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ORIGINAL ARTICLE

Resistance Rates of *Mycobacterium tuberculosis* Complex Isolates to First-line Anti-tuberculosis Drugs: A 5-Year Retrospective Study

Mycobacterium tuberculosis Kompleks İzolatlarının Birinci Basamak Anti-tüberküloz İlaçlara Direnç Oranları: 5 Yıllık Retrospektif Araştırma

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ABSTRACT

Background/Aim: Tuberculosis (TB) remains a major global health problem with a high morbidity and mortality rate, approximately a quarter of the population is infected with tuberculosis. Drug susceptibility testing is an essential tool to identify and manage drug-resistant tuberculosis. This study was conducted to evaluate the drug susceptibility pattern of Mycobacterium tuberculosis complex strains isolated from a university hospital.
Methods: A total of 10900 samples sent to the microbiology laboratory with the suspicion of tuberculosis clinically between January 2018 and January 2022 were analyzed retrospectively. The automated BACTEC MGIT 960 (Becton Dickinson, USA) was used for sample culture and susceptibility testing. The obtained data were statistically analyzed with the Statistical Package for Social Sciences (SPSS version 20).
Results: Out of the 154 isolated positive samples, males and females constituted equal parts of the study population (50%). The majority of tuberculosis cases were in the age group of 56–75 years (42.2%). Pulmonary tuberculosis was detected in 139 (90.3%) of the patients while extrapulmonary TB cases were observed in 15 (9.7%) patients. As a result of susceptibility studies on positive samples, isoniazid resistance was 5.2%; streptomycin resistance 1.3%; ethambutol resistance was detected at a rate of 0.6% while no rifampicin resistant sample was found. Both streptomycin and isoniazid resistance were seen together in 1.3% of the samples.
Conclusion: A similar resistance pattern of the first-line antituberculosis drugs was observed in other studies conducted in different provinces of Turkiye. The absence of multi-drug resistant and extensively drug-resistant tuberculosis in our study indicates that the tuberculosis surveillance program implemented in our region was successful.

Keywords: Mycobacterium tuberculosis complex, tuberculosis, anti-tuberculosis drug, drug susceptibility testing.

ÖZ

Giriş/Amaç: Tüberküloz, yüksek morbidite ve mortalite oranı ile önemli bir küresel sağlık sorunu olmaya devam etmektedir ve nüfusun yaklaşık dörtte biri tüberküloz ile enfektedir. İlaç duyarlılık testleri, ilaca dirençli tüberkülozu tanımlamak ve yönetmek için önemlidir. Bu çalışmada, bir üniversite hastanesinden izole edilen Mycobacterium tuberculosis kompleks suşlarının ilaca duyarlılık paterninin değerlendirilmesi amaçlanmıştır.
Yöntemler: Ocak 2018-Ocak 2022 tarihleri arasında tüberküloz şüphesi ile mikrobiyoloji laboratuvarına gönderilen toplam 10900 örnek retrospektif olarak incelenmiştir. Örneklerin kültürü ve duyarlılık testleri için BACTEC MGIT 960 (Becton Dickinson, ABD) otomatize sistem kullanılmıştır. Elde edilen veriler Statistical Package for Social Sciences (SPSS version 20) ile istatistiksel olarak analiz edilmiştir.
Bulgular: Pozitif olarak bulunan 154 hastada erkek ve kadın oranı eşit olarak bulunmuştur. Tüberküloz olgularının çoğunluğu 56-75 yaş grubunda (%42,2) olup, hastaların %90,3'ünde akciğer tüberkülozu saptanırken, %9,7 oranında akciğer dışı tüberküloz tespit edilmiştir. Pozitif örneklerde yapılan duyarlılık çalışmaları sonucunda izoniazid direnci %5,2; streptomisin direnci %1,3; etambutol direnci %0,6 oranında tespit edilirken, rifampisin dirençli örnek bulunmamıştır. Örneklerin %1,3'ünde hem streptomisin hem de izoniazid direnci birlikte görülmüştür.
Sonuç: Türkiye'de farklı illerde yapılan diğer çalışmalarda birinci basamak antitüberküloz ilaçlarda benzer direnç paterni gözlenmiştir. Çalışmamızda çok ilaca dirençli tüberküloz ve yaygın ilaca dirençli tüberküloz suşlarının bulunmaması, bölgemizde uygulanan tüberküloz gözetleme programının başarılı olduğunu göstermektedir.

Anahtar Kelimeler: Mycobacterium tuberculosis kompleksi, tüberküloz, anti-tüberküloz ilaç, ilaç duyarlılık testi.

Introduction

Tuberculosis (TB) is a communicable disease caused by Mycobacterium tuberculosis complex, an organism that spreads slowly and broadly in the lungs creating hard nodules with the possibility of infecting other organs in the body (1). TB has affected humans for over 5000 years (2) and continued to be among the top ten causes of death due to an individual infectious agent until the COVID-19 pandemic (3). The latest World Health Organization (WHO) 2022 Global TB report estimates an incidence rate of 10.6 million new TB cases and 1.6 million deaths globally (4). In 2020, the incidence of tuberculosis in Turkiye was 15 cases per 100,000 people. Statistics provided by the WHO and the European Centre for Disease Prevention and Control (CDC), show that the rate of tuberculosis cases in Turkiye has witnessed a gradual decline, with a mean

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annual change (-4.5%) between 2016–2020 (5).

The disease is transmitted through the inhalation of infected aerosols. TB bacilli have a unique ability to survive intracellularly. After being taken up by alveolar macrophages, which in most cases kill the entering bacteria, some may avoid being killing and remain inactive for a long period of time until the development of a favorable environment. The critical point in TB treatment is the completion of the treatment within the expected period which is at least six months (6). Two groups of drugs are used. First-line drugs e.g. (isoniazid, rifampicin, pyrazinamide, and streptomycin), most effective and least toxic for use in the treatment of TB, while the second-line therapeutic drugs, less effective, more expensive and have higher toxicities and more difficult to tolerate, e.g. (rifabutin, cycloserine, amikacin, capreomycin, para-aminosalicylic acid, levofloxacin and gatifloxacin) are the drugs available (7). A 4–6-month uptake of anti-TB drug can successfully treat 85% of patients with TB (4). Shortly after the implementation of streptomycin in clinical use, drug resistance to anti-TB drugs developed (3).

The emergence of drug-resistant Mycobacterium tuberculosis strains is one of the major public health problems of this century (8). Multidrug-resistant TB (MDR-TB) is the condition in which M. tuberculosis develops resistance to the first-line anti-TB drugs, isoniazid, and rifampicin, simultaneously whereas extensively drug-resistant TB (XDR-TB) is identified as resistant to secondary anti-TB injectable drugs and fluoroquinolones in addition to MDR-TB (9). In 2020 the nationwide incidence of multidrug-resistant/ rifampicin-resistant tuberculosis (MDR/RR-TB) was 3.3% in new cases and 18% in formerly treated cases (1). According to the instruction of the American Thoracic Society and the CDC, drug susceptibility testing must be done for at least the first-line anti-TB drugs in all older and new TB cases to guarantee the proper treatment for patients and to hinder the development of anti-TB drugs resistance (10). Drug susceptibility testing is critical for recognizing and managing drug-resistant TB (11). This study was intended to assess the drug susceptibility pattern of Mycobacterium tuberculosis complex strains isolated from the university hospital in Konya, Turkiye through 5 years of results.

Material And Methods

Study design

This laboratory-based descriptive retrospective study was conducted at a university hospital in Turkiye, and approved by the Ethics Committee of the Necmettin Erbakan University (Decision no. 2023/4443). The study was carried out using presumptive TB patient records who were referred to different health centers between January 2018 and January 2022. Epidemiological, clinical, and laboratory data were collected from the lab database and registration books. Over the five years, a total of 10900 samples were received for culture for Mycobacteria, patients with positive automated culture results at any age were selected. Any repeated samples for confirmation or follow-up were not included in the study. Culture and susceptibility to anti-TB drugs results of isolated Mycobacterium tuberculosis complex were reviewed.

Microbiological methods

All procedures in the laboratory were carried out in Class II biosafety cabins using the required personal protective equipment. Sterile samples such as pleural fluid and cerebrospinal fluid which were obtained with aseptic techniques, were handled without being decontaminated; whereas other samples such as sputum, bronchoalveolar lavage (BAL), and abscess were examined after homogenization and decontamination with N-acetyl-L-cysteine and sodium hydroxide (10). The material obtained after the preliminary preparation was inoculated on BACTEC MGIT 960 TB automated system (Becton Dickinson, USA) and Löwenstein-Jensen (LJ) medium according to the recommendations of the manufacturer. The Ehrlich-Ziehl-Neelsen (EZN) staining method was used for acid-fast bacilli (AFB) detection in direct smear preparations (12). Cultures were left for incubation for up to 42 days (10). Drug susceptibility testing was achieved by BACTEC MGIT 960 following the manufacturer's procedures (13). Reference strain H37RV (ATCC 27294) was used as a quality control of culture and drug susceptibility test, and the strain was sensitive to all standard anti-TB drugs (10).

Statistical analysis

The obtained data were statistically analyzed by The Statistical Package for Social Sciences (SPSS version 20). Continuous variables were described as mean ± Standard deviation (SD) while descriptive statistics were used to calculate the frequency and percentage of age categories, gender, organism isolated, sensitivity and resistance.

Results

The number of male and female patients was equal in 154 positive samples (77 males, 77 females). The mean ± standard deviation of the participant age was 57.87± 20.872 (range 1 year to 93 years). The majority of TB cases were in the age group 56–75 years (42.2%), whereas the lowest TB cases were at the age of ≤ 15 years (2.6%), followed by 16–35 years (15.6%), ≥ 76 years (19.4%), and 36–55 years (20.1%) as illustrated in figure 1. The obtained clinical samples were distributed as the following: Sputum 94 (61%), bronchoalveolar fluid 44 (28.6%), pleural effusion 5 (3.2%), body fluids 4 (2.6%), biopsy 2 (1.3), gastric juice, drainage fluid, cerebrospinal fluid, urine and abscess 1 (0.6%). Pulmonary TB was detected in 139 (90.3%) of the patients, while extrapulmonary TB cases were observed in 15 (9.7%) as shown in Table 1.

Of the total isolated strain 101 (65.6%) samples were detected positive using EZN staining method and 111 (72%) samples were evaluated positive by growing on the LJ medium. As Table 2 demonstrates, the susceptibility pattern against first-line anti-tuberculosis drugs, 145 (94.1%) of the isolated strains were sensitive to all tested drugs. Only isoniazid resistance was detected in 6 samples, both isoniazid and streptomycin

resistance in 2 samples, and ethambutol resistance in one sample. Among the first-line antituberculosis drugs, the highest resistance was isoniazid with 5.2%, followed by streptomycin resistance with 1.3% and ethambutol resistance with 0.6%. (Table 2). Neither rifampicin resistance nor multidrug resistance has been observed in this study.

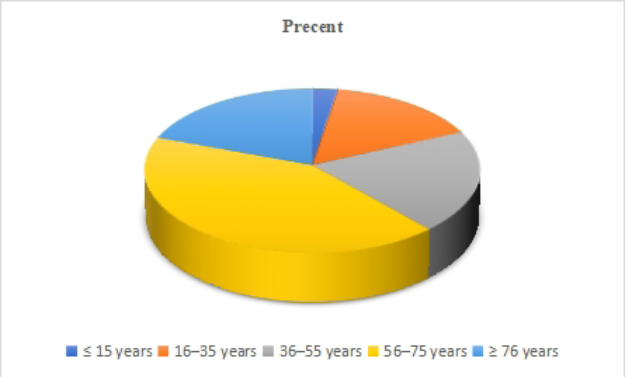

Fig 1: The distribution of tuberculosis-positive patients by age

Table 1: Distribution of *Mycobacterium tuberculosis* isolated strains according to clinical samples

	n (%)
Pulmonary TB	139(90.3)
Sputum	94(61)
Bronchoalveolar fluid	44(28.6)
Gastric juice	1(0.6)
Extrapulmonary TB	15(9.7)
Pleural effusion	5(3.2)
Biopsy	2(1.3)
Drainage	1(0.6)
CSF	1(0.6)
Body Fluids	4(2.6)
Urine	1(0.6)
Abscess	1(0.6)
Total	154(100)

Table 2: The susceptibility pattern of *Mycobacterium tuberculosis* complex isolates to first-line anti-tuberculosis drugs by years

	2018	2019	2020	2021	2022	Total
Characteristics	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Tested isolate	41 (100)	19 (100)	28 (100)	26 (100)	40 (100)	154 (100)
Sensitive to anti-TB drugs	38 (92.6)	14 (73.7)	28 (100)	23 (88.5)	40 (100)	146 (94.8)
Resistance to any drug	3 (7.3)	5 (26.3)	0 (0)	3 (11.5)	0 (0)	8 (5.2)
Streptomycin	0 (0)	2 (10.5)	0 (0)	0 (0)	0 (0)	2 (1.3)
Isoniazid	3 (7.3)	3 (15.8)	0 (0)	2 (7.7)	0 (0)	8 (5.2)
Rifampicin	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ethambutol	0 (0)	0 (0)	0 (0)	1 (3.8)	0 (0)	1 (0.6)
Single drug Resistant						
Streptomycin	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Isoniazid	3 (7.3)	1 (2.4)	0 (0)	2 (7.7)	0 (0)	6 (3.9)
Rifampicin	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ethambutol	0 (0)	0 (0)	0 (0)	1 (3.8)	0 (0)	1 (0.6)
Poly Resistant						
Streptomycin and Isoniazid	0 (0)	2 (10.5)	0 (0)	0 (0)	0 (0)	2 (1.3)
Multidrug-Resistant						
Isoniazid and Rifampicin	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Discussion

Mycobacterium tuberculosis complex is a group of diverse bacteria species that cause TB, a serious chronic infection recognized by the high rate of morbidity and mortality (14,15). Globally, around 25% of the population is infected with TB (16), with an annual death rate of 1.6 million people in 2021 according to WHO reports (4). TB mortality has surpassed that of acquired immunodeficiency syndrome (AIDS), making Mycobacterium tuberculosis the leading infectious agent that threatens human well-being (16). TB control strategies have been massively hindered by the emergence and transmission of antituberculosis-resistant strains, specifically rifampicin-resistant and MDR-TB isolates despite the striking declines in the prevalence of TB in recent years (17). The estimated annual incidence of RR-TB in new cases was 3.4% (18). Performing drug susceptibility testing not only assists to identify MDR-TB/ RR-TB but also provides a solid base for clinicians to prescribe the appropriate regimens (19). Our study was conducted to evaluate the antimicrobial susceptibility patterns of Mycobacterium tuberculosis complex strains over the past five years.

This study revealed an equal prevalence of TB among males and females (50%) which is consistent with studies conducted in central Ethiopia and Pakistan (13,20). This can be explained by the equivalent involvement of both genders in the community and the exposure to the same environment. However the ratio differs from the results obtained by Quezel-Guerraz et al and Al-Shahrani et al (21,22), stating that TB has a higher incidence in men due to greater exposure to the surrounding, alcohol-abusing and other factors that may constitute a risk to acquire the bacterium. Despite many studies in the literature have reported that tuberculosis is common among young people (22–25), in our study the vast majority of TB cases were in the age group 56–75 years (42.2%), With aging, many elements can play a crucial role in acquiring TB such as suppressed immune system due to drugs or other conditions, higher tendency to respiratory diseases, and activation of latent TB infection. The most frequent clinical manifestation of TB infections was pulmonary TB 139 (90.3%) while extrapulmonary cases were only 15 (9.7%), in accordance with many previous literature (12,13,25–27). Since the primary location of the bacteria is the lungs, extrapulmonary involvement is expected to be low. In addition, the atypical course of extra-pulmonary infections makes it more difficult to diagnose, which may be one of the reasons for the low rates. In our study, 65.6% of the samples detected positive by automated culture were found positive by EZN staining method. EZN staining positivity rate was which is in line with studies done by Behcet et al and Balcı et al (12,26). Although direct microscopy examination is broadly used in TB diagnosis, the sensitivity varies according to numerous factors such as the density of bacilli in the sample, decontamination procedures and the examiner experience.

Regarding antimicrobial resistance, 5.2% of

Mycobacterium tuberculosis complex isolates were resistant to at least one of the tested antituberculosis drugs. This rate is lower to some extent than the registered frequencies in Turkiye (26–28). This disparity can be due to the difference in the geographical region of the country, population, and sample size. In studies conducted in Turkiye in recent years, the resistance rates have been reported as 3.2-9.4% for isoniazid, 1.8-10.3% for streptomycin, 0-3.6% for ethambutol and 0-1.8% in the range for rifampicin 10,26–29%, which are comparable with the findings in our study where the detected resistance against isoniazid, streptomycin, and ethambutol, was 5.2%, 1.3%, and 0.6% respectively, and no resistance was observed against rifampicin. Among the tested drugs, isolated strains displayed high resistance against isoniazid, followed by streptomycin, and poly resistance of both drugs (1.3%) was also observed. The wide resistance of these regimens was attributed to their extensive implication in prophylaxis and treatment. Moreover, streptomycin is used in the treatment of conditions other than TB. The absence of rifampicin resistance is contradictory to a study conducted in the same province (30), the disparity can be explained by the difference in the sensitivity of the automated system used at the time of the study. Supported by the study conducted in Eastern Anatolia (27), no MDR was also observed in our study which can be accredited to the successful TB control strategies or low rifampicin resistance rate despite the high isoniazid resistance.

Conclusion

Despite the similar resistance pattern of the first-line antituberculosis drugs to other studies performed in different provinces in Turkiye, lower resistance against TB regimens was observed in our study. In addition to the absence of RR-TB and MDR strains, the finding is a good suggestion for the effective TB surveillance program in Konya province. Stating the fact that the study finding is based on a single-center experience, hence, more studies are required to reflect the real situation in the province.

Ethical aspects of the research: This laboratory-based descriptive retrospective study was conducted at a university hospital in Turkiye, and approved by the Ethics Committee of the Necmettin Erbakan University (Decision no. 2023/4443).

Author contributions: Assoc. Prof. Fatma Esenkaya Taşbent: Generating ideas for the article, supervising, taking responsibility for executing the project, and intellectually examining the study content before submission. Doc. Stud. Sondos A. A. Ibnouf: Data Collection, Processing, and Reporting, Logical interpretation and presentation of findings, conducting the literature review, and writing the article.

References

1.Diriba G, Alemu A, Tola HH, Eshetu K, Yenew B, Amare M, et al. Detection of Mycobacterium tuberculosis and rifampicin resistance by Xpert® MTB/RIF assay among presumptive tuberculosis patients in Addis Ababa, Ethiopia from 2014 to 2021. IJID Regions. 2022; 5: 97–103.

2.Sah SK, Bhattarai PR, Shrestha A, Dhami D, Guruwacharya D, Shrestha R. Rifampicin-resistant Mycobacterium tuberculosis by GeneXpert MTB/RIF and Associated Factors among Presumptive Pulmonary Tuberculosis Patients in Nepal. Infect Drug Resist. 2020;13:2911–9.

3.Lavania M, Kunja Mohanty K, Sha W, Ameni G. Drug sensitivity of clinical isolates of Mycobacterium tuberculosis and its association with bacterial genotype in the Somali region, Eastern Ethiopia. Front Public Health. 2022;10:1–10.

4.Global Tuberculosis Report 2022 [Internet]. 2022. Available from: http://apps.who.int/bookorders.

5.Tuberculosis surveillance and monitoring in Europe 2022 – 2020 data. [Internet]. 2022. Available from: http://apps.who.int/bookorders.

6.Silas G, Ollor OA, Agi VN, Nwokah EG, Wokem GN, Enoch AS. Resistance Profile of Mycobacterial Strains Causing Cluster Pulmonary Infection in Bayelsa State, Nigeria. South Asian Journal of Research in Microbiology. 2022;13(1):1–7.

7.Terzi A, Aydemir Ö, Karakeçe E, Köroğlu M, Altındiş M. Changes in antituberculosis drug resistance rates of M. tuberculosis complex isolates by years; Sakarya. Online Türk Sağlık Bilimleri Dergisi. 2019;4(1):47–56.

8.Farra A, Manirakiza A, Yambiyo BM, Zandanga G, Lokoti B, Berlioz-Arthaud A, et al. Surveillance of rifampicin resistance with GeneXpert MTB/RIF in the National Reference Laboratory for tuberculosis at the Institut Pasteur in Bangui, 2015-2017. In Open forum infectious diseases (Vol. 6, No. 3, p. ofz075). US: Oxford University Press, 2019.

9.Iem V, Dean A, Zignol M, Vongvichit P, Inthavong D, Siphanthong S, et al. Low prevalence of MDR-TB in Lao PDR: results from the first national anti-tuberculosis drug resistance survey. Tropical Medicine and International Health. 2019; 24(4):421–31.

10.Yılmaz A, Afşin D. Investigation of the Sensitivity of Mycobacterium Tuberculosis Strains Isolated from Various Clinical Samples in Eastern Turkiye to Major Anti-tuberculosis Drugs. Journal of Contemporary Medicine. 2021;11(1):92–6.

11.Faksri K, Kaewprasert O, Ong RTH, Suriyaphol P, Prammananan T, Teo YY, et al. Comparisons of whole-genome sequencing and phenotypic drug susceptibility testing for Mycobacterium tuberculosis causing MDR-TB and XDR-TB in Thailand. Int J Antimicrob Agents. 2019;54(2):109–16.

12.Behcet M, Karabork S, Avcioglu F, Karaibrahim A, Kurtoglu MG. Evaluation of the resistance patterns of Mycobacterium tuberculosis complex strains to antituberculous drugs. Experimental Biomedical Research. 2019;2(4):143–8.

13.Khursheed N, Asif S, Bano S, Ali MM, Adnan F. Susceptibility pattern of Mycobacterium tuberculosis over a period of five years at Indus Hospital and Health Network, Karachi, Pakistan. Pak J Med Sci. 2022;38:399–404.

14.Addo SO, Mensah GI, Mosi L, Abrahams AOD, Addo KK. Genetic diversity and drug resistance profiles of Mycobacterium tuberculosis complex isolates from patients with extrapulmonary tuberculosis in Ghana and their associated host immune responses. IJID Regions. 2022;4:75–84.

15.Arrigoni R, Ballini A, Topi S, Bottalico L, Jirillo E, Santacroce L. Antibiotic Resistance to Mycobacterium tuberculosis and Potential Use of Natural and Biological Products as Alternative Anti-Mycobacterial Agents. Vol. 11, Antibiotics. MDPI; 2022.

16.Xu G, Liu H, Jia X, Wang X, Xu P. Mechanisms and detection methods of Mycobacterium tuberculosis rifampicin resistance: The phenomenon of drug resistance is complex. Vol. 128, Tuberculosis. Churchill Livingstone; 2021.

17.Mesfin EA, Merker M, Beyene D, Tesfaye A, Shuaib YA, Addise D, et al. Prediction of drug resistance by Sanger sequencing of Mycobacterium tuberculosis complex strains isolated from multidrug resistant tuberculosis suspect patients in Ethiopia. PLoS One. 2022;17(8): e0271508

18.Liu CF, Song YM, He P, Liu DX, He WC, Li YM, et al. Evaluation of Multidrug Resistant Loop-mediated Isothermal Amplification Assay for Detecting the Drug Resistance of Mycobacterium tuberculosis.

Biomedical and Environmental Sciences. 2021;34(8):616–22.

19.Mansoori N, Pahlavanzadeh B, Atarjalali M. A Report on Drug Resistance Patterns of Mycobacterium tuberculosis Isolates in Northern Iran. Arch Iran Med. 2022;25(3):161–5.

20.Tilahun M, Ameni G, Desta K, Zewude A, Yamuah L, Abebe M, et al. Molecular Epidemiology and Drug Sensitivity Pattern of MycobacteriumTuberculosis Strains Isolated from Pulmonary Tuberculosis Patients in and around Ambo Town, Central Ethiopia. PLoS One. 2018; 13(2): e0193083.

21.Quezel-Guerraz N, Sánchez-Porto A, Torres M, Santos Ma Jesús P, Federico A, Guzman A, et al. Antituberculosis Drug Resistance in Isolates of Mycobacterium tuberculosis complex in Southeast Spain. J Glob Antimicrob Resist. 2020;20:183–6.

22.Al-Shahrani MS, Hakami MI, Younis MA, Fan HA, Jeraiby MA, Alraey Y. Prevalence of Primary Anti-tuberculosis Drug Resistance at the Tertiary Center in Saudi Arabia and Associated Risk Factors. Saudi Med J. 2021;42(7):728–34.

23.Mohammed KAS, Khudhair GS, Al-Rabeai DB. Prevalence and Drug Resistance Pattern of Mycobacterium tuberculosis Isolated from Tuberculosis Patients in Basra, Iraq. Pol J Microbiol. 2022;71(2):205–15.

24.Mutayoba BK, Ershova J, Lyamuya E, Hoelscher M, Heinrich N, Kilale AM, et al. The second national anti-tuberculosis drug resistance survey in Tanzania, 2017–2018. Tropical Medicine and International Health. 2022;27(10):891–901.

25.Song WM, Li YF, Ma X Bin, Liu JY, Tao NN, Liu Y, et al. Primary drug resistance of mycobacterium tuberculosis in Shandong, China, 2004-2018. Respir Res. 2019;20(1):1-12

26.Balcı A, Günay E, Demir C, Çilekar Ş, Coşğun İG, Aydın S. Sensitivity Status of Mycobacterium tuberculosis Complex Strains Isolated in our Clinic to Antituberculosis Drugs. Kocatepe Medical Journal 2021;22:488-93

27.Aydın E, Tarhan G, Şahin F, Eren S. Molecular Epidemiological Typing of M. Tuberculosis Isolates Isolated From Turkiye's Eastern Anatolia With In-House PCR Method. Cukurova Medical Journal. 2022;47(1):191–8.

28.Aktaş A, Nakipoğlu Y, Şatana D. An Up-To-Date Overview of Our Country's Data on Tuberculosis. Sakarya Medical Journal. 2022;12(3):586–95.

29.Öztürk T, Arıdoğan B, Çetin ES. Investigation of the Effectiveness of 'Reverse Blot Hybridization Assay Mycobacterium tuberculosis Drug Resistance' Method for the Rapid Diagnosis of Isoniazid and Rifampicin Resistance in Mycobacterium tuberculosis Complex Clinical Isolates. SDÜ Tıp Fakültesi Dergisi . 2019;26(4):444–51.

30.Esenkaya Taşbent F, Doğan M. Resistance Rates of Mycobacterium tuberculosis Complex Strains to the Primary Anti-tuberculosis Drugs in Konya Province, Turkiye. Turk Mikrobiyol Cem Derg. 2016;46(4):165–71. Available from: https://dx.doi.org/10.5222/TMCD.2016.165