Research Article / Araştırma Makalesi

Factors Affecting Treatment Outcomes for Tuberculosis Patients: A Retrospective Cohort Study

Tüberküloz Hastalarında Tedavi Sonuçlarını Etkileyen Faktörler: Retrospektif Bir Kohort Çalışması

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Abstract

Background: Tuberculosis (TB) is one of the ten leading causes of death globally. The present study aims to examine the treatment outcomes in TB patients and to determine the factors associated with unsuccessful treatment outcomes.
Materials and Methods: This study was a retrospective registry-based cohort study conducted in Ordu province of Turkey between 2017-2021. Logistic regression analysis was used to explore the risk factors associated with unsuccessful outcomes.
Results: A total of 400 TB patients were included in the analysis. The observed overall treatment success rate (TSR) (cured or treatment completed) was 87.7% (351). 49 patients (12.3%) had unsuccessful treatment results (death, failure or loss to follow-up). Age>65 years (odds ratio [OR] =12.2, 95% confidence intervals [CI] =4.03-36.85), male gender (OR = 2.2, 95% CI = 1.05-4.45) and being foreign-born (OR = 9.2, 95% CI = 1.16-73.72) were identified as risk factors associated with unsuccessful outcomes in patients (p<0.05).
Conclusions: Age>65 years, male gender and foreign-born patients tend to have unsuccessful treatment outcomes. Careful monitoring of patients with any of these characteristics and taking special precautions for them may help to decrease unsuccessful treatment outcomes.

Key Words: Tuberculosis, Tuberculosis control, Risk factor, Treatment success rate

Öz

Amaç: Tüberküloz dünya çapında önde gelen on ölüm nedeninden biridir. Bu çalışmanın amacı TB hastalarında tedavi sonuçlarını incelemek ve tedavi başarısızlığı ile ilişkili faktörleri belirlemektir.
Materyal ve Metod: Bu çalışma, 2017-2021 yılları arasında Türkiye'nin Ordu ilinde gerçekleştirilen, retrospektif, kayıt tabanlı bir kohort çalışmasıdır. Başarısız sonuçlarla ilişkili risk faktörlerini araştırmak için lojistik regresyon analizi kullanıldı.
Bulgular: Analize toplam 400 TB hastası dahil edildi. Gözlemlenen genel tedavi başarı oranı (TSR) (tedavi edilen veya tedavi tamamlanan) %87,7'dir (351). Hastaların 49' unda (%12,3) başarısız tedavi sonucu elde edildi (ölüm, başarısızlık veya takip kaybı). Yaş>65 (olasılık oranı [OR] =12,2, %95 güven aralığı [CI] =4,03-36,85), erkek cinsiyet (OR = 2,2, %95 CI = 1,05-4,45) ve yabancı uyruklu olmak (OR = 9,2, %95 CI = 1,16-73,72) başarısız sonuçlarla ilişkili risk faktörleri olarak belirlendi (p<0,05).
Sonuç: Yaş>65, erkek cinsiyet ve yabancı uyruklu hastalar başarısız tedavi sonuçlarına sahip olma eğilimindedir. Bu özelliklerden herhangi birine sahip olan hastaların dikkatle izlenmesi ve özel önlemler alınması, başarısız tedavi sonuçlarının azaltılmasına yardımcı olabilir.

Anahtar Kelimeler: Tüberküloz, Tüberküloz kontrol, Risk faktör, Tedavi başarı oranı

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Introduction

Tuberculosis (TB) is one of the ten leading causes of death globally, as well as the leading cause of morbidity and mortality from an infectious agent. Although it mostly affects the lungs, it is a disease that can be nestled in many places such as the lymph nodes, bones, prostate and ovaries (1). In 2019, the worldwide incidence of the disease was reported as 130 cases per 100,000 people and 18.7 deaths per 100,000 people. Worldwide, 10 million new cases of tuberculosis are reported each year. According to the World Health Organization (WHO), 1.5 million TB-related deaths occur each year (2). In Turkey, the incidence of TB in 2018 was 14.1 per 100,000 people and 0.39 deaths per 100,000 people. According to 2018 data, the incidence of TB in Ordu is 17.5 per hundred thousand (3). On the other hand, drug-resistant TB stands before the world as a public health crisis. Estimates suggest that at least 6 million people will have drug-resistant TB infections over the next ten years (2,4).

TB treatment has been applied in our country since 2006, with the "Directly Observed Treatment Strategy (DOTS)", under the knowledge and supervision of a healthcare professional (5). Hospital data conforming to the relevant ICD 10 (International Statistical Classification of Diseases) codes for the diagnosis of TB and data of patients with evidence of granulomatous inflammation suspected for TB in pathology laboratories are collected during regular visits to health facilities at regular intervals. With this active surveillance system, TB patient records have been collected throughout the country since 2015 and reported to WHO through the Turkish National Tuberculosis Surveillance Network (TNTSN) (6). The goal of the WHO's End TB strategy is to reduce the number of deaths due to active TB by 95% and the incidence of TB by 90% by 2035 compared to 2015 (7). Although TB incidence and TB mortality are the main indicators of TB burden, assessment of risk factors affecting TB treatment outcomes is important in monitoring the effectiveness of control programs. In various studies around the world evaluating risk factors for TB treatment failure, sociodemographic characteristics of TB patients, characteristics of TB disease, drug resistance and underlying comorbidities have been shown as important factors associated with treatment outcomes (8-11). The findings regarding the risk factors identified in the studies differ between countries and regions. There are few studies investigating the results of tuberculosis treatment in Turkey. This study was conducted in Ordu province between 2017-2021 to examine the treatment results in TB patients and to determine the factors associated with treatment failure.

Materials and Methods

Study Design and Population

This study was a retrospective registry-based cohort study in which all patients diagnosed with TB with full registry information in TB dispensaries in Ordu province between July 1, 2017 and December 31, 2021 were included.

Ordu province, located in the Central Black Sea region in the north of Turkey, has a population of 760872. The demographic, clinical and laboratory characteristics of the patients were analyzed and the treatment results were determined. A total of 479 TB patients diagnosed based on laboratory or clinical criteria according to national TB management guidelines were included in the study. The exclusion criteria were determined as a change in the outcome diagnosis, transfer to another country during the follow-up period, and unknown outcome as the treatment was ongoing. For these reasons, 79 patients were excluded from the study. The study was conducted on data from 400 patients. Each patient was included in the analysis once in a 12 months period.

The independent variables of the study included age, gender, nationality, method of diagnosis, types of TB diagnosed, HIV positivity, presence of drug resistance, treatment classification (first-line, second-line).

Data Collection

The diagnosis of TB patients was made according to sputum culture which is main diagnostic test, smear microscopy (Acid Fast Bacilli "AFB"), rapid molecular tests (GeneXpert MTB/RIF) or clinical criteria including radiological findings (12). The diagnosis of MDR-TB patients was made according to GeneXpert results when resistance to RIF was observed. All TB cases underwent human immunodeficiency virus (HIV) testing with the enzyme-linked immunosorbent assay (ELISA) technique as part of the routine evaluation of such patients. In our country, TB notification is mandatory when clinician-confirmed or suspected TB is diagnosed. Within the scope of the routine DOTS program, all tuberculosis patients are followed until the tuberculosis treatment is completed and their follow-up is terminated when the final treatment result is reported to WHO.

Treatment outcomes

Treatment outcomes were categorized into unsuccessful outcome (death, failure and loss to follow-up) and successful outcome (cured and completed treatment) according to the NTPC guideline (3).

Operational terms

It was created based on the standard definitions of the National TB Control Program (NTCP) guidelines adopted by WHO (13). Patients were classified as new and recurrent cases.

The TB site is categorized by the source of the sample submitted for culture and information from medical records: pulmoner TB (PTB) if TB is confined to the lungs, tracheobronchial tree, or larynx, extra-pulmoner TB (EPTB) if TB includes organs not included in PTB, and finally PTB+EPTB.

TB case reporting rate: It is the number of new cases per 100,000 population per year.

Relapse: Patients who have recovered or have completed treatment for TB and are subsequently diagnosed with a recurrent episode of TB.

Seasons: Summer (June-August), Autumn (September-November), Winter (December-February), Spring (March-May).

Smear-positive PTB: Patients with a positive direct smear microscopy result and/or a sputum sample result that is positive for acid-fast bacilli (AFB) with the Gene Xpert MTB/RIF test.

Smear-negative PTB: Two negative sputum smear microscopy results and one of the radiological signs and respiratory symptoms consistent with active TB are patients with >2 weeks cough, weight loss, fever, and hemoptysis.
EPTB: Patients in whom AFB can be demonstrated in samples taken from organs other than the lung parenchyma or who have histological and clinical findings compatible with TB are included in this group (3).

Treatment Options: Major treatment under NTCP; It is continued for 2 months with INH, RIF, ethambutol and pyrazinamide, followed by 4 months with INH and RIF. The drugs used in this regimen are called first-line drugs. In treatment centers for MDR-TB patients (four in Turkey, one in Ankara, two in Istanbul and one in Izmir) alternative treatments such as para-aminosalicylic acid (PAS), cycloserine, linezolid, ethionamide and amikacin are applied. This treatment is called minor therapy, and the drugs used in this regimen are called second-line drugs (13).

Cure: In a pulmonary TB patient with an initial bacteriological diagnosis, clinical and radiological recovery is accompanied by the demonstration of smear or culture negativity at least twice, one during the maintenance period of treatment and the other in the month of completion of treatment (3).

Treatment outcome: The treatment outcome of PTB patients was evaluated based on direct sputum smear microscopy results, and the treatment outcome of Smear-negative PTB and EPTB patients based on clinical evaluation at the end of treatment (3).

Loss to follow-up: Patients whose records indicate that they did not attend their clinical appointments 2 or more times (3).

Death: The WHO definition of 'death due to TB' was used in this study and was defined as TB patients who died from any cause during treatment against TB, regardless of the actual cause of death. TB-related death was confirmed by death certificate or medical records of responsible physician (3).

Statistical Analysis
Variables included demographic and clinical features of TB patients, analyzed using SPSS 21.0 software package. Continuous variables are expressed as means and standard deviations or medians and quartiles. Pearson's chi-square test or Fisher's exact test was used to compare qualitative data. The type of statistical method for comparing quantitative data was determined according to the number of groups and parametric or non-parametric type of data. To explore the risk factors associated with unsuccessful outcomes, binary logistic regression models were fitted with having unsuccessful treatment outcomes versus those having successful treatment outcomes as the outcome variables. Multivariable logistic regression was used for the final analysis, and adjusted all odds ratios (OR) and 95% confidence intervals (95% CI) were estimated by four variables known to affect the outcome based on the univariate analysis: age, gender and nationality.

Results

Main characteristics of the patients in the study
The flow chart showing the TB diagnosis types of the patients is given in Figure 1. The results of TB treatment among the cases diagnosed with TB are presented in Table 1. Of all patients diagnosed with TB, 140 (35.0%) recovered, and 211 (52.7%) of them completed their treatment. The observed overall treatment success rate (TSR) (cured or treatment completed) was 87.7% (351). Death occurred in 34 (8.5%), treatment failure in 1 (0.3%) patient, and loss to follow-up in 14 (3.5%) patients. In total, 49 patients (12.3%) had unsuccessful treatment results.
Sociodemographic data and clinical characteristics of the patients in the study are presented in Table 2. The average age of the patients (±standard deviation, range) was (49.08 ±19.28, 1-92) years. The age group with the highest number of cases is 51-65 years old. 274 (68.5%) of the patients were male. Overall, the E:K ratio was 2.2:1. Among the diagnosed TB patients, there were 263 (65.8%) PTB cases and 115 (28.7%) EPTB cases, 22 (5.5%) PTB+EPTB cases. Recurrence was recorded in 46 (17.5%) of PTB patients, 6 (5.2%) of EPTB patients and 4 (18.2%) of PTB+EPTB patients. TB lymphadenitis and pleural TB were the predominant types of EPTB during the study period. 5 (%1.2) of registered TB patients were diagnosed as HIV positive.
When the TB diagnosis was examined, 178 (44.5%) cases were diagnosed on smear positivity, 125 (31.3%) cases were diagnosed on pathological basis, 122 (30.5%) cases on clinical or radiological basis and 101 (25.2%) cases on culture positivity. Of the 115 EPTB patients, 71 (61.7%) cases were diagnosed on pathological basis, 41 (35.6%) cases were diagnosed on clinical or radiological basis, 9 (7.8%) cases on culture positivity and 8 (6.9%) cases on smear positivity. The highest incidence occurred during the winter season.

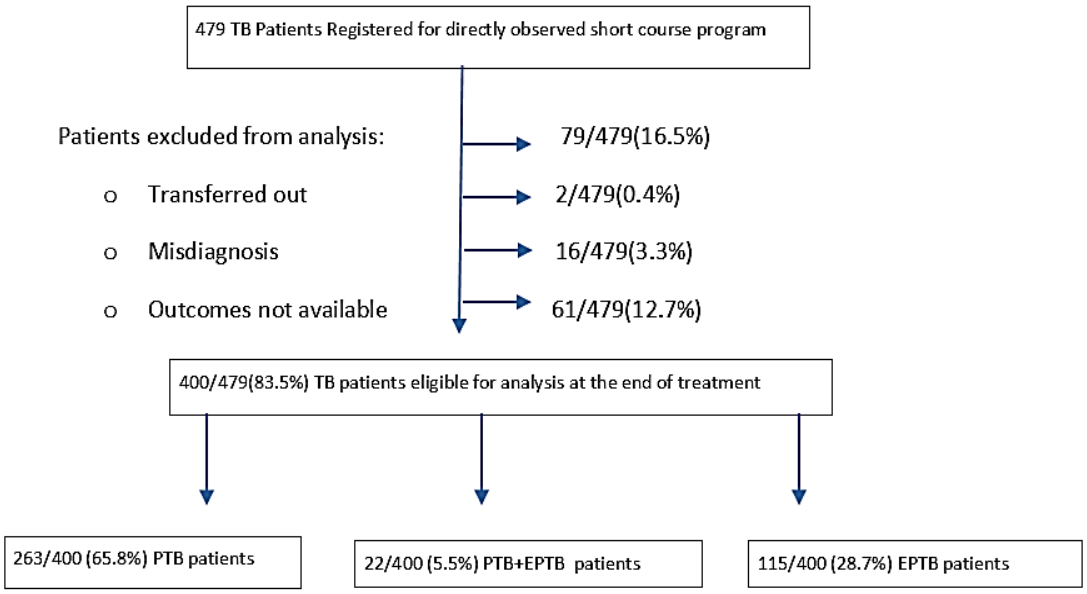

Figure 1. Flowchart showing the type of tuberculosis diagnosed. PTB: Pulmonary tuberculosis, EPTB: Extra pulmonary tuberculosis

Table 1. Tuberculosis treatment outcomes and treatment success rate at the end of tuberculosis treatment in Ordu, Turkey.

Treatment Outcomes		**n(%)**
Successful	Cured	140 (35.0)
	Completed	211 (52.7)
	Total	351 (87.7)
Unsuccessful	Died	34 (8.5)
	Failure	1 (0.3)
	Loss to follow-up	14 (3.5)
	Total	49 (12.3)

TB, tuberculosis

Table 2, also shows the factors associated with unsuccessful treatment outcomes. The mean age of the patients whose treatment was unsuccessful was 62.94±19.86 years. As age increases, the rate of unsuccessful treatment rate is higher. PTB was the most common (65.8%) disease type, and there was no significant difference between unsuccessful and successful treatment. Unsuccessful treatment rate (12.3%) was lower in smear-positive TB patients. For both all patients and only EPTB patients, no significant difference was found between smear-positive and smear-negative with respect to treatment failure.

There was no significant difference in the rate of TB treatment failure between the different seasons. In univariate analysis, the risk of treatment failure was increased in older patients, those with a history of previous TB treatment, male patients and patients born outside of Turkey ($p < 0.05$ for all). In multivariate analysis, male gender was associated with 2.2-fold higher odds ratio. In comparison of TB treatment failure among age groups, <35 years old group was accepted as the reference group. The probability of TB treatment failure was 1.5 and 1.2-fold higher for patients aged 35-50 and 51-65 years, and 12.2-fold higher for patients >65 years, respectively, compared to the reference age group. Unsuccessful treatment outcome was 9.2-fold higher in foreign-born TB cases. There was no significant difference in treatment outcome between TB patients without HIV infection and HIV co-infected TB patients. Smear-negative TB did not increase the risk of treatment failure compared to smear-positive patients.

Table 2. Demographic and clinical characteristics of 400 patients diagnosed with TB between 1 July 2017 and 31 December 2021, Ordu, Turkiye.

Variable	Treatment Success			p	OR(95%CI)
	No n(%)	Yes n(%)	Total		
Age (years) (mean ±SD)	62.94±19.86	47.14±18.41	49.08±19.28	p<0.001[b]	
Sex					
Male	42(15.3)	232(84.7)	274(68.5)	p=0.037[a]	2.16(1.05-4.45)
Female	10(7.9)	116(92.1)	126(31.5)		-1.0-
Age group (years)					
<35	4(4.0)	96(96.0)	100(25.0)	p<0.001[a]	-1.0-
35-50	9(9.4)	87(90.6)	96(23.5)		1.53(0.42-5.53)
51-65	7(5.7)	115(94.3)	122(30.5)		1.16(0.32-4.18)
>65	29(35.4)	53(64.6)	82(20.5)		12.18(4.03-36.85)
Types of TB diagnosed					
PTB	35(13.3)	228(86.7)	263(65.8)	p=0.310[a]	
EPTB	10(8.7)	105(91.3)	115(28.7)		
PTB+EPTB	4(18.2)	18(81.8)	22(5.5)		
Previous treatment					
None	38(10.9)	310(89.1)	348(87.0)	p=0.007[a]	-1.0-
Any	11(21.2)	41(78.8)	52(13.0)		2.14(0.90-5.10)
Relapsed	7(16.7)	35(83.3)	42(10.5)		
İnterrupted	3(33.3)	6(66.7)	9(2.3)		
Treatment failure	1(100.0)	0(0.0)	1(0.3)		
Country of origin					
Turkish	47(11.9)	349(88.1)	396(99.0)	p=0.029[a]	-1.0-
Others (like Syria, Iraq, Iranian)	2(50.0)	2(50.0)	4(1.0)		9.24(1.16-73.72)
Smear acid-fast bacilli					
Negative	14(14.9)	80(85.1)	94(34.6)	p=0.558[a]	
Positive	22(12.4)	156(87.6)	178(65.4)		
Clinical presentations of EPTB					
Lymph node	2(4.1)	47(95.9)	49(35.8)	p=0.260[a]	
Pleural	5(14.3)	30(85.7)	35(25.5)		
Osteo-articular	3(27.3)	8(72.7)	11(8.0)		
Central nervous system	0(0.0)	4(100.0)	4(2.9)		
Genito-urinary	2(18.2)	9(81.8)	11(8.0)		
Pericarditis	0(0.0)	2(100.0)	2(1.5)		
Others	2(8.0)	23(92.0)	25(18.2)		
AFB culture test results					
Negative	9(17.0)	44(83.0)	53(21.1)	p=0.249[a]	
Positive	22(11.1)	176(88.9)	198(78.9)		
Drug resistance					
No	45(12.6)	312(87.4)	357(89.3)	p=0.533[a]	
Yes	4(9.3)	39(90.7)	43(10.8)		
İnitial treatment regimen					
First-line	42(11.2)	333(88.8)	375(94.5)	p=0.320[a]	
First-line + Second-line	4(18.2)	18(81.8)	22(5.5)		
HIV status					
Negative	25(8.0)	286(92.0)	311(77.8)	p=0.060[a]	
Positive	2(40.0)	3(60.0)	5(1.2)		
Unknown	22(26.2)	62(73.8)	84(21.0)		
Season					
Summer	9(10.7)	75(89.3)	84(21.0)	p=0.903[a]	
Autumn	11(11.1)	88(88.9)	99(24.8)		
Winter	15(13.6)	95(86.4)	110(27.5)		
Spring	14(13.1)	93(86.9)	107(26.8)		

[a]Chi-square test; [b]Mann-Whitney U test; CI: confidence interval; Odds ratios based on logistic regression model adjusted for age category (<35/35–50/51–65/>65 years) and history of previous treatment (none/any). TB, tuberculosis; PTB, pulmoner TB; EPTB, extra pulmoner TB; SD, standart deviation; AFB, acid-fast bacilli

Discussion

This study was conducted with the data of 479 TB patients registered in Ordu province between July 1, 2017 and December 31, 2021 to collect data about unsuccessful treatment outcomes and associated risk factors in tuberculosis patients in the Central Black Sea region of Turkey. In our study, the annual TB case reporting rate was 14.0 per 100,000 people. In another study conducted in Turkey, the annual incidence was reported as 17.0 (14). The target set by WHO for 2020 within the scope of TB end strategy is a 20% decrease compared to 2015. In our study, the incidence in 2020 and 2021 was found to be 10.9 and 9.6, respectively. These rates are lower than the TB End Strategy targets (7). As of 2020, the WHO declared a pandemic and the reduction in TB transmission due to the Covid-19 measures implemented in our country may have been effective.

This study reports 87.7% successful treatment outcome in TB patients. Overall TB treatment success was found to be 91% in a study of 1010 patients in Turkey (14). In another study reported from Turkey, this rate was found to be 87% in PTB patients (5). Treatment success was found to be 83% in Uzbekistan, 84% in Iran, and 86% in Pakistan (15-17). In other countries with limited resources, such as Turkey, the target of 90% treatment success before 2026, which was determined by the WHO within the scope of the TB End Strategy, has not yet been reached appears to be unreachable (7). In our country, in addition to equal and free access to health services, the DOT strategy is successfully implemented in TB patients. Despite this, a significant proportion of patients fail their TB treatment.

Past history of TB, older age, male gender, drug resistance, comorbidity, HIV co-infection are the risk factors most commonly associated with treatment failure in previous studies (5,15-18). In this study, the effects of age, gender and nationality on treatment outcomes were consistent with outcomes in other populations.

In our cohort, the mean E:K ratio was 2.2:1. It is known that TB disease is mostly seen in men in Turkey and in the world (13). In addition to the biological differences between the sexes, it can be thought that social factors such as active participation in social life in men, high smoking rates and cultural differences may lead to this result. In our study, male gender causes an increase in the risk of treatment failure. This finding is in line with the results of studies reporting that male gender is associated with failing treatment outcomes worldwide (19,20).

The most commonly affected age groups in this study were 35-50 and 51-65 years, respectively, which is consistent with the findings of most countries (20,21). It is known that TB disease is common in people who work and participate in active social life, especially in developing countries, so this is an expected finding. In our study, old age was found to be a risk factor for unsuccessful treatment outcome. Patients aged 65 and over are approximately 12.2 times more likely to have treatment failure. In a study conducted in Kocaeli province of Turkey, the probability of unsuccessful treatment outcomes was found 5 times more in patients aged 65 and over (5). Other studies conducted in our country have also shown the relationship between old age and unsuccessful treatment (18,22). This may be associated with increasing age-related comorbidity and decreased immune response (23). In addition, atypicality of symptoms and difficulty in diagnosis may occur with age. Decreased treatment adherence and difficulty in accessing healthcare are other factors that cause unsuccessful treatment outcomes in the elderly. These findings emphasize the importance of close monitoring of elderly patients to increase the success of treatment.

In this study, the rate of EPTB was found to be 34.2%. Similar rates were found in studies in the literature (24,25). It was found that the most common prevalence is lymph node in EPTB patients in this study. In the literature, the most common involvement was found to be in the lymph node (26). In some studies, pleural involvement is dominant (27). In this study, PTB was not found to be a risk factor for unsuccessful treatment outcome. However, in some studies, symptoms such as dyspnea and respiratory comorbidities in patients with PTB increase the possibility of hospitalization and intensive care unit admission. As a result, the likelihood of unsuccessful treatment outcome increases (28).

The prevalence of smear-positive TB cases in our study stayed unchanged during the years. On average, about half of the cases were diagnosed with smear-positive TB. It is consistent with smear-positive TB distributions found in other studies (21). In the literature, patients with smear-positive PTB are less likely to result in unsuccessful treatment than other types of TB (24). Some patients have basic clinical and radiological indicators and the clinician may want to make a diagnosis quickly without waiting for smear microscopy with relatively low sensitivity (1). Due to the ease of diagnosis, early diagnosis and treatment may explain the higher rate of unsuccessful treatment outcomes in smear-negative TB cases. In this study, no significant difference was found between smear-positive patients and smear-negative patients with respect to treatment failure.

The season with the highest TB incidence was determined as winter in this study. In some studies, it is stated that the incidence of TB increases in the summer months (29). In a study conducted in Spain, it was reported that the disease peaks in the winter months (30). We evaluate that the susceptibility may increase due to low vitamin D levels and frequent respiratory tract infections in winter.

In this study, patients born outside of Turkey were more likely to fail treatment than those born in Turkey. Studies conducted in other countries have also reported that the risk of treatment failure is higher among those born in foreign countries (31). Inequalities in access to health services and differences in treatment compliance due to socioeconomic and cultural reasons might have caused this increase. There are many studies in Turkey showing that the success of treatment decreases in previously treated cases

(5,14,18). Prior suboptimal therapy may result in increased treatment failure associated with the frequency of drug resistance. Babalik et al. showed that the risk of treatment failure is increased in case of resistance to any of the TB drugs. There are many studies in the literature with similar results (17,22). However, the presence of drug resistance was not found to be a risk factor for unsuccessful treatment outcome in our study. In addition, there was no significant difference between newly diagnosed patients and relapsed cases in terms of unsuccessful treatment outcomes.

In the literature, HIV coinfection and comorbidity in TB patients are factors that contribute to unsuccessful treatment outcomes (5,14,32). In our study, the presence of additional disease was not found in the records except HIV positivity. When HIV positivity was evaluated in terms of treatment success, no difference was found compared to HIV negative patients.

Strengths of the study

One of the strengths of this study is that it was conducted with data collected from a large number of TB patients in one of Turkey's metropolitan cities. It is significant that the factors associated with 87.7% treatment success and treatment failure were identified.

Limitations of the study

The most effective limitation of our study is the retrospective study design. There may be a very small number of TB patients undetected by the national health system, which may have led to an underestimation of incidence than it actually is. It is also the patients who are expected to increase the rate of treatment failure, given that undetected people may be marginal groups such as the homeless. In addition, the registration of the completion of the treatment was accepted as a successful treatment result, but in reality, these individuals may have experienced treatment failure. For these reasons, the treatment success rate may have been overestimated than it actually was, which is one of the limitations of the study. Another limitation is that since the study was based on secondary data, comorbidities such as diabetes mellitus, socio-economic status, education level, nutritional status, smoking and alcohol use were not available in the records.

Conclusion

The overall treatment success rate was lower than that of targeted ≥90% End TB Strategy success rate and still need to be improved. The unsuccessful treatment outcome was documented more in advanced age, male gender and patients born outside of Turkey. For this reason, additional medical and social support including housing and cost of living should be provided for these patients. Additionally research investigating other possible risk factors such as smoking, alcohol, education level, nutritional level, comorbidities and drug side effects are needed.

Ethical Approval: *The study was approved by the Ordu University Clinical Research ethics committee with number: 2022/151; date:17/06/2022.*

Author Contributions:
Concept: F.N.T.Y.
Literature Review: F.A., F.N.T.Y.
Design : F.N.T.Y.
Data acquisition: F.A.
Analysis and interpretation: F.A.
Writing manuscript: F.N.T.Y., F.A.
Critical revision of manuscript: F.N.T.Y., F.A.

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