

Demographic and microbiological characteristics and mortality status of patients diagnosed with tuberculosis and treated between 2018 and 2023

2018 ve 2023 yılları arasında tüberküloz tanısı ile tedavi uygulanan hastaların demografik ve mikrobiyolojik özellikleri ve mortalite durumları

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Abstract

Purpose: We aimed to determine the demographic data, radiological findings, comorbid conditions, antituberculosis drug resistance rates, and tuberculosis-related mortality of patients with pulmonary and pleural tuberculosis where mycobacterium tuberculosis growth was detected in culture.

Materials and methods: Data from 439 patients diagnosed with pulmonary and pleural tuberculosis in the chest diseases hospital clinic between January 2018 and December 2023 were retrospectively evaluated. Patients whose sputum, bronchial lavage and pleural fluid samples were positive for Mycobacterium tuberculosis complex in BACTEC 460 TB system medium were included in the study. We recorded the patients' demographic data, nationality, concomitant diseases, chest X-ray findings, drug resistance, and mortality status. We recorded the single, double, triple, and quadruple drug resistance rates against four main antituberculosis drugs using the Mycobacterium tuberculosis complex susceptibility tests.

Results: We tested sputum from 338 patients, bronchial lavage from 87 patients, and pleural fluid culture from 14 patients. EZN staining showed that acid-resistant bacillus was present in 224 (51%). Comorbidities were Chronic Obstructive Pulmonary Disease (36.4%), hypertension (26.4%), and bronchiectasis (18.7%). The evaluation of the patients' chest x-rays revealed that 45.1% had infiltration, 33.3% had cavitation and infiltration, and 7.1% had cavitation. Exitus occurred in 7.7% of the patients due to tuberculosis. Drug resistances were isoniazid 47 (10.7%), rifampin 15 (3.4%), ethambutol 4 (0.9%), streptomycin 37 (8.4%), and multidrug-resistant 15 (14 + RR (1)) (3.4%). We detected single drug resistance in 44 patients, double drug resistance in 18 patients, triple drug resistance in 2 patients, and quadruple drug resistance in 4 patients.

Conclusion: Tuberculosis incidence and mortality are decreasing; it is still an important public health problem. It can be mortal, especially in patients with advanced age and comorbidities.

Keywords: Tuberculosis, drug resistance, comorbidities.

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Öz

Amaç: Mycobacterium tuberculosis üremesi halinde saptanan akciğer ve plevra tüberkülozlu olguların demografik verileri, radyolojik bulguları, komorbid hastalıkları, antitüberküloz ilaç direnç oranları ve tüberküloza bağlı mortalite oranlarının belirlenmesi amaçlandı.

Gereç ve yöntem: Ocak 2018 ile Aralık 2023 arasında göğüs hastalıkları hastanesi kliniğinde akciğer ve plevra tüberkülozu tanısı konulan 439 hastanın verileri retrospektif olarak değerlendirildi. Balgam, bronş lavaj ve plevral sıvıdan alınan örneklerde, BACTEC 460 TB sistem besisi yerinde mycobacterium tuberculosis kompleks üremesi saptanan hastalar çalışmaya alındı. Hastaların demografik verileri, uyruğu, eşlik eden hastalıkları, göğüs röntgen bulguları, ilaç direnci ve mortalite durumu kaydedildi. Mycobacterium tuberculosis kompleks duyarlılık testlerinde dört ana antitüberküloz ilacına karşı tek, çift, üçlü ve dördü ilaç direnci oranları kaydedildi.

Bulgular: 338 hastada balgam, 87 hastada bronş lavajı, 14 hastadan plevra sıvısı kültürü gönderilmiş ve 224 hastada (%51) EZN boyama ile aside dirençli basil tespit edilmiş. Eşlik eden hastalıklar Kronik Obstrüktif Akciğer Hastalığı (%36,4), hipertansiyon (%26,4) ve bronşektazi (%18,7) olarak tespit edilmiştir. Hastaların PA Akciğer grafleri değerlendirildiğinde %45,1'inde bilateral üst zonlarda infiltrasyon, %33,3'ünde kavitasyon ve infiltrasyon, %7,1'inde ise kavitasyon mevcuttu. Hastaların %7,7'sin de tüberküloz nedeni ile exitus geliştiği belirlendi. İlaç dirençleri isoniazid 47 (%10,7), rifampin 15 (%3,4), etambutol 4 (%0,9), streptomisin 37 (%8,4) ve çoklu ilaca dirençli 15 (14 + RR (1)) (%3,4) idi. 44 hastada tek ilaç direnci, 18 hastada çift ilaç direnci, 2 hastada üçlü ilaç direnci ve 4 hastada dördü ilaç direnci tespit edildi.

Sonuç: Tüberküloz insidansı ve mortalitesi azalmakla birlikte, hala önemli bir halk sağlığı sorunudur. Özellikle ileri yaş ve eşlik eden hastalıkların da hastalarda mortaliteyi artırdığı görülmüştür.

Anahtar kelimeler: Tüberküloz, ilaç direnci, eşlik eden hastalıklar.

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Introduction

Tuberculosis (TB) is an important public health problem caused by *Mycobacterium tuberculosis*, which causes mortality and morbidity in Türkiye as well as all over the world. According to the World Health Organization (WHO) data for 2022, it was determined that 10.6 million people were infected with tuberculosis bacilli, and 1.13 million people lost their lives due to tuberculosis disease. Similarly, in our country, it was determined that the incidence of TB has decreased significantly in the data collected from 2005 to the present. In 2020, the incidence was determined as 10.6 per hundred thousand [1, 2].

Tuberculosis, a treatable and preventable disease, typically affects the lungs but can also affect the other organs. The disease is more common in adults and men. In the diagnosis of pulmonary TB, the disease is suspected based on history, physical examination findings, and PA chest X-rays and can be diagnosed using bacteriological or histopathological methods. Risk factors and comorbidities are very important in the development of TB. There is an increased risk of developing tuberculosis in advanced age, HIV infection, immunosuppressive therapy, tumor necrosis factor alpha (TNF- α) antagonists, steroid use, close contact with infected individuals, chronic renal failure, dialysis, leukemia, lymphoma, head and neck malignancies, diabetes, cachexia, smoking, and alcohol abuse [3].

Drug resistance is still one of the important problems in tuberculosis treatment. Among people diagnosed with TB, it includes all patients with rifampin-resistant TB (RR-TB) and multidrug-resistant TB (MDR-TB), defined as resistance to both rifampin (R) and isoniazid (H) (MDR/RR-TB). WHO data indicates that the number of MDR patients has declined over time, reaching 410 thousand in 2020 (1). Türkiye is not among the 30 countries with a high disease burden in terms of MDR-TB. In the Global TB 2020 Report, the estimated number of MDR cases in Türkiye was 2.2% in new cases in 2020 and 8.6% in previously treated patients; the RD/MDR-TB rate was given as 2.4% in new cases and 9.7% in previously treated cases [2].

In this study, we aimed to determine the demographic data, radiological findings, comorbid conditions, antituberculosis drug resistance rates, and tuberculosis-related mortality of patients with pulmonary and pleural tuberculosis where *mycobacterium tuberculosis* growth was detected in culture between 2018 and 2023. We present our data to contribute national data about tuberculosis.

Materials and methods

Approval was obtained from the Samsun University Non-Interventional Clinical Research Ethics Committee for the study (approval date: 11/09/2024, approval number: 2024/16/3).

We retrospectively evaluated the data of 452 patients diagnosed with pulmonary and pleural tuberculosis at the chest diseases hospital clinic between January 2018 and December 2023. The study excluded 13 patients whose data were not accessible. Patients with *mycobacterium tuberculosis complex* growth in sputum, bronchial lavage and pleural fluid were included in the study, while patients with non-tuberculosis *mycobacterium tuberculosis* were excluded from the study.

We recorded the patients' demographic information, nationality, comorbid conditions, chest X-ray findings, drug resistance, and mortality status.

Two separate specialist physicians evaluated the chest X-ray findings. The chest X-ray findings of the patients were categorized as infiltration, cavitation and infiltration, cavitation, mass, and pleural fluid.

Samples of sputum, bronchial lavage, and pleural fluid from the patients were stained with the EZN method to look for acid-resistant bacillus. These were then grown in the BACTEC 460 TB system. In the *Mycobacterium tuberculosis complex* susceptibility tests, the rates of single, double, triple, and quadruple drug resistance to four major antituberculosis drugs (H, R, streptomycin (S), and ethambutol (E)) were investigated using the BACTEC 460 TB system recommended by the National Committee Clinic Laboratory Standards (NCCLS).

Patients who exitus while under tuberculosis treatment were considered tuberculosis-related deaths.

The SPSS 23.0 (SPSS Inc., Chicago, IL, USA) program was used for statistical evaluation. We calculated the frequencies and percentages of categorical variables, as well as the mean and standard deviation values of numerical variables. We applied the chi-square for categorical variables and the independent sample t-test for numerical data.

Results

We detected *Mycobacterium tuberculosis* growth in 439 patients with pulmonary tuberculosis, of whom 100 were female and 339 were male. The mean age of the patients was 52.7 ± 18.4 (F: 50.1 ± 21.9 , M: 53.4 ± 17.2).

5.2% (n=23) of the patients were foreign nationals. We tested sputum from 338 patients, bronchial lavage from 87 patients, and pleural fluid culture from 14 patients. EZN staining showed that acid-resistant bacillus was present in 224 (51%). 62.6% of the patients had comorbidities. The most common comorbidities were Chronic Obstructive Pulmonary Disease (COPD) (36.4%), hypertension (26.4%), and bronchiectasis (18.7%). Evaluation of the patients' chest x-rays revealed 45.1% with infiltration, 33.3% with cavitation and infiltration, and 7.1% with cavitation only. We determined that tuberculosis claimed the lives of 7.7% of the patients (Table 1). No statistically significant difference was found between foreign patients and the local population in terms of multidrug resistance, widespread drug resistance and tuberculosis-related mortality.

Table 1. Demographic characteristics

Age	
Female	52.7 ± 18.4 50.1 ± 21.9
Male	53.4 ± 17.2
Gender	
Female n (%)	100 (22.8)
Male n (%)	339 (77.2)
Nationality	
Turkish citizen (%)	416 (94.8)
Foreign national (%)	23 (5.2)
Culture	
Sputum	338 (77)
Bronchial lavage	87 (19.8)
Pleural fluid	14 (3.2)
Comorbidity and risk factors n (%)	
COPD	160 (36.4)
Hypertension	116 (26.4)
Bronchiectasis	82 (18.7)
Ischemic heart disease	82 (18.7)
Diabetes	72 (16.4)
Malignite	24 (5.4)
History of chemotherapy	20 (4.6)
Chronic kidney failure	19 (4.3)
Cerebrovascular disease	12 (2.7)
Corticosteroid treatment history	12 (2.7)

Table 1. Demographic characteristics (continued)

Asthma	11 (2.5)
HIV infected	6 (1.4)
Chest deformity	6 (1.4)
DIAH	5 (1.1)
Dialysis	3 (0.7)
Previous history of TB	2 (0.5)
AntiTNF treatment history	2 (0.5)
Chest x-ray	
Infiltration	198 (45.1)
Cavitation and infiltration	146 (33.3)
Cavitation	31 (7.1)
Mass	24 (4.8)
Pleural effusion	14 (3.2)
Missing data	29 (6.6)
Exitus from TB	34 (7.7)

COPD: Chronic obstructive pulmonary disease, DIAH: Diffuse interstitial lung disease, HIV: Human Immunodeficiency Virus
 TNF: tumor necrosis factor, TB: Tuberculosis

When we looked at the patients who died during tuberculosis treatment, it was found that the ages and underlying diseases of the deceased patients were statistically higher and that deaths occurred in patients with COPD, DIAH, and cerebrovascular disease (Table 2). The comorbidity and drug resistance status of patients who exited are shown in Table 3.

Evaluation of the patients' culture results revealed that 68 (15.5%) patients were resistant to at least one tuberculosis drug. H was detected

in 47 (10.7%), R in 15 (3.4%), E in 4 (0.9%), S in 37 (8.4%), and MDR in 15 (14 + RR (1)) (3.4%) (Figure 1). Single drug resistance was detected in 44 patients, double in 18 patients, triple in 2 patients, and quadruple drug resistance was detected in 4 patients (Table 4). Previous history of TB (n=1), bronchiectasis (n=1), malignancy (n=1), HIV infection (n=1), and diabetes (n=1) were detected as risk factors in 5 (35.7%) of the MDR patients. Antituberculosis resistance rates between 2018 and 2023 are given in Table 5.

Table 2. Mortality, age, gender, and comorbidity rates

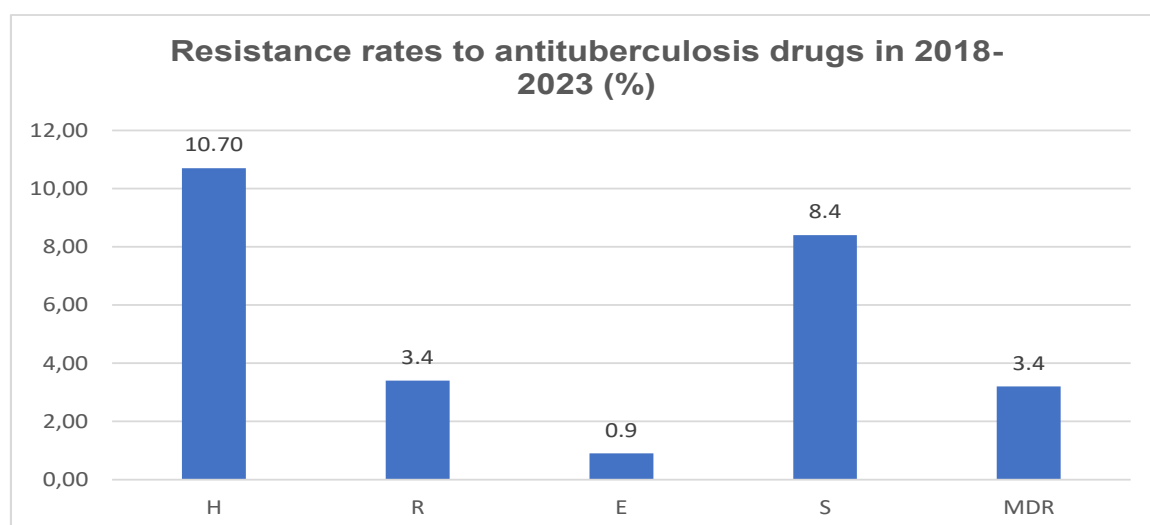
	Exitus (n, %)	Alive (n, %)	χ^2	t	p
Age	69.8±12.2	48.4±17.5	-	-10.2	0.000*
Gender					
Male	28 (6.4)	307 (70.5)	0.59	-	0.441
Female	6 (1.3)	94 (21.6)			
Comorbidity and risk factors n (%)	31 (91.2)	243 (60.6)	36.57	-	0.000*

*= $p < 0.05$, Independent samples t test was conducted on independent groups,
 The Pearson Chi-Square test was used for the categorical variables, χ^2 = Chi-square test and t = Independent samples t-test

Table 3. Comorbidity and drug resistance status in patients with exitus

Co-morbidity n (%)	34
COPD	23 (67.6%)
Bronchiectasis	9 (26.5%)
Hypertension	6 (17.6%)
Ischemic heart disease	6 (17.6%)
Diabetes	6 (17.6%)
Cerebrovascular disease	4 (11.8%)
Chronic kidney failure	3 (8.8%)
DIAH	3 (8.8%)
Malignite	2 (5.9%)
Chest deformity	2 (5.9%)
History of chemotherapy	1 (1.9%)
Corticosteroid treatment history	1 (2.9%)
Dialysis	1 (2.9%)
AntiTNF treatment history	1 (2.9%)
Drug resistance n (%)	
Single drug resistance	
H	2 (%5.9)
S	1 (2.9)
Double drug resistance	
HS	2 (%5.9)
Quadruple drugs resistance	
HRSE	1 (%2.9)

H: isoniazid, R: rifampicin, E: ethambutol, S: streptomycin, MDR: multidrug resistance, COPD: Chronic obstructive pulmonary disease
DIAH: Diffuse interstitial lung disease, TNF: tumor necrosis factor

**Figure 1.** Resistance rates to antituberculosis drugs in 2018-2023 (%)

H: isoniazid, R: rifampicin, E: ethambutol, S: streptomycin, MDR: multidrug resistance, The BACTEC 460 TB system recommended by the National Committee for Clinical Laboratory Standards (NCCLS) was used in Mycobacterium tuberculosis complex susceptibility testing

Table 4. Drug resistance rates

	n (%)
Single drug resistance	44 (9.9)
H	23 (5.2)
R	1 (0.2)
E	0
S	20 (4.5)
Double drug resistance	18 (4.1)
HR	8 (1.8)
HS	10 (2.3)
Triple drugs resistance	
HRS	2 (0.5)
Quadruple drugs resistance	
HRES	4 (0.9)

H: isoniazid, R: rifampicin, E: ethambutol, S; streptomycin, These findings were compared with WHO global resistance rates (see Discussion)

Table 5. Drug resistance rates between 2018-2023

	H (%)	R (%)	E (%)	S (%)	MDR (%)
2018	14 (15.1)	9 (9.7)	2 (2.2)	10 (10.8)	9 (9.7)
2019	7 (9.2)	3 (3.9)	0	7 (9.2)	3 (3.9)
2020	8 (11.9)	1 (1.5)	1 (1.5)	3 (4.5)	1 (1.5)
2021	6 (9.8)	0	0	3 (4.9)	0
2022	10 (13.9)	2 (2.8)	1 (1.4)	8 (11.1)	2 (2.8)
2023	2 (2.9)	0	0	6 (8.6)	0
Total	47 (10.7)	15 (3.4)	4 (0.9)	37 (8.4)	15 (3.4)

H: Isoniazid, R: Rifampicin, E: Ethambutol, S; Streptomycin, MDR: Multidrug Resistance

Discussion

In our study, we found the mortality rate due to tuberculosis to be 7.7%. We observed that mortality was higher in patients with advanced age and those with comorbidities such as COPD, DIAH, and cerebrovascular disease. In addition, while MDR was found to be 3.4%, we also found that MDR was higher in individuals with a history of TB, bronchiectasis, DM, malignancy, and HIV infection as risk factors. Risk factors and comorbidities are quite important in the development of pulmonary TB. Studies have found different rates of diseases accompanying TB. In studies conducted by Sağiroğlu et al. [4], Dolla et al. [5], Hase et al.

[6], Giridharan et al. [7], and Liu et al. [8], TB-accompanying diseases were found at different rates. The different study results suggest that the relationship between comorbidity and TB has not been fully determined, and its interaction with living conditions is unknown. In studies, DM, hypertension, COPD, bronchiectasis, and malignancies were the most frequently detected comorbid diseases. In our study, COPD, hypertension, bronchiectasis, and diabetes were the most frequently detected diseases, similar to other studies.

Chest radiographs can provide important clues in patients with TB symptoms. The sensitivity of chest radiographs in the diagnosis

of active TB is 70-80%, and the specificity is 60-70% [3]. Di Gennaro et al. [9], Alavi et al. [10], Oriekot et al. [11], Hase et al. [6], Piccazzo et al. [12], and Xie et al. [13] found infiltration and cavitory lesions in the bilateral upper zones and these findings were the most common chest radiograph findings. In our study, similar to other studies, the most common chest radiograph findings were 45.1% infiltration and 33.3% cavitation and infiltration.

Mortality due to tuberculosis in the world varies between 7% and 35% depending on the tuberculosis burden of the countries, socioeconomic status, non-infectious concomitant diseases, presence of HIV infection, and MDR. Mortality rates were found to be 8% in the study of Di Gennaro et al. [9], less than 10% in the study of Suhairi et al. [14], 6.5% in the study of Abedi et al. [15], and 4.6% in the study of Xie et al. [13]. The study by Sağıroğlu et al. [4] reported our national data at 6.83%. Studies have determined that DM, HIV, and malignancy are important in mortality. Alavi et al. [10] found that the elderly population had a higher mortality rate (26.5%) compared to the young population (4.1%). In the study conducted by Zahar et al. [16] in patients who developed respiratory failure due to TB, a mortality rate was 26.2%. In the study conducted by Elhisdi et al. [17], the mortality rate was 47.7%, and comorbidities were COPD, hypertension, DM, and bronchiectasis. In the study conducted by Hase et al. [6], mortality independent of age was found to be 11.3%, while in terms of early mortality, the rate was found to be 28.1%, especially in patients over the age of 84. Other studies evaluating early mortality found the rates of 19.6% and 14.4%, respectively [18]. In most of the studies, risk factors for mortality were identified as low socio-economic level, severe malnutrition, recurrent infection, smear-positive pulmonary TB, MDR cases, high average age, DM, COPD, and malignancy [8-18]. We found that our study's TB-related mortality rate was comparable to studies conducted in our own country. The common characteristics of the patients were having comorbidities and being older (average age 69.8 ± 12.2).

Drug resistance surveillance in tuberculosis is an important component of the tuberculosis control program. Drug resistance is the

most important factor determining the type of treatment, duration, and prognosis of the disease in TB treatment. The estimated rate of new TB cases with MDR/RR-TB worldwide was 4% in 2015, decreasing to 3.3% in 2022; the estimated rate of previously treated MDR/RR-TB cases was 25% in 2015, decreasing to 17% in 2022 [19]. In the Global TB 2020 Report, the estimated number of MDR cases in Türkiye was 2.2% for new cases in 2020, 8.6% for previously treated patients, and the RR/MDR-TB rate was 2.4% for new cases and 9.7% for previously treated cases [2]. The most comprehensive article reflecting the resistance status in our country includes data from a meta-analysis study covering the results of 21 studies and 27,959 strains conducted between 1984-1989 and 1990-1995. In 1984-1989, H was 27.8%, S was 22.5%, E was 7.8%, R was 22.3%, and PRZ was 1.6%, while in 1990-1995, H was 23.8%, S was 17.9%, E was 7.7%, R was 22.1%, and PRZ was 6.5% [20]. When the resistance studies conducted in our country were examined, Tarhan et al. [21] H 6.5%, R 6.5%, E 4.3%, S 10.8%, MDR 2.17%, Perincek et al. [22] H 10.4%, R 3%, E 0.7%, S 0.7%, MDR 2.2%, Aslan et al. [23] H 7.1%, R 2.6%, S 6.6%, E 0.5%, MDR 3.5%, Porsuk et al. [24] H 9.9%, R 1.8%, E 1.2%, and S 4.7%, MDR 3.5%, Sağıroğlu et al. [4] H 7.1%, R 2%, E 5.6%, S 5.1%, MDR 2.5%, Yakupoğlu Y. et al. [25] H 8%, R %1.2, S 4.1%, E 0.2%. According to the data of the Tuberculosis Control Department of the Ministry of Health, antituberculosis drug resistance rates in all cases (2010-2020) are summarized in Table 6. From 2010 to 2020, there was a significant decrease in all drug resistances. In 2020, H was found to be 10.7%, R to be 2.9%, E to be 2.8%, S to be 9.1%, and MDR to be 2.6% [2]. In studies conducted in our country, resistance rates are similar to the data from the Tuberculosis Control Department of the Ministry of Health, according to the years in which they were conducted. A study conducted in Iran observed that drug resistance rates in relapse cases were higher than the world average. Any resistance 68%, mono-resistance 19%, multi-drug resistance 28% [26]. In our study, while the H (10.7%), R (3.4), and S (8.4%) rates were similar, the E (0.9%) rate was low, and our MDR (3.4) rates were high. The high rate of MDR was thought to be due to regional differences.

Table 6. According to the data of the Tuberculosis Control Department of the Ministry of Health, antituberculosis drug resistance rates in all cases (2010-2020)

	Drug Resistans				
	H (%)	R (%)	E (%)	S (%)	MDR (%)
2010	13.3	6.8	5.2	9.1	5
2011	13.7	6.7	5	10.3	5.4
2012	15.4	6.6	5.4	11.3	5.4
2013	13.6	5.1	4.2	9.4	4.1
2014	13.8	6.4	5	10.6	4.6
2015	13.7	5.4	4.4	11.3	4.1
2016	11.9	4.2	3.7	10.6	3.3
2017	12.5	4.2	4	10.5	3.2
2018	12.6	4.1	3.1	10.4	3.2
2019	10.8	1.4	2.3	9.3	2.3
2020	10.7	2.9	2.8	9.1	2.6

H: Isoniazid, R: Rifampicin, E: Ethambutol, S: Streptomycin, MDR: Multidrug Resistance

Patients with MDR are special patients in TB treatment and follow-up. Therefore, it is crucial to evaluate risk factors thoroughly. Results from studies by Xie et al. [13], Blöndal et al. [27], and Pradipra et al. [28] showed that MDR developed more in patients who had TB in the past, HIV, diabetes, or COPD. Similarly, in our MDR cases, there were previous TB, HIV infection, malignancy, diabetes, and bronchiectasis.

The retrospective nature of our study and the small number of patients were limitations.

As a result, although TB incidence and mortality are decreasing, it is still an important public health problem. It can be mortal, especially in patients with advanced age and comorbidities.

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