Acıbadem Univ. Sağlık Bilim. Derg. 17 (April, May, June) 2026
https://doi.org/10.31067/acusaglik.1881966

ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Infectious Diseases/Bulaşıcı Hastalıklar

Investigation of Trends in Tuberculosis Drug Resistance in Türkiye

Meltem Ayaş[1,2], Aylin Suran[3], Ravel Deniz Saygı[3], Neval Yurttutan Uyar[2,4]

[1] Department of Medical Laboratory Techniques, Vocational School of Health Services, Acibadem Mehmet Ali Aydinlar University, Istanbul, Türkiye

[2] Department of Medical Microbiology, School of Medicine, Acibadem Mehmet Ali Aydinlar University, Istanbul, Türkiye

[3] Medical Student, School of Medicine, Acibadem Mehmet Ali Aydinlar University, Istanbul, Türkiye

[4] Acibadem Labmed Medical Laboratories, Istanbul, Türkiye

Meltem AYAŞ
0000-0003-1920-9261

Aylin SURAN
0009-0002-3980-8616

Ravel Deniz SAYGI
0009-0000-1059-6512

Neval YURTTUTAN UYAR
0000-0002-6198-3296

Correspondence: Meltem Ayaş
Department of Medical Laboratory Techniques, Vocational School of Health Services, Acibadem Mehmet Ali Aydinlar University, Istanbul, Türkiye
Phone: +90 537 560 95 47
E-mail: meltem.ayas@acibadem.edu.tr

Neval Yurttutan Uyar
Department of Medical Microbiology, School of Medicine, Acibadem Mehmet Ali Aydinlar University, Istanbul, Türkiye
Phone: +90 530 614 31 81
E-mail: neval.uyar@acibademlabmed.com.tr

Received: 04.02.2026
Accepted: 11.03.2026

ABSTRACT

Purpose: The emergence of drug-resistant *Mycobacterium tuberculosis complex* (MTC) strains poses a significant challenge to global tuberculosis (TB) control efforts. This study aimed to evaluate the trends of primary resistance to first-line anti-tuberculosis drugs among clinical MTC isolates obtained in Türkiye over an eight-year period.

Methods: This retrospective study included 408 culture-confirmed MTC isolates collected between 2017 and 2024. Drug susceptibility testing for isoniazid (INH), rifampicin (RIF), ethambutol (EMB), and streptomycin (SM) was performed using the Sensititre MYCOTB MIC plate method. Resistance patterns were analyzed according to demographic characteristics and time period.

Results: Resistance to at least one first-line drug was detected in 19.3% of isolates. The highest resistance rate was observed for INH, followed by SM, RIF, and EMB. Multidrug-resistant TB (MDR-TB), defined as resistance to both INH and RIF, was detected in 4.16% of cases. Drug resistance was significantly associated with patient age ($p < 0.05$), whereas no significant relationship was found with gender. Resistance rates were higher during the COVID-19 pandemic period, although the difference was not statistically significant.

Conclusion: Primary resistance among MTC strains remains an ongoing concern in Türkiye. Continuous monitoring of resistance patterns is essential to support effective treatment strategies and tuberculosis control programs.

Key words: Mycobacterium tuberculosis, Antitubercular Agents, Drug Resistance, Tuberculosis, Epidemiology.

ÖZET

Amaç: İlaç dirençli Mycobacterium tuberculosis kompleks (MTK) suşlarının ortaya çıkışı, küresel tüberküloz (TB) kontrol çabaları için önemli bir zorluk teşkil etmektedir. Bu çalışma, Türkiye'de sekiz yıllık bir süre içinde elde edilen klinik MTK izolatları arasında birinci basamak anti-tüberküloz ilaçlarına karşı birincil direnç eğilimlerini değerlendirmeyi amaçlamıştır.

Yöntemler: Bu retrospektif çalışmaya, 2017 ile 2024 yılları arasında toplanan kültürle doğrulanmış 408 adet MTK izolatı dahil edilmiştir. İzoniazid (INH), rifampisin (RIF), ethambutol (EMB) ve streptomisin (SM) için ilaç duyarlılık testi, Sensititre MYCOTB MIC plaka yöntemi kullanılarak gerçekleştirilmiştir. Direnç paternleri, demografik özelliklere ve zaman dilimine göre analiz edilmiştir.

Bulgular: İzolatların %19,3'ünde en az bir tane birinci basamak ilaca direnç tespit edilmiştir. En yüksek direnç INH' ye, ardından SM, RIF ve EMB' ye karşı bulunmuştur. Çok ilaca dirençli tüberküloz (MDR-TB), INH ve RIF' in ikisine birden direnç olarak tanımlanmış ve olguların %4,16'sında belirlenmiştir. İlaç direnci ile hasta yaşı arasında istatistiksel olarak anlamlı ilişki saptanırken ($p<0,05$), cinsiyet ile anlamlı ilişki bulunmamıştır. COVID-19 pandemisi döneminde direnç oranları daha yüksek bulunmuş ancak bu fark istatistiksel olarak anlamlı değildir.

Sonuç: MTC suşları arasında birincil direnç, Türkiye'de halen önemli bir sorun olmaya devam etmektedir. Etkili tedavi stratejilerini ve tüberküloz kontrol programlarını desteklemek için direnç modellerinin sürekli izlenmesi büyük önem taşımaktadır.

Anahtar Kelimeler: Mycobacterium tuberculosis, Anti-tüberküloz Ajanlar, İlaç Direnci, Tüberküloz, Epidemiyoloji.

Tuberculosis (TB) is a contagious disease caused by members of the *Mycobacterium tuberculosis complex (MTC)*, primarily transmitted through inhalation of airborne droplets expelled by individuals with active pulmonary TB (1,2). MTC includes *M. tuberculosis*, *M. bovis*, *M. africanum*, *M. canettii*, *M. caprae*, *M. microti*, and *M. pinnipedii* (3). Although the lungs are the most affected organs (pulmonary TB), the infection can also involve other tissues and organs, leading to extrapulmonary manifestations such as lymphadenitis, pleural effusion, meningitis, or skeletal TB (4,5). The clinical presentation of TB varies but often includes symptoms such as a persistent cough, production of sputum, hemoptysis, chest pain, unintentional weight loss, prolonged fever, and night sweats (6). TB continues to represent a major global public health concern and remains one of the leading causes of morbidity and mortality worldwide. Prior to the emergence of the COVID-19 pandemic, TB was the leading cause of death from a single infectious agent globally (1). According to the World Health Organization (WHO) Global Tuberculosis Report 2024, approximately 10.8 million individuals developed TB in 2023, and an estimated 1.25 million people died because of the disease. These figures highlight the ongoing global burden of TB and the urgent need for effective prevention, early diagnosis, and treatment strategies (1). Drugs used in the treatment of TB can be classified into two groups as primary and secondary anti-tuberculosis drugs. Primary agents consist of isoniazid (INH), rifampicin (RIF), ethambutol (ETM), pyrazinamide (PZA), and streptomycin (SM). Amikacin, kanamycin, levofloxacin, rifabutin, which are more toxic and difficult to tolerate compared to primary anti-TB drugs, are some of the secondary anti-TB drugs (4,5). According to WHO report (Global Programme on Tuberculosis & Lung Health) definitions for drug-resistant TB are summarized in the Table 1 (7).

Table 1. Types of TB drug-resistance (7).

Resistance Profile	Definition
Mono-resistance:	resistance to one first-line anti-TB drug only.
Poly-resistance:	resistance to more than one first-line anti-TB drug, other than both isoniazid and rifampicin.
Multidrug resistance (MDR):	resistance to at least both isoniazid and rifampicin.
Extensive drug resistance (XDR):	resistance to any fluoroquinolone, and at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin), in addition to multidrug resistance.
Rifampicin resistance (RR):	resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, in the form of mono-resistance, poly-resistance, MDR or XDR.

Due to factors including migration and shortcomings in the infrastructure system for public health, tuberculosis continues to be an issue for public health in our nation and around the world despite the advancement of diagnostic, treatment, and control strategies. One of the main reasons tuberculosis cannot be prevented is the emergence of drug resistance to anti-tuberculosis medications (8). The most significant contributors to the bacteria's inherent resistance are its multilayered cell wall and its multi-drug efficient efflux pumps (4). On the other hand, acquired drug resistance happens because of an increase of resistant mutants due to factors such as inadequate treatment regimens throughout treatment and patient incompatibility (4,10). Globally, the burden of drug-resistant tuberculosis is rising (1,9).

Current tuberculosis management guidelines emphasize the importance of determining first-line drug susceptibility in all cases. Assessing drug resistance prior to treatment is critical for guiding effective therapy and controlling the spread of resistant strains. Given the regional and temporal variability in resistance patterns, regular drug susceptibility testing is essential for informed treatment decisions and TB control. Moreover, regional resistance data and epidemiological insights significantly contribute to the global efforts against antimicrobial resistance (10,11).

The aim of this study was to provide a retrospective evaluation of the patterns and evolving trends of primary resistance to first-line anti-tuberculosis drugs in MTC isolates obtained from clinical specimens in our laboratory for 8 years period.

Material and Methods

This retrospective study evaluated the primary anti-tuberculous drug susceptibility patterns of MTC isolates obtained from various clinical specimens sent to our tuberculosis laboratory between 2017 and 2024. A total of 408 MTC isolates, each recovered from a different patient, were included in the study. Only isolates obtained from newly diagnosed tuberculosis patients with no previous history of anti-tuberculosis treatment were included in the study in order to evaluate primary drug resistance.

Clinical specimens were processed using the Decomics kit (TIBO, Türkiye) method for homogenization and decontamination according to the manufacturer's instructions. Sterile samples were included in the study without undergoing homogenization and decontamination procedures. The concentrated samples were inoculated into TK medium (TIBO, Türkiye) and Löwenstein-Jensen medium for culture in 37^{0}C, 54 days. Smears were prepared and initially stained with fluorescent auramine O dye and examined under fluorescence microscopy. Confirmatory staining was performed using the Ehrlich-Ziehl-Neelsen method.

To differentiate MTC from nontuberculous mycobacteria (NTM), the Bioline™ TB Ag MPT64 (Abbott, USA) test was performed. Susceptibility testing for first-line antituberculous drugs; streptomycin, isoniazid, rifampicin, and ethambutol was carried out using the Sensititre MYCOTB MIC plate (MYCOTB; Trek Diagnostic Systems, Cleveland, OH) in accordance with the manufacturer's instructions. For quality control purposes, *M. tuberculosis* ATCC 27294 (H37Rv), known to be susceptible to the tested drugs, was used throughout the susceptibility testing procedures.

Statistical analysis

All statistical analyses were performed using Python (version 3.9.6). Data processing and statistical analyses were conducted using the Pandas, SciPy, Statsmodels and NumPy libraries. Categorical variables were summarized as frequencies and percentages. Comparisons between categorical variables were performed using the chi-square test when the assumptions of the test were satisfied. When expected cell frequencies were less than 5, Fisher's exact test was applied. Odds ratios (OR) with 95% confidence intervals (CI) were calculated to evaluate the strength of associations between variables. A p-value < 0.05 was considered statistically significant.

Ethics Committee Approval

This study was approved by the Ethics Committee of Acıbadem Mehmet Ali Aydınlar University (No: ATADEK-2025/06).

Results

In this study, 408 MTC strains isolated between 2017 and 2024 were included. 86.02% of these samples (n = 351) are obtained from sputum samples, 5.8% (n = 24) from bronchoalveolar lavage, and 3.43% (n = 14) from fasting gastric lavage, 0.7% (n=3) from transtracheal aspirate, 1.7% (n=7) from pleural fluid, 1.22% (n=5) was obtained from tissue samples, 0.9% (n=4) was obtained from Cerebrospinal Fluid (CSF). The distribution of the clinical samples from which the isolates were obtained is presented in Figure 1.

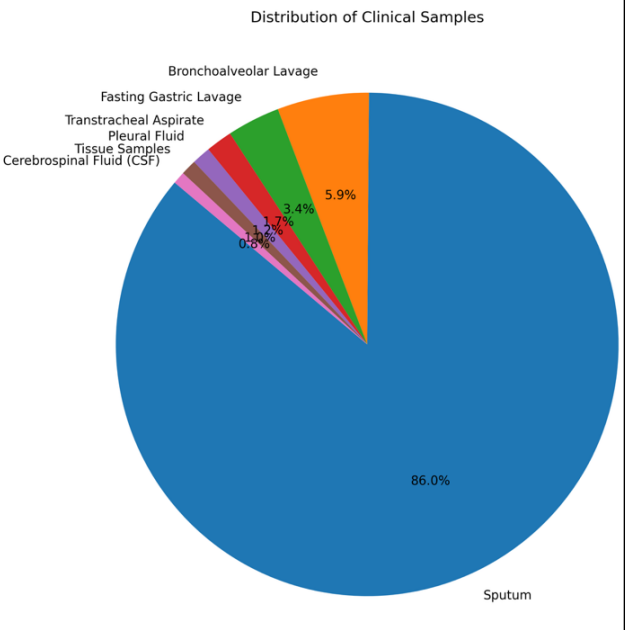

Figure 1: Distribution of clinical samples that MTC strains isolated.

A total of 9.1% (n=37) of the isolates were obtained from patients aged 0–15 years, 71% (n=289) from those aged 16–64 years, and 20.2% (n=82) from patients aged 65 years and above. The relationship between age groups and drug resistance in tuberculosis patients was evaluated,

revealing a statistically significant difference (p = 0.0076). The highest resistance rate was observed in the 20–29 age group (34.4%), while the lowest was found in the 40–49 age group (5.8%) (Figure 2).

Furthermore, out of these samples, 38.7% (n=158) belong to patients who are female, and 61.3% (n=250) belong to patients who are male. In our study, the relationship between gender and tuberculosis drug resistance was not statistically significant (chi-square p = 0.314; Fisher exact p = 0.303). The resistance rate was 17.6% in males and 22.2% in females, and the resistance rate was slightly higher in females, but this difference was not significant (OR: 1.33, 95% CI: 0.81–2.19) (Figure 3).

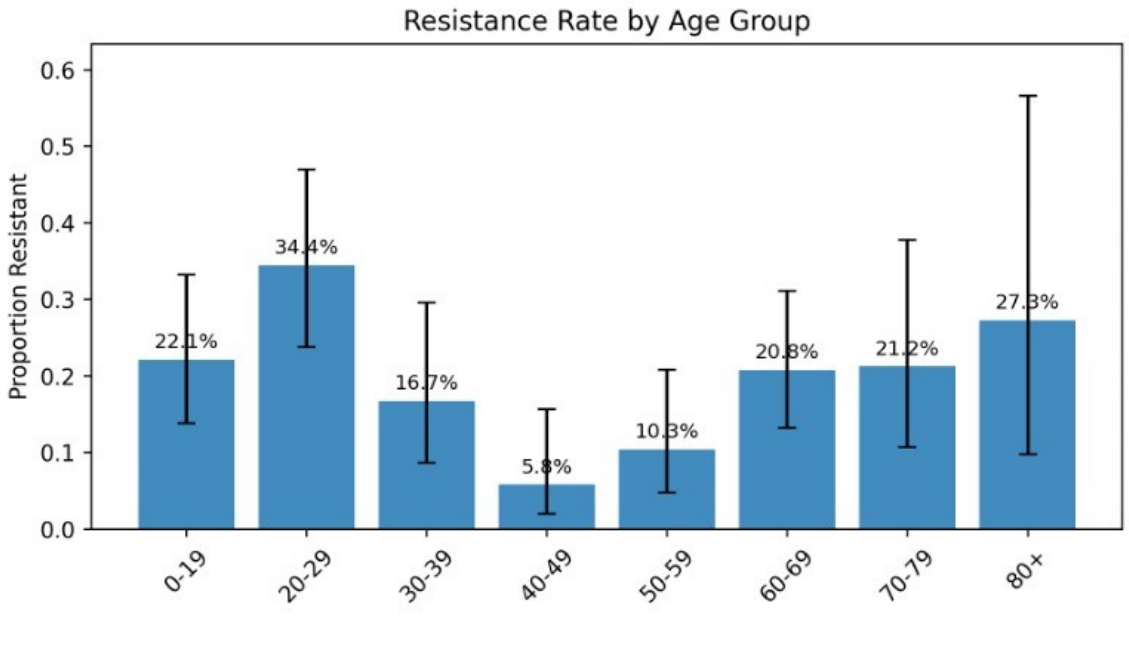

Figure 2: Resistance ratio of first-line anti-tuberculosis drugs according to age of patients.

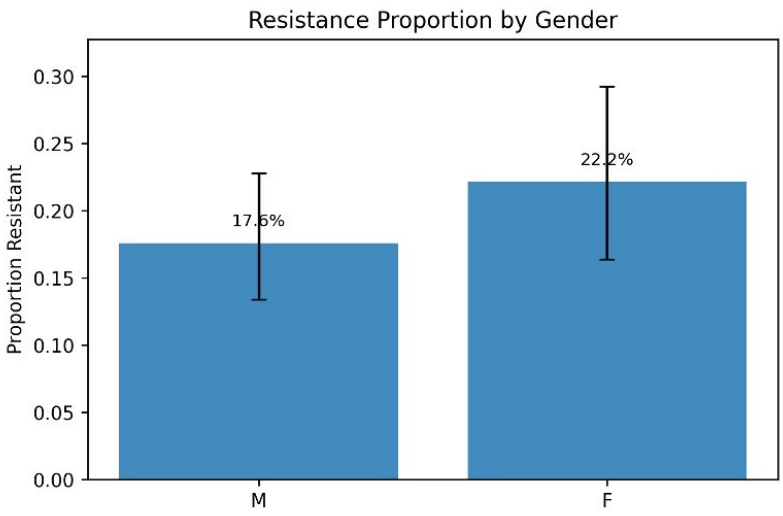

Figure 3: Resistance ratio of first-line anti-tuberculosis drugs according to gender of patients.

Total 329 of 408 isolates (80.6%) were susceptible to all first-line drugs, 79 of 408(19.3%) were resistant to at least one antibiotic. In our study, 44 of the isolates were identified as mono-resistant tuberculosis bacilli. The number of strains that were simultaneously resistant to isoniazid and rifampicin was 17. 12 strains were resistant to all primary antituberculosis drugs while 1 strain was susceptible only to ethambutol. These strains have been identified as multidrug-resistant TB (Table 2).

Table 2. Resistance Patterns of *M. tuberculosis complex* Isolates to First-line anti-tuberculosis drugs.

Resistance pattern	2017	2018	2019	2020*	2021*	2022*	2023*	2024	Total
Susceptible to all first-line drugs	**16**	**10**	**99**	**32**	**26**	**36**	**33**	**77**	329
Mono-resistance[a]									
EMB (only)	0	0	0	0	0	2	0	0	2
SM (only)	5	1	2	0	0	7	2	2	19
INH (only)	3	0	1	4	4	3	0	4	19
RIF (only)	2	0	2	0	0	0	0	0	4
Total (Mono-resistance)	**10**	**1**	**5**	**4**	**4**	**12**	**2**	**6**	44
Poly-resistance[b]									
SM + INH (only)	3	0	2	2	1	3	0	4	15
EMB + INH (only)	0	0	0	0	0	0	2	0	2
EMB + SM + INH	0	0	0	0	0	1	0	0	1
Total (Poly-resistance)	**3**	**0**	**2**	**2**	**1**	**4**	**2**	**4**	18
Multidrug resistance[c]									
INH + RIF (only)	3	0	1	0	0	0	0	0	4
INH + RIF + SM	0	0	1	0	0	0	0	0	1
INH + RIF + SM + EMB	0	0	1	3	0	4	2	2	12
Total (Multidrug resistance)	**3**	**0**	**3**	**3**	**0**	**4**	**2**	**2**	17

*INH: Isoniazid, RIF: Rifampicin, SM: Streptomycin, EMB: Ethambutol. * COVID-19 pandemic period (11 March 2020 – 5 May 2023, [a.] Mono-resistance: resistance to one first-line anti-TB drug only., [b.] Poly-resistance: resistance to more than one first-line anti-TB drug, other than both isoniazid and rifampicin. [c.] Multidrug resistance (MDR): resistance to at least both isoniazid and rifampicin.*

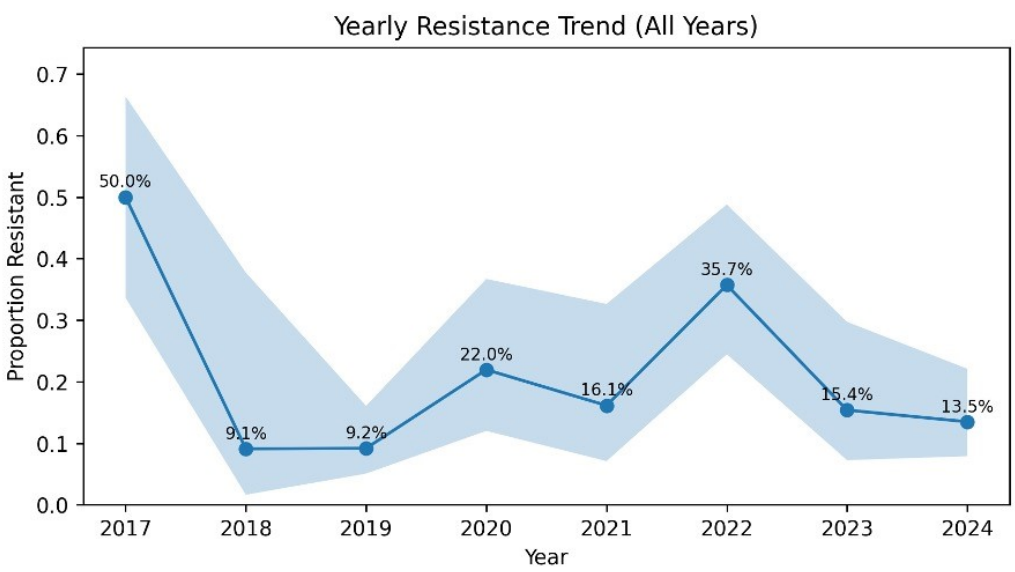

Figure 4: Trends in primer drug resistance for MTC isolates in all years (The shaded area indicates the confidence interval of the estimated trend line. Points represent the yearly resistance proportions.)

The proportion of resistant isolates was higher during the Covid-19 pandemic period (11March 2020 – 5th May 2023) (23.95%, 40/167) compared to the non-pandemic years (16.18%, 39/241). However, this difference was not statistically significant (chi-square p = 0.068; Fisher's exact p = 0.056), yearly resistance trend shown in Figure 4.

Discussion

Tuberculosis is a major public health issue. Early diagnosis of TB patients, initiation of appropriate treatment regimens, and close monitoring of therapy are among the key components of effective TB control programs. Therefore, isolation of *MTC* strains and performing antibiotic susceptibility testing play a critical role in guiding proper treatment decisions (12).

The emergence and spread of resistance to anti-tuberculosis (anti-TB) drugs represents a critical global health threat, affecting both high-burden and low-incidence countries, including Türkiye (1). Drug-resistant tuberculosis, particularly multidrug-resistant (MDR-TB) and extensively drug-resistant TB (XDR-TB), has significantly complicated TB control efforts worldwide. Inadequate treatment regimens, poor adherence to therapy, incorrect drug prescriptions, and interruptions in drug supply are among the primary factors driving the selection and amplification of resistant MTC strains (13). Mismanagement in TB treatment not only reduces treatment success rates but also facilitates the transmission of resistant strains within communities. According to the WHO, nearly half a million new cases of rifampicin-resistant TB were reported in 2022, of which 78% were classified as MDR-TB (1). This trend underscores the urgent need for robust diagnostic infrastructure, adherence monitoring systems, and the implementation of individualized treatment protocols based on drug susceptibility testing. Without such interventions, the global burden of drug-resistant TB is expected to increase, undermining progress toward TB elimination goals.

Resistance to tuberculosis drugs poses an obstacle in proper and effective treatment of tuberculosis. According to 2021 Report of Tuberculosis of Ministry of Health of Türkiye; in 2020, 4335 isolates were evaluated for drug resistance. Of the 4335 cases studied, 10.7% were resistant to isoniazid, 2.9% to rifampicin, 2.8% to ethambutol, 9.1% to streptomycin; also 2,6% of isolates showed multidrug resistance (14). In the study conducted by Terzi *et al.* in 2019, out of 466 samples isolated between 2012-2017, 9.8% were found to be resistant to INH, 4.1% were resistant to RIF, 7.7% were resistant to SM, 4% were resistant to ETM (4). In this study, as in our study, the highest resistance rate was found against isoniazid. According to another retrospective study conducted by Yakupoğulları *et al.* in 2023, out of isolates obtained between 2014 and 2022, 8% of 415 samples were found to be resistant to INH and 0.2% to ETM (15). Gorgun *et al.* (16), in their study, resistance rates in isolates were 10.6% for isoniazid; rifampicin 2.8%; ethambutol 1.1%; and streptomycin was found to be 7.0%. All isolates that were resistant to rifampicin were also found to be resistant to isoniazid, and therefore the rate of multidrug-resistant isolates was found to be 2.8%. The single drug resistance rate was found to be 14%. In our study, 13,2% of the MTC isolates were resistant to INH, 11,7% to SM, 5,14% to RIF, 4,16% to ETM, and 4,16 % were resistant to multiple drugs. These findings indicate that resistance to isoniazid and streptomycin remains relatively high, around 10%, and overall resistance patterns are consistent with previous national studies.

In our study, tuberculosis drug resistance rates in different age groups were compared and the possible relationship between age and resistance development was evaluated. According to our findings, there was a statistically significant difference in drug resistance distribution between age groups (p = 0.0076). Especially in the 40-49 age group, the resistance rate was found to be the lowest among all age groups with 5.8%. This rate was as high as 34.4% in the 20-29 age group and 22.1% in the 0-19 age group. These findings reveal that drug resistance does not show a linear distribution according to age; on the contrary, there are significant increases or decreases in some age groups. The findings suggest that age is an important but complex determinant of tuberculosis epidemiology.

When compared with the literature, the results obtained in this study present partially overlapping and partially divergent findings. In a comprehensive retrospective analysis conducted in South Korea (17), it was shown that multidrug-resistant tuberculosis (MDR-TB) rates were higher in the 15-34 age group, and that resistance rates decreased with increasing age. Similarly, in multicenter analyses conducted with WHO data covering 85 countries, it was reported that the prevalence of MDR-TB in childhood and young adults may be higher in some regions (e.g. South Africa, Germany, Namibia) than in adults (18). From this point of view, the high resistance rate (34.4%) in the 20-29 age group in our study is consistent with these international data.

On the other hand, some studies in the literature have also reported that the incidence of MDR-TB is higher in older individuals. For example, in the 2019 Global Burden of Disease (GBD) analysis, it was reported that the incidence of MDR/XDR-TB peaked in the 35-44 and 55-64 age groups (19). In our study, it was observed that resistance rates increased again in groups over 60 years of age (with rates ranging between 20-27%) and this finding is in line with the GBD data. However, as a remarkable finding, the fact that the resistance rate in the 40-49 age group was the lowest among all age groups is a situation that is not widely emphasized in the literature. Data on this age group are usually included in aggregate analyses and not specifically addressed. Therefore, the low resistance rate obtained in this study suggests that the 40-49 age group may be a relatively more protected period in terms of drug susceptibility. Possible explanations include better adherence to treatment in this age group, a stronger immune system, and more regular access to health services.

This observation may also reflect the effective follow-up and treatment monitoring activities conducted by Tuberculosis Control Dispensaries in Türkiye, which play a central role in ensuring treatment adherence and preventing the development of drug resistance.

In conclusion, the distribution of TB drug resistance by age groups has been addressed multidimensionally in the literature and findings may show regional differences. This study makes a new contribution to the literature by demonstrating that resistance rates are low in the 40-49 age group and draws attention to the importance of age-targeted TB control strategies. Most of the studies conducted in Türkiye have conducted resistance analyses by combining age groups or separating them into child/adult groups. The unique contribution of this study is that it presents resistance rates by age group in detail.

In our study, the relationship between gender and tuberculosis drug resistance was not statistically significant (chi-square $p = 0.314$; Fisher exact $p = 0.303$). The resistance rate was 17.6% in males and 22.2% in females, and the resistance rate was slightly higher in females, but this difference was not significant (Odds ratio = 1.33). This finding suggests that tuberculosis drug resistance does not vary significantly based on gender alone.

Results on this issue vary in the literature. Although global TB reports published by the WHO indicate that men have a higher rate of TB infection, there is no consistent evidence that drug resistance is directly related to gender. Some studies have reported higher rates of drug resistance in women. For example, studies conducted in India and Ethiopia reported that women were more likely to develop MDR-TB compared to men (20,21). On the other hand Madaki *et al.* reported that drug-resistant tuberculosis was more common in males and individuals aged 40 or younger, with this age group having a fourfold increased risk (22).

In conclusion, the findings obtained in our study are consistent with many national and international studies and show that gender is not a determining factor in terms of TB drug resistance. However, it should be taken into consideration that small differences in resistance rates may be affected by variables such as socio-cultural, access to treatment and utilization level of health services in different geographies.

During the COVID-19 pandemic, a significant increase in antibiotic resistance was observed in many bacterial species. This rise is thought to be related to the frequent use of broad-spectrum antibiotics during the pandemic (23,24). Resistance rates in *Mycobacterium tuberculosis* strains have been reported to increase during the COVID-19 pandemic (25). A review of 17 studies found that the COVID19 pandemic exacerbated the risk of MDR-TB by disrupting healthcare access and increasing household transmission, especially in populations with low socioeconomic status, greater distances to clinics, and high TB burden (26). In our study, the resistance rates obtained between March 2020 and May 2023, which is defined as the active covid period in the world, were found to be high. Between 2020 and 2023, our study observed fluctuations in tuberculosis drug resistance rates, with a notable increase in resistant cases in 2022 (20 resistant cases). However, this increase did not reach statistical significance ($p = 0.073$). These findings reflect the complex impact of the COVID-19 pandemic on tuberculosis diagnosis, treatment, and control programs.

The literature reports that the pandemic has disrupted TB healthcare services, causing delays in diagnosis and interruptions in treatment (27, 28). Such disruptions potentially contribute to an increased risk of drug-resistant tuberculosis. Many countries have experienced declines

in TB case detection and treatment coverage, which are linked to higher risks of resistance development (29).

Nonetheless, current data remain insufficient to definitively determine the pandemic's impact on drug resistance. Similar studies have reported variable resistance rates, often limited by small sample sizes and challenges in data collection during the pandemic. In Türkiye, while disruptions in TB services during COVID-19 have been noted, comprehensive data on changes in drug resistance trends are scarce. Therefore, strengthening TB diagnosis and treatment services post-pandemic, early detection of drug-resistant cases, and multidisciplinary follow-up programs have become increasingly important. Longitudinal and large-scale epidemiological studies are essential to better understand the effects of COVID-19 on TB drug resistance.

One limitation of this study is the absence of pyrazinamide (PZA) susceptibility testing. Although PZA is considered a first-line anti-tuberculosis drug, resistance testing for this drug is not routinely performed in many laboratories due to methodological challenges. Therefore, the absence of PZA susceptibility data does not affect the interpretation of resistance patterns for the other first-line drugs evaluated in this study. Nevertheless, inclusion of PZA resistance data in future studies may provide a more comprehensive assessment of drug resistance patterns in MTC isolates.

Conclusion

In conclusion, the implementation of comprehensive TB control programs is strongly recommended to prevent the development and spread of resistance in TB, which remains a major public health problem. Furthermore, continuous monitoring of resistance patterns in both newly diagnosed and previously treated TB cases is essential. Such monitoring can guide the selection of effective treatment regimens and contribute to the long-term prevention of drug resistance. According to our findings, there is a significant relationship between age and TB drug resistance, and this relationship varies according to age groups. These data may guide the identification of risk groups according to age and the development of strategies to prevent resistant tuberculosis. Longitudinal and large-scale epidemiologic studies are needed to better understand the effects of COVID-19 on TB drug resistance.

Declarations

Funding

This research received no external funding.

Conflict of Interest

The authors have no conflicts of interest to declare.

Ethical Approval

This study was approved by the Ethical board of Acıbadem Mehmet Ali Aydınlar University (No: ATADEK-2025/06).

Availability of Data and Materials

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

Concept: M.A, Literature Review: M.A, Design: M.A

Data acquisition: M.A, A.S, R.D.S and N.Y.U, Analysis and interpretation: M.A, A.S and R.D.S, Writing manuscript: M.A,

Critical revision of manuscript: M.A and N.Y.U.

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