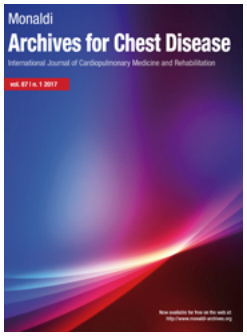

Monaldi Archives for Chest Disease

eISSN 2532-5264 https://www.monaldi-archives.org/

Monaldi Arch Chest Dis 2024 [Online ahead of print]

To cite this Article:
Khelghati F, Nasirpour Seilakhori F, Goudarzi M, et al. **Multidrug-resistant tuberculosis in Iran: a multicenter study.** *Monaldi Arch Chest Dis* doi: 10.4081/monaldi.2024.2844

Multidrug-resistant tuberculosis in Iran: a multicenter study

Fatemeh Khelghati,[1] Fatemeh Nasirpour Seilakhori,[1] Mehdi Goudarzi,[1] Shima Malekloo,[1] Amir Hashem Shahidi Bonjar,[2] Hossein Goudarzi,[1] Mohammad Javad Nasiri[1]

[1]Department of Microbiology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran; [2]School of Dentistry, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Correspondence: Mohammad Javad Nasiri, Department of Microbiology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
E-mail: mj.nasiri@hotmail.com

Contributions: all authors contributed equally.

Conflict of interest: the authors report no conflicts of interest.

Ethics approval and consent to participate: the study was approved by the Ethics Committee of the Shahid Beheshti University of Medical Sciences, Tehran, Iran (IR.SBMU.MSP.REC.1400.677).

Funding: this study was supported by the Research Department of the School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran (Grant number: 31200).

Availability of data and materials: data and materials are available from the corresponding author.

Abstract

The worldwide incidence of multi-drug-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 PCR 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 towards improving the current situation.

Key words: tuberculosis, MDR, drug resistance, Iran.

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 (TRTB-RL). 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 M. tuberculosis

The molecular identification of *M. tuberculosis* was achieved through the utilization of IS6110-based PCR assay and Xpert MTB/RIF. Genomic DNA extraction for IS6110-based PCR assay employed the QIAamp DNA Mini Kit (QIAGEN, 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 Mycobacterium 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, *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, two 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 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 combat 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.

References

1. Millard J, Ugarte-Gil C, Moore DA. Multidrug resistant tuberculosis. BMJ 2015;350:h882.
2. Saderi L, Cabibbe AM, Puci M, et al. A systematic review of the costs of diagnosis for multidrug-resistant/extensively drug-resistant TB in different settings. Int J Tuberc Lung Dis 2023;27:348-56.
3. Maier C, Chesov D, Schaub D, et al. Long-term treatment outcomes in patients with multidrug-resistant tuberculosis. Clin Microbiol Infect 2023;29:751-7.
4. Chakaya J, Khan M, Ntoumi F, et al. Global Tuberculosis Report 2020 - reflections on the global TB burden, treatment and prevention efforts. Int J Infect Dis 2021;113:S7-S12.
5. Nasiri MJ, Dabiri H, Darban-Sarokhalil D, et al. Prevalence of drug-resistant tuberculosis in Iran: systematic review and meta-analysis. Am J Infect Control 2014;42:1212-8.
6. Bahraminia F, Zangiabadian M, Nasiri MJ, et al. Rifampicin resistance in Mycobacterium tuberculosis in Iran: a two-centre study. New Microbes New Infect 2021;42:100909.
7. Metanat M, Sharifi-Mood B, Shahreki SH, Dawoudi SH. Prevalence of multidrug-resistant and extensively drug-resistant tuberculosis in patients with pulmonary tuberculosis in zahedan, southeastern iran. Iran Red Crescent Med J 2012;14:53-5.

8. Nasiri MJ, Rezaei F, Zamani S, et al. Drug resistance pattern of Mycobacterium tuberculosis isolates from patients of five provinces of Iran. Asian Pac J Trop Med 2014;7:193-6.
9. Mohajeri P, Norozi B, Atashi S, Farahani A, et al. Anti tuberculosis drug resistance in west of Iran. J Glob infect Dis 2014;6:114-7.
10. Farazi A, Sofian M, Zarrinfar N, et al. Drug resistance pattern and associated risk factors of tuberculosis patients in the central province of Iran. Caspian J Int Med 2013;4:785-9.
11. Atashi S, Izadi B, Jalilian S, et al. Evaluation of GeneXpert MTB/RIF for determination of rifampicin resistance among new tuberculosis cases in west and northwest Iran. New Microbes New Infect 2017;19:117-20.
12. Yaacoub H, Farhat AM, Najjar-Pellet J, et al. Planning for TB elimination in Lebanon. Int J Tuberc Lung Dis 2023;27:171-4.
13. Migliori GB, Dowdy D, Denholm JT, et al. The path to tuberculosis elimination: a renewed vision. Eur Respir J 2023;61:2300499.
14. Millard J, Rimmer S, Nimmo C, O'Donnell M. Therapeutic failure and acquired bedaquiline and delamanid resistance in treatment of drug-resistant TB. Emerg Infect Dis 2023;29:1081-4.
15. Vanino E, Granozzi B, Akkerman OW, et al. Update of drug-resistant tuberculosis treatment guidelines: a turning point. Int J Infect Dis 2023;130:S12-S15.
16. Bossù G, Autore G, Bernardi L, et al. Treatment options for children with multi-drug resistant tuberculosis. Expert Rev Clin Pharmacol 2023;16:5-15.
17. Padmapriyadarsini C, Vohra V, Bhatnagar A, et al. Bedaquiline, delamanid, linezolid, and clofazimine for treatment of pre-extensively drug-resistant tuberculosis. Clin Infect Dis 2023;76:e938-46.
18. Nasiri MJ, Zangiabadian M, Arabpour E, et al. Delamanid-containing regimens and multidrug-resistant tuberculosis: a systematic review and meta-analysis. Int J Infect Dis 2022;124:S90-S103.
19. Hatami H, Sotgiu G, Bostanghadiri N, et al. Bedaquiline-containing regimens and multidrug-resistant tuberculosis: a systematic review and meta-analysis. J Bras Pneumol 2022;48:e20210384.
20. Tiberi S, Utjesanovic N, Galvin J, et al. Drug resistant TB-latest developments in epidemiology, diagnostics and management. Int J Infect Dis 2022;124:S20-5.
21. Perrin C, Athersuch K, Elder G, et al. Recently developed drugs for the treatment of drug-resistant tuberculosis: a research and development case study. BMJ Glob Health 2022;7:e007490.
22. Umar F, Hatta M, Husain DR, et al. The effect of anti-tuberculosis drugs therapy on mRNA efflux pump gene expression of Rv1250 in Mycobacterium tuberculosis collected from tuberculosis patients. New Microbes New Infect 2019;32:100609.
23. Resch SC, Salomon JA, Murray M, et al. Cost-effectiveness of treating multidrug-resistant tuberculosis. PLoS Med 2006;3:e241.
24. Tiberi S, Muñoz-Torrico M, Duarte R, et al. New drugs and perspectives for new anti-tuberculosis regimens. Pulmonology 2018;24:86-98.
25. Migliori, G.B., et al., MDR/XDR-TB management of patients and contacts: Challenges facing the new decade. The 2020 clinical update by the Global Tuberculosis Network. International Journal of Infectious Diseases, 2020. 92: p. S15-S25.
26. Migliori GB, Tiberi S. WHO drug-resistant TB guidelines 2022: what is new? Int J Tuberc Lung Dis 2022;26:590-1.

27. WHO. WHO consolidated guidelines on tuberculosis. Module 4: treatment-drug-resistant tuberculosis treatment, 2022 update. Available from: https://iris.who.int/bitstream/handle/10665/365308/9789240063129-eng.pdf?sequence=1.
28. Schön T, Miotto P, Köser CU, et al. Mycobacterium tuberculosis drug-resistance testing: challenges, recent developments and perspectives. Clin Microbiol Infect 2017;23:154-60.
29. Kim SJ. Drug-susceptibility testing in tuberculosis: methods and reliability of results. Eur Respir J 2005;25:564-9.
30. Van Deun A, Wright A, Zignol M, et al. Drug susceptibility testing proficiency in the network of supranational tuberculosis reference laboratories. Int J Tuberc Lung Dis 2011;15:116-24.
31. Amini S, Hoffner S, Torkaman MRA, et al. Direct drug susceptibility testing of Mycobacterium tuberculosis using the proportional method: a multicenter study. J Glob Antimicrob Resist 2019;17:242-4.
32. Dean AS, Auguet OT, Glaziou P, et al. 25 years of surveillance of drug-resistant tuberculosis: achievements, challenges, and way forward. Lancet Infect Dis 2022;22:e191-6.
33. Ntoumi F, Nachega JB, Aklillu E, et al. World tuberculosis day 2022: aligning COVID-19 and tuberculosis innovations to save lives and to end tuberculosis. Lancet Infect Dis 2022;22:442-4.
34. Gotham D, McKenna L, Frick M, Lessem E. Public investments in the clinical development of bedaquiline. PLoS One 2020;15:e0239118.
35. Aldridge BB, Barros-Aguirre D, Barry CE 3rd, et al. The tuberculosis drug accelerator at year 10: what have we learned? Nat Med 2021;27:1333-7.
36. Kendall EA, Sahu S, Pai M, et al. What will it take to eliminate drug-resistant tuberculosis?. Int J Tuberc Lung Dis 2019;23:535-46.

Table 1. Basic characteristics.

Variable	No. of *M. tuberculosis* (%)	No. of MDR-TB	P-value
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)	

MDR-TB, multi-drug-resistant tuberculosis; *M. tuberculosis, Mycobacterium tuberculosis*.

Table 2. Drug-resistant patterns.

Type of resistance	No. of *M. tuberculosis* (%)
Pan-susceptible	445 (99.4)
Multidrug resistance	3 (0.6)

M. tuberculosis, Mycobacterium tuberculosis.