The delineated core areas, encompassing political commitment to research investment, provide a comprehensive roadmap for TB elimination [12]. The urgency is underscored by immediate health risks, socioeconomic impacts, and the looming threat of drug resistance. Initiating the path toward TB elimination demands collective efforts, political resolve, and sustained resources. Progress in this direction empowers countries to substantially alleviate the disease burden, enhance population health, and contribute to the global TB eradication endeavor. The proposed framework underscores the importance of tailored interventions, robust surveillance, research endeavors, and international collaboration to envision a future marked by reduced TB incidence and mortality [13].

One of the significant implications of our study revolves around the availability of novel treatment regimens and advanced anti-TB drugs such as bedaquiline and delamanid [14-22]. Despite the global strides made in TB research and drug development, it is evident that many of these innovative treatment options have not yet found their way into the armamentarium of TB management in Iran. The existence of MDR-TB cases within our study population emphasizes the pressing need for the introduction of these new treatment modalities. MDR-TB requires specialized, longer, and more costly therapeutic regimens compared to drug-susceptible TB [23-25]. The availability of novel drugs and regimens could substantially improve treatment outcomes, minimize the risk of further drug resistance, and enhance the overall prognosis for MDR-TB patients [26,27].

Furthermore, our study shed light on the prevailing limitations within TB laboratory infrastructure in Iran. While accurate and timely diagnosis of drug-resistant TB is pivotal for patient management and disease control, it is apparent that several TB laboratories in the country are not still fully equipped to perform DST to the required standards [28-31]. This deficiency in laboratory capacity can lead to misdiagnoses and treatment failures, thus perpetuating the transmission of drug-resistant TB strains. The expansion and strengthening of laboratory facilities across Iran, coupled with training and proficiency programs for laboratory personnel, should be prioritized to address this critical gap in TB management.

The occurrence of MDR-TB within our study population should serve as a catalyst for strategic planning and policy formulation at both the national and regional levels. To effectively fight the rise of MDR-TB, Iran must intensify efforts to facilitate the timely adoption of new treatment regimens and drugs. Collaborative initiatives with international organizations and partners can aid in accessing these cutting-edge therapies. Additionally, investment in the reinforcement of laboratory infrastructure and the enhancement of DST capabilities is paramount for precise diagnosis and tailored treatment, ultimately curbing the spread of drug-resistant TB strains [32-36].

Conclusions

In conclusion, our study underscores the necessity for an urgent and comprehensive response to the emergence of MDR-TB in Iran. The unavailability of novel treatment options, coupled with inadequate laboratory infrastructure, poses significant challenges to TB control efforts. By prioritizing the introduction of advanced treatment regimens, expanding laboratory capacity, and investing in diagnostic capabilities, Iran can better confront the evolving threat of drug-resistant TB and improve the outlook for affected individuals while contributing to global TB control endeavors.

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