Taylor & Francis
Taylor & Francis Group

Postgraduate Medicine

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ipgm20

Characteristics of tuberculosis-related deaths and risk factors: a retrospective cohort study in Samsun province of Turkey

Muhammet Ali Oruç, Sule Ozdemir & Derya Oztomurcuk

To cite this article: Muhammet Ali Oruç, Sule Ozdemir & Derya Oztomurcuk (2022) Characteristics of tuberculosis-related deaths and risk factors: a retrospective cohort study in Samsun province of Turkey, Postgraduate Medicine, 134:2, 217-223, DOI: 10.1080/00325481.2022.2029106

To link to this article: https://doi.org/10.1080/00325481.2022.2029106

Published online: 26 Jan 2022.

POSTGRADUATE MEDICINE
2022, VOL. 134, NO. 2, 217–223
https://doi.org/10.1080/00325481.2022.2029106

Taylor & Francis
Taylor & Francis Group

CLINICAL FEATURES
ORIGINAL RESEARCH

Characteristics of tuberculosis-related deaths and risk factors: a retrospective cohort study in Samsun province of Turkey

Muhammet Ali Oruç [a], Sule Ozdemir [b] and Derya Oztomurcuk [b]

[a]Department of Family Medicine, Faculty of Medicine, Ahi Evran University, Kirsehir, Turkey; [b]Department of Public Health, Provincial Health Directorate, Samsun, Turkey

ABSTRACT

Objectives: Tuberculosis (TB) remains one of the top ten leading causes of death worldwide despite effective therapy. The present study aims to examine the characteristics of TB-related deaths in Samsun Province and to determine the risk factors.

Methods: In this retrospective registry-based cohort study, the medical records of patients registered with Samsun Tuberculosis Control Dispensary between 1 January 2018 and 31 December 2019 were retrospectively reviewed. The Cox proportional-hazards model was used to determine the factors associated with the risk of death in patients with TB.

Results: The treatment outcomes of a total of 382 patients were reviewed. It was found that the treatment was successful in 346 patients (90.6%), and 31 patients (8.1%) died before or during TB therapy. The median survival time of patients who died during the therapy was 1.86 months (95% CI = 0.07–5.17 months), and more than 50% (13/25) of the deaths occurred in the first two months of the treatment. Age above 70 years (HR 15.06 (3.33–67.95)), male gender (HR 2.74 (1.02–7.33)), pulmonary TB (HR 2.92 (1.002–8.52)), multidrug-resistant (MDR) tuberculosis (HR 1.69 (1.22–12.75)), and a delay in the treatment of more than ten days (HR 2.71 (1.22–6.04)) were identified as risk factors associated with mortality in TB patients ($p < 0.05$).

Conclusion: The majority of deaths in our cohort occurred within the first two months after starting the treatment. Advanced age, male sex, a new diagnosis of TB, pulmonary TB, MDR-TB, and a treatment delay of more than ten days after diagnosis increased the risk for mortality during antituberculosis treatment.

ARTICLE HISTORY
Received 5 August 2021
Accepted 6 January 2022

KEYWORDS
Tuberculosis control; mortality; risk factor; health policy

Introduction

Tuberculosis (TB) is a severe public health problem and remains one of the top ten leading causes of death worldwide [1]. According to the 2020 Global Tuberculosis Report published by the World Health Organization (WHO), 10 million new TB cases occur every year, resulting in 1.4 million TB-related deaths while an estimated 3 million cases of TB are underreported. Approximately one-fourth of the world's population is infected by TB bacilli, and 5–15% of the infected people develop active disease. In 2019, the reported incidence of TB was 130 cases per hundred thousand people worldwide, with a mortality rate of 18.7 deaths per hundred thousand people. Turkey is located in the European Region of the WHO. While TB incidence is 26 cases per hundred thousand people with a mortality rate of 2.7 deaths per hundred thousand people in the European region, lower incidence and mortality rates are observed in Turkey than in the European region. The incidence of TB is 16 cases per hundred thousand people, and the mortality rate is 0.39 deaths per hundred thousand people in Turkey [2].

Effective disease management is one of the critical components in tuberculosis control. The National Tuberculosis Control Program (NTCP) has been implemented to promote rapid diagnosis of TB cases and to reduce the disease spread. Tuberculosis cases are reportable within 24 hours after the diagnosis, and the patients are registered with the local dispensary for follow-up where the patient resides. As of 2020, there are a total of 173 TB dispensaries in Turkey, at least in each province, and three TB dispensaries in Samsun province [3]. Tuberculosis Control Dispensaries provide free diagnosis, treatment, follow-up, reporting, registration, vaccination, contact screening, drug dispensing, education, and counseling services. The 'Directly Observed Therapy' (DOT) strategy recommended by the WHO to improve treatment success and to increase survival has been implemented in the healthcare facilities of Turkey in 2006 [4]. Since 2005, the records of TB patients in Turkey have been collected through a surveillance study entitled Turkey National Tuberculosis Surveillance Network (TNTSN) from the dispensaries on a case basis and reported to the WHO. In addition, TB active surveillance research has been practiced in our province since 2012 and countrywide since 2015. In the scope of the active surveillance research, the reports of patients with a definitive diagnosis of TB, the hospital data matching the relevant ICD 10 (International Statistical Classification of Diseases) codes for

CONTACT Sule Ozdemir sule_ozt@hotmail.com Department of Public Health, Provincial Directorate of Health, Samsun, Turkey

the diagnosis of TB, and the data of patients with an evidence of granulomatous inflammation suspected for TB in pathology laboratories are collected during regular visits to healthcare facilities with certain intervals and scrutinized for TB [5]. Despite all these effective measures, patients die before receiving or during TB therapy. The WHO defines 'TB-related deaths' as the number of TB patients dying during the treatment regardless of the actual cause of death [6]. TB mortality is an important indicator to evaluate the effectiveness of TB control programs and to measure TB burden. It is essential to investigate the risk factors for TB-related mortality to improve survival. Various studies evaluating the risk factors for mortality during TB treatment have suggested that factors such as age, gender, comorbidities, and HIV infection might be associated with mortality; however, these risk factors vary across countries [7–9]. There is a paucity of studies in Turkey examining the characteristics of TB-related deaths and the associated risk factors. The present study aims to examine the characteristics of TB-related deaths in Samsun Province and determine the risk factors.

Materials and methods

Study group

In this retrospective registry-based cohort study, the data of 408 patients registered with TB dispensaries in Samsun province between 1 January 2018 and 31 December 2019 were collected. Twenty-six patients were excluded from the study due to the rejection of anti-tuberculosis therapy, the identification of a condition other than TB, and the evacuation to another country during the follow-up period. The study was conducted on the data of 382 patients. Samsun province is located in the Central Black Sea region in the north of Turkey and has a population of 1.4 million people. In 2017, the incidence of TB in our province was 13.5 (per hundred thousand), while the incidence of TB in our country was 14.6 (per hundred thousand) [3].

The data such as age, gender, nationality, family history, sputum smear results at the time of diagnosis, method of diagnosis, involvement site in the body, extrapulmonary involvement sites, human immunodeficiency virus (HIV) test results, the presence of drug resistance, the treatment classification (first-line and second-line), duration of anti-tuberculosis therapy, length of hospital stay, and prognostic data were retrieved from the registry information system while paying attention to confidentiality. According to the WHO guideline, the patients were classified as new and relapsing cases, and each patient was included in the analysis once during a 12-month period [10]. Along with the written data on the patients' charts regarding the cause of death in 31 patients for whom the treatment outcome was reported as 'death' to the TNTSN, the information provided on the death reporting system (DRS) was also checked to confirm the cause of death. The DRS is a web-based application allowing data exchange among the relevant units of the Republic of Turkey Ministry of Health, General Directorate of Civil Registration and Citizenship, and Turkish Statistical Institute for thorough, rapid, and quality compilation of death statistics [11].

The study was approved by the Clinical Research Ethics Committee of Ondokuz Mayıs University.

Definitions

Survival Time: The observance survival time was defined as the time from the onset of anti-tuberculosis therapy to the end of the observance period. The survival time in non-survivors was defined as the time from the onset of anti-tuberculosis therapy or registry to the TB dispensaries without receiving therapy to death.

Delay in Therapy: The time from the diagnosis to the onset of therapy is that more than ten days (time unit = day).

Treatment Options: In Turkey, the treatment of patients with TB consists of a 2-month intensive phase with isoniazid, rifampicin, ethambutol, and pyrazinamide followed by a 4-month continuation phase with isoniazid and rifampicin as stipulated by the NTCP. This regimen is called major therapy, and the drugs are called first-line drugs. In centers providing therapy to patients with drug resistance (four centers available in Turkey, one center in Ankara, two centers in İstanbul, and one center in İzmir), para-aminosalicylic acid (PAS), cycloserine, linezolid, ethionamide, and amikacin are alternative therapies in patients with multidrug-resistant tuberculosis (MDR-TB) and in the case of drug-related side effects or treatment failure. This therapy is called minor therapy, and the drugs included in this regimen are called second-line drugs [3].

Treatment Outcomes: The study used the definitions and recommendations of the WHO related to the recovery, completion of therapy, treatment failure, and death [6].

Cure (recovery): The demonstration of at least two negative sputum smears or culture negativity, one in the continuation phase of the therapy and the other upon completion of the therapy, along with evidence of clinical and radiological recovery in a patient with pulmonary TB who initially received a bacteriological diagnosis.

Completion of therapy: This refers to the discontinuation of therapy in patients completing the courses of therapy as expected in whom sputum examination could not be performed during the continuation phase or at the end of therapy, considering that treatment success has been achieved based on clinical and radiological evidence (Patients with extrapulmonary TB are also added to this group if treatment success has been achieved).

Treatment success: This refers to the sum of cured patients and those who have completed the therapy.

Loss to follow-up (Treatment rejection in old terms): This refers to a patient who did not start treatment or who interrupted TB treatment for two consecutive months or more.

Treatment failure: Treatment failure refers to sputum smear or sputum culture positivity at five months or later after the initiation of anti-TB treatment.

Death: This refers to the death of the TB patient for any reason during treatment (TB patients dying before receiving any therapy are also registered with the TCD, and the treatment outcome is recorded as "death".

Statistical analysis

SPSS 21.0 software package was used in the statistical analysis, and parametric and non-parametric descriptive statistics included mean ± standard deviation, median (interquartile range (IQR)) and number (%), where appropriate. A chi-square 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 the data type (parametric or non-parametric). The survival was evaluated using the Kaplan-Meier method, and the Cox proportional-hazards model was used to determine the factors associated with the risk of death. Examination of survival in univariate analyzes was performed with the log rank test. In multivariate analysis, independent factors in predicting survival were analyzed using the backward selection method and Cox regression analysis using possible factors identified in previous analyzes. Among the interrelated parameters with similar effects on survival, clinically significant ones were selected for the model. The level of statistical significance was set to an alpha of 0.05 ($p < 0.05$) in all statistical analyses.

Results

Patient characteristics

Sociodemographic data of the study patients are presented in Table 1. The median age of the patients was 54.0 years (34.0–67.0), and 237 (62.0%) were male. Of the non-survivors, 16 (51.6%) were aged over 70 years. Of the patients, 361 (94.5%) were recently diagnosed, and there was no significant difference in disease type between survivors and non-survivors ($p = 0.161$).

When the treatment outcomes were examined, the treatment was successful in 346 patients (90.6%); of these patients, 164 (42.9%) were cured, and 182 (47.6%) completed their courses of therapy. The treatment outcome was death in 31 patients (8.1%), treatment failure in two patients (0.5%), and loss to follow-up in three patients (0.8%).

Mortality data

The mean age of 31 patients who underwent active surveillance was 71.32 ± 13.56 years (median 69.0 [65.0–82.0]). A total of six patients (19.3%) died before the initiation of treatment, and the diagnosis had been confirmed by sputum culture in all six patients (100.0%). The mean age of 25 patients who died during the treatment was 70.56 ± 13.23 years (median 68.0 [65.0–81.0]). The mean age was significantly higher in patients who died before commencing treatment (74.33 ± 16.10 years (median 80.0 [64.0–86.0]) than in patients who died during the treatment (70.56 ± 13.23 years, $p < 0.001$). The diagnosis of cancer was significantly more common among patients who died during the treatment ($p = 0.044$). Of non-survivors, 21 (67.7%) had previously received treatment in the hospital, and the mean length of hospital stay was 24.14 ± 18.34 days. It was found that 80.6% (n = 25) of TB-related deaths (n = 31) occurred in the hospital while 194% (n = 6) occurred at home. The median survival time was 1.86 months (95% CI = 0.07–5.17) in patients who died during the treatment, and more than 50% of deaths (13/25) occurred in the first two months of treatment. The one-year cumulative survival rate of TB patients was 93.3%.

As shown in Table 1, pulmonary TB (PTB) was the most common (65.4%) disease manifestation and significantly more common among non-survivors ($p = 0.038$). The mean delay in treatment in all patients was 10.59 ± 40.91 days (0.0–465.00). In addition, the number of patients with a treatment delay of fewer than ten days was significantly higher in survivors than in non-survivors ($p = 0.012$).

The results of the Cox proportional hazards regression analysis are presented in Table 2, age over 70 (HR 15.06 (3.33–67.95)), male gender (HR 2.74 (1.02–7.33)), PTB (HR 2.92 (1.002–8.52)), MDR-TB (HR 1.69 (1.22–12.75)) and delay in treatment (HR 2.71 (1.22–6.04)) increased the risk of death ($p < 0.05$).

Kaplan-Meier survival curves showed a significant difference in survival between the sub-groups (Figures 1 and 2). When the patients were stratified according to gender, the survival was shorter in males than in females (log-rank test, $p < 0.001$). When stratified according to age, the survival was shorter in patients aged 70 years and over (log-rank test, $p < 0.001$).

Discussion

The present research is a pilot study of 382 TB patients registered between 2018 and 2019 in the province of Samsun to gather information about the causes of death and the associated risk factors in TB patients in order to reduce TB-related mortality. Despite free and equal access to healthcare services, the use of effective anti-TB drugs, and the low incidence of TB, the present study reports that all-cause mortality rate in TB patients is approximately 8% in our province. This figure suggests that a considerable number of deaths occur related to TB.

In Turkey and the world, TB is more common in males than in females [12]. The number of males was higher in our cohort and among patients who died of TB. Many studies have not detected a significant difference in terms of gender between survivors and non-survivors [13–15]. However, some studies, similar to the present study, have identified the male gender as an independent risk factor for TB-related mortality [8,16]. The role of gender in mortality varies between the studies but factors such as the difference in males and females regarding compliance to treatment, higher exposure of men to infections as a result of participating in social life more, and women's more difficult access to health institutions due to various socioeconomic reasons may explain this results.

The mean age was higher than 70 years in 31 TB-related deaths that underwent active surveillance, and advanced age was significantly associated with death. Similar to the present study, previous studies have also found that deaths were more common in the older population, and the increase in age was associated with a 1.05 to 37.91-fold increase in the risk of death [16–18]. The decline in the immune system with advancing age may result in disease

Table 1. Characteristics of 382 patients diagnosed with TB between January 2018 and December 2019, Samsun, Turkey.

Variable	Total N(%)	Death status		p
		Died N(%)	Alive N(%)	
Age (years)(mean ± SD)	50.74 ± 20.43	71.32 ± 13.56	48.92 ± 19.94	<0.001**
Age group (years)				<0.001*
0–50	169(44.2)$^{+}$	3(1.8)$^{++}$	166(98.2)$^{++}$	
51–69	142(37.1)$^{+}$	12(8.5)$^{++}$	130(91.5)$^{++}$	
>70	71(18.5)$^{+}$	16(22.5)$^{++}$	55(74.5)$^{++}$	
Gender				0.086*
Male	237(62.0)$^{+}$	22(9.3)$^{++}$	215(90.7)$^{++}$	
Female	145(38.0)$^{+}$	9(6.2)$^{++}$	136(93.8)$^{++}$	
Patient type				0.161*
New	361(94.5)$^{+}$	31(8.6)$^{++}$	330(91.4)$^{++}$	
Relapse	21(5.5)$^{+}$	0(0.0)$^{++}$	21(100.0)$^{++}$	
Country of origin				0.648*
Turkey	359(94.0)$^{+}$	30(8.4)$^{++}$	329(91.6)$^{++}$	
Others (Syria, Iraq, Iranian et al.)	23(6.0)$^{+}$	1(4.3)$^{++}$	22(95.7)$^{++}$	
HIV status				
Negative	382(100.0)$^{+}$	31(8.2)$^{++}$	351(91.8)$^{++}$	
Pulmonary TB				0.038*
No	132(34.6)$^{+}$	4(3.0)$^{++}$	128(97.0)$^{++}$	
Yes	250(65.4)$^{+}$	27(10.8)$^{++}$	223(89.2)$^{++}$	
TB site				0.055*
Pulmonary	238(62.3)$^{+}$	27(11.3)$^{++}$	211(88.7)$^{++}$	
Extra-pulmonary	132(34.6)$^{+}$	4(3.0)$^{++}$	128(97.0)$^{++}$	
Pulmonary+Extra-pulmonary	12(3.1)$^{+}$	0(0.0)$^{++}$	12(100.0)$^{++}$	
Bacteria smear results				0.022*
Negative	136(35.6)$^{+}$	11(8.1)$^{++}$	125 (91.9)$^{++}$	
Positive	129(33.8)$^{+}$	19(14.7)$^{++}$	110(85.3)$^{++}$	
Culture results				<0.001*
Negative	51(13.4)$^{+}$	2(3.9)$^{++}$	49(96.1)$^{++}$	
Positive	212(55.5)$^{+}$	23(10.8)$^{++}$	189(89.2)$^{++}$	
TB diagnosis				0.261*
Bacteria smear positive	121(31.7)$^{+}$	11(9.1)$^{++}$	110(90.9)$^{++}$	
Culture positive	83(21.7)$^{+}$	10(12.0)$^{++}$	73(88.0)$^{++}$	
Clinical or radiological positive	73(19.1)$^{+}$	7(9.6)$^{++}$	66(90.4)$^{++}$	
Histopathological positive	105(27.5)$^{+}$	3(2.9)$^{++}$	102(97.1)$^{++}$	
Multi-drug resistance(MDR) results				0.086*
No	198(51.8)$^{+}$	20(10.1)$^{++}$	178(89.9)$^{++}$	
Yes	7(1.8)$^{+}$	2(28.6)$^{++}$	5(71.4)$^{++}$	
Treatment options				0.034*
First-line drugs	361(94.8)$^{+}$	22(6.1)$^{++}$	339(93.9)$^{++}$	
First-line drugs + second-line drugs	15(3.9)$^{+}$	3(20.0)$^{++}$	12(80.0)$^{++}$	
Delay in treatment (date)				0.012*
<10	299(84.3)$^{+}$	15(5.0)$^{++}$	284(95.0)$^{++}$	
≥10	77(15.7)$^{+}$	10(13.0)$^{++}$	67(87.0)$^{++}$	

P*; Chi-square test, p**; Mann-Whitney U test, $^{+;}$ column percentage, $^{++}$; row percentage
SD; Standart deviation

Table 2. Results of multivariate analysis with a Cox proportional hazard model of risk factors for death during the treatment period in TB patients.

Variable	β	S.E.	Wald χ2	HR	95.0% CI		p
					Lower	Upper	
Age group (years)							
0–50	Referance						
51–69	1.995	0.764	6.825	7.354	1.646	32.861	0.009
>70	2.712	0.769	12.446	15.061	3.338	67.953	0.000
Gender							
Female	Referance						
Male	1.011	0.501	4.064	2.747	1.028	7.338	0.044
Patient type							
Relapse	Referance						
New	3.090	3.798	0.662	2.070	1.281	15.266	0.045
Pulmonary TB							
No	Referance						
Yes	1.071	0.546	3.856	2.919	1.002	8.505	0.047
MDR results							
No	Referance						
Yes	0.525	1.031	0.260	1.691	1.224	12.751	0.041
Delay in treatment (date)							
<10	Referance						
≥10	1.067	.408	5.993	2.717	1.221	6.048	0.014

progression, and adverse drug reactions can also increase the risk of death [19]. The higher mean age in patients who died before starting TB treatment than patients who died during TB treatment may be linked to the high burden of comorbidities in older patients. It can be suggested that comorbid conditions may cause atypical presentation of TB symptoms in older people that may pose challenges in the diagnosis [8,20,21]. In addition, our mortality data show that all deaths occurring before starting treatment, and the majority of deaths occurred in the hospital. For this reason, the suspicion of TB must always be kept in mind while treating older in-patients with comorbid conditions representing challenges in diagnosis, and screening for tuberculosis must be increased.

According to Turkey 2018 data, the treatment success is 85.0% in new and relapsing cases. The reported success rate for our province 84.2%, which is similar to the national average [22]. It is observed that the treatment success is reduced in previously treated cases (patients after treatment failure and returning cases after loss to follow-up) [22]. Retreatment of TB is mostly complex and serious, primarily due to irregular or unreasonable chemotherapy. Therefore, it is more difficult to retreat from TB than to provide initial treatment, making the mortality rate higher. A Chinese cohort study involving approximately 7,000 TB cases between 2014 and 2017 reported that the risk of death has increased by 1.77 old in relapsing cases [16]. Unlike the literature, the present study found that a new diagnosis of TB is a risk factor for death. The discrepancy between the present findings and the literature data may have been caused by the absence of relapsing cases among TB-related deaths in our cohort.

The Cox proportional-hazards model in our study showed that survival outcome is poor in patients with PTB. Similar to our study, other studies in the literature have reported that PTB is a risk factor for death [17,23]. The treatment of patients with PTB is often administered in the hospital setting, and these patients have a high rate of intensive care unit admission [23]. The presence of dyspnea, respiratory comorbidities, and presence of extensive disease are considered as factors accelerating progress toward mortality. Treatment failure, presence of chronic disease, patient's residence in an area of a high rate of drug resistance, sputum smear positivity after three months in the contacts of patients with resistant strains, and lack of improvement in clinical condition should raise the

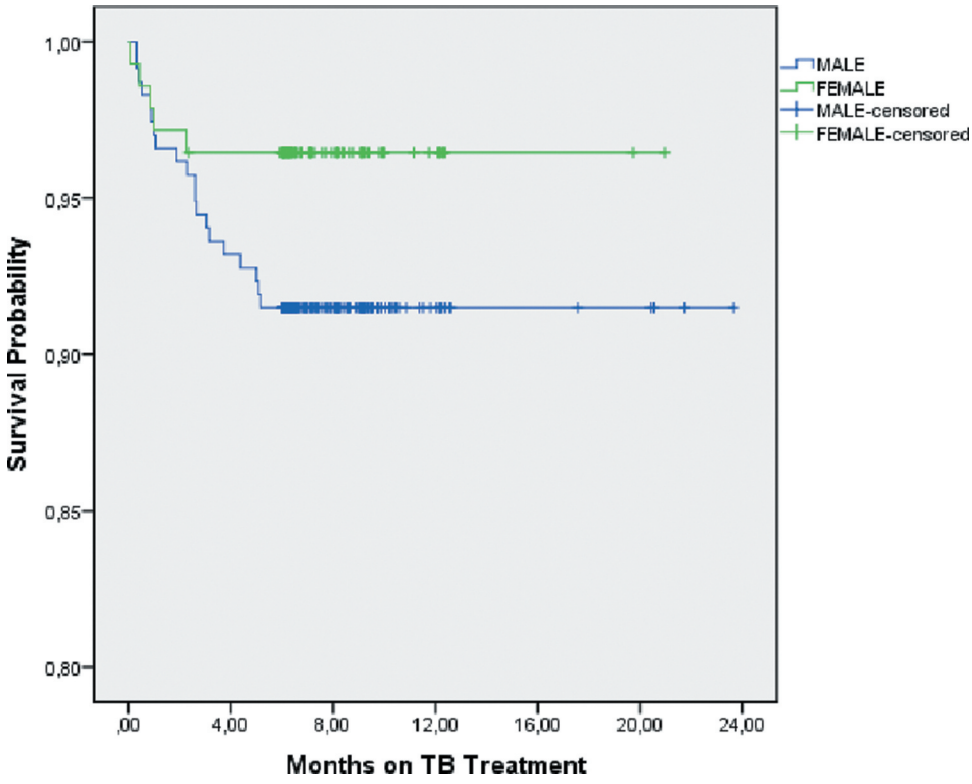

Figure 1. Kaplan-Meier curves showing survival by sex (log-rank test, $p < 0.001$).

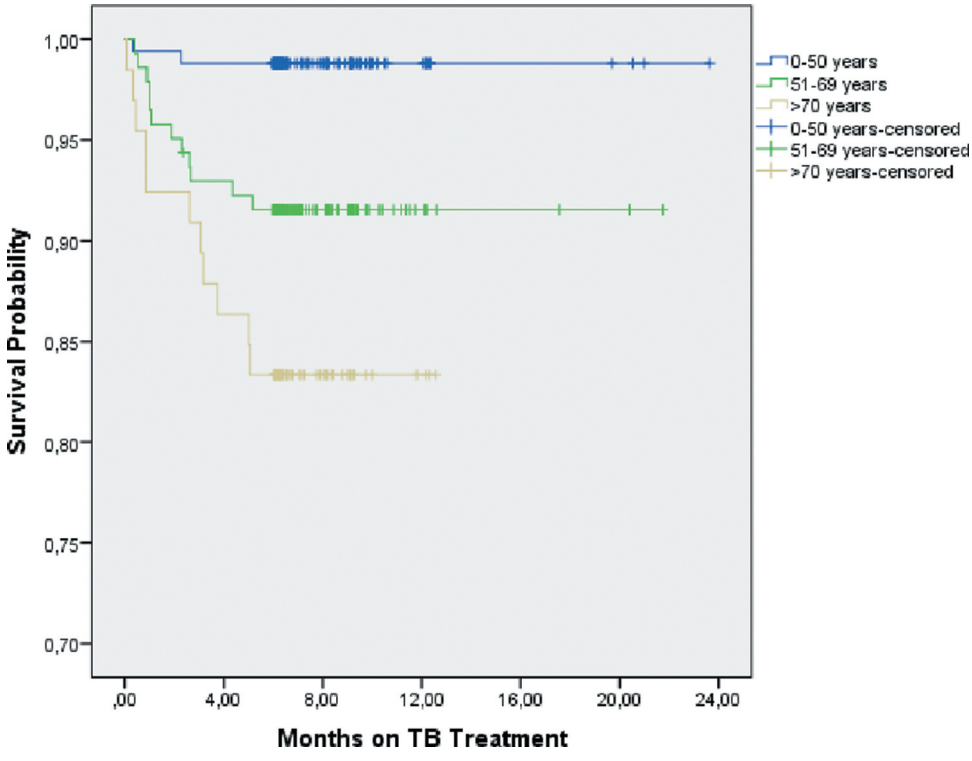

Figure 2. Kaplan-Meier curves showing survival for age (log-rank test, $p < 0.001$).

suspicion of MDR-TB. The treatment of these patients is undertaken in four reference hospitals in Turkey using the second-line drug therapies, and referral of patients with suspected MDR-TB to these hospitals is required in an expeditious manner [3]. Consistent with the literature the present study found no difference between survivors and non-survivors concerning drug resistance, but MDR-TB significantly increased the risk of death [14,16]. Many studies have previously

shown that patients with MDR-TB are at increased risk of death during treatment [24–26]. A previous study conducted in Turkey involving TB patients hospitalized in intensive care units found a substantial increase in the risk of death among intensive care unit patients with drug resistance [23]. It is considered that mortality rates can be considerably reduced if MDR-TB is detected early and necessary interventions are made promptly.

In many disease conditions, delays occur due to delays in seeking medical care, diagnosis, treatment, or a combination of all [27,28]. Delay in treatment is one of the factors, and a delay of more than ten days in the initiation of treatment after ascertaining the diagnosis of TB was found to be an independent risk factor for TB-related death. Some studies suggest that delays in starting the treatment are caused by asking for advice from the healers and private and public healthcare facilities before starting the treatment [28,29]. Due to the paucity of collected data in the present study, there is limited information about the factors that might affect delay in treatment. As recommended by the WHO, healthcare workers in the TB dispensaries have an essential role in accessing patients swiftly to start the treatment early in an attempt to increase treatment efficacy. In addition, a study examining the factors related to the delays in diagnosis and treatment in 853 patients with pulmonary tuberculosis in Turkey found that the mean delay in treatment was 0.90 ± 2.39 days, which is lower than the delay found in the present study [30]. The rate of TB-related mortality in Samsun province is slightly higher than the national average, and the difference in the treatment delay supports the factors associated with the increased risk of death [22].

HIV infection is an important problem contributing to TB-related mortality, particularly in African countries. According to the WHO data, 1.2 million of 10.4 million new cases of TB are also HIV-positive [31]. TB patients in our country undergo HIV testing, and the rate of HIV-positive cases among patients with TB increases every passing year [32]. However, no patient in the present study tested positive for HIV infection, thus, its contribution to TB-related mortality could not be evaluated. There is a need for more extensive cohort studies to investigate the effect of HIV positivity on the survival of TB patients.

The median survival time from the onset of treatment to death was 1.8 months in the present study. The one-year cumulative survival rate after TB treatment was 93%. In a study conducted in China, the survival was 1.9 months, with a cumulative survival rate of 94.1% [16]. Their findings are consistent with the present findings.

The retrospective study design is the most important limitation of the present study. Accurate identification of the cause of death requires autopsy investigation, which is considered the gold standard in this regard; however, no patient in the present cohort study underwent postmortem examination. The end-point of the study was all-cause mortality, and TB-related deaths could not be differentiated from incidental deaths. Furthermore, survival analysis did not consider the data on educational level, nutritional status, socioeconomic status, tobacco-alcohol use, and liver and kidney functions.

Conclusion

The majority of deaths in our cohort occurred within the first two months after starting the treatment, and male gender, advanced age, a new diagnosis of TB, PTB, MDR-TB, and a treatment delay of more than ten days after diagnosis were identified as the risk factors associated with mortality. To the best of our knowledge, the present study is a pilot study presenting the risk factors associated with TB-related mortality in Turkey, and the present findings can guide future studies. For this reason, there is a need for multicenter, prospective cohort studies establishing a more robust risk model incorporating the relevant risk factors and educational status, employment status, income level, HIV co-infection, comorbidities, drug side effects, nutritional status, smoking, alcohol, etc.

Disclosure of financial/other conflicts of interest

The authors have no relevant conflicts of interest to disclose. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Authors contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by SO and DO. The first draft of the manuscript was written by DO and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Consent for publication

All participants have agreed for their responses to be anonymized and presented for publication purposes.

Ethics approval

The study was approved by the Clinical Research Ethics Committee of Ondokuz Mayıs University.

Institutional Review Board protocol approval number: **2021/158**
Institutional Review Board protocol approval number date: **18.3.2021**

Funding

The authors have no funding to report.

ORCID

Muhammet Ali Oruç http://orcid.org/0000-0002-4320-8579
Sule Ozdemir http://orcid.org/0000-0002-0366-7455
Derya Oztomurcuk http://orcid.org/0000-0003-3004-9270

References

1. Dirlikov E, Raviglione M, Scano F. Global Tuberculosis Control: toward the 2015 Targets and Beyond. Ann Intern Med. 2015;163 (1):52–58.
2. World Health Organization. Global tuberculosis report 2020. 2020 cited 2021 Mar 28. https://www.who.int/publications-detail-redirect/9789240013131
3. Republic of Turkey Ministry of Health. The Guideline of Tuberculosis Diagnosis and Treatment 2019. Ankara Turkey: cited

2021 May 05. https://hsgm.saglik.gov.tr/tr/tuberkuloz-haberler/t%C3%BCberk%C3%BCloz-tan%C4%B1-ve-tedavi-rehberi.html
4. Sengul A, Akturk UA, Aydemir Y, et al. Factors affecting successful treatment outcomes in pulmonary tuberculosis: a single-center experience in Turkey, 2005-2011. J Infect Developing Countries. 2015;9(8):821–828.
5. Republic of Turkey Ministry of Health. Tuberculosis active surveillance criteria. cited 2021 May 14. http://tuberkuloz.saglik.gov.tr
6. WHO Tuberculosis Programme. WHO Tuberculosis Programme: framework for effective tuberculosis control. World Health Organization; 1994 cited 2021 May 15. https://apps.who.int/iris/handle/10665/58717
7. Birlie A, Tesfaw G, Dejene T, et al. Time to Death and Associated Factors among Tuberculosis Patients in Dangila Woreda, Northwest Ethiopia. PLoS One. 2015;10(12):e0144244.
8. Kwon YS, Kim YH, Song JU, et al. Risk factors for death during pulmonary tuberculosis treatment in Korea: a multicenter retrospective cohort study. J Korean Med Sci. 2014;29(9):1226–1231.
9. Abedi S, Moosazadeh M, Afshari M, et al. Determinant factors for mortality during treatment among tuberculosis patients: cox proportional hazards model. Indian J Tubercul. 2019;66(1):39–43.
10. World Health Organization. Definitions and reporting framework for tuberculosis – 2013 revision: updated December 2014 and January 2020. World Health Organization; 2013 cited 2021 May 14. https://apps.who.int/iris/handle/10665/79199
11. Republic of Turkey Ministry of Health. Death Notification System Circular 2012/ 05. Presidency of Public Health Institution of Turkey; 2012 cited 2021 Mar 03. https://www.saglik.gov.tr/TR,11167/olum-bildirim-sistemiobs-genelgesi.html
12. Republic of Turkey Ministry of Health. Turkish Public Health Institution, Department of Tuberculosis. Tuberculosis War in Turkey 2014 Report, Ankara: 2015 cited 2021 May 22. https://hsgm.saglik.gov.tr/depo/birimler/tuberkuloz_db/dosya/raporlar/Turkiyede_Verem_Savasi_2014_Raporu.pdf?type=file
13. Erbes R, Oettel K, Raffenberg M, et al. Characteristics and outcome of patients with active pulmonary tuberculosis requiring intensive care. Eur Respir J. 2006;27(6):1223–1228.
14. Lin SM, Wang TY, Liu WT, et al. Predictive factors for mortality among non-HIV-infected patients with pulmonary tuberculosis and respiratory failure. Int J Tuberc Lung Dis. 2009;13(3):335–340.
15. Silva DR, Menegotto DM, Schulz LF, et al. Mortality among patients with tuberculosis requiring intensive care: a retrospective cohort study. BMC Infect Dis. 2010;10(1):1–7.
16. Xie Y, Han J, Yu W, et al. Survival Analysis of Risk Factors for Mortality in a Cohort of Patients with Tuberculosis. Can Respir J. 2020;2020:1654653.
17. Holden IK, Lillebaek T, Andersen PH, et al. Characteristics and predictors for tuberculosis related mortality in Denmark from 2009 through 2014: a retrospective cohort study. Plos One. 2020;15(6):e0231821.
18. Lin YS, Yen YF. Determinants of mortality before start of and during tuberculosis treatment among elderly patients: a population-based retrospective cohort study. Age Ageing. 2015;44(3):490–496.
19. Rajagopalan S. Tuberculosis in Older Adults. Clin Geriatr Med. 2016;32(3):479–491.
20. Kwon YS, Chi SY, Oh IJ, et al. Clinical characteristics and treatment outcomes of tuberculosis in the elderly: a case control study. BMC Infect Dis. 2013;13(1):121.
21. Adamu AL, Gadanya MA, Abubakar IS, et al. High mortality among tuberculosis patients on treatment in Nigeria: a retrospective cohort study. BMC Infect Dis. 2017;17(1):170.
22. Tuberculosis War in Turkey. Report. In: Republic of Turkey Ministry of Health Publication No: 1109. Ankara: 2018.
23. Filiz KA, Levent D, Emel E, et al. Characteristics of Active Tuberculosis Patients Requiring Intensive Care Monitoring and Factors Affecting Mortality. Tuberc Respir Dis (Seoul). 2016;79(3):158–164.
24. Hannah HA, Miramontes R, Gandhi NR. Sociodemographic and Clinical Risk Factors Associated With Tuberculosis Mortality in the United States, 2009-2013. Public Health Rep. 2017;132(3):366–375.
25. Chung-Delgado K, Guillen-Bravo S, Revilla-Montag A, et al. Mortality among MDR-TB cases: comparison with drug-susceptible tuberculosis and associated factors. PloS One. 2015;10(3):e0119332.
26. Waitt CJ, Squire SB. A systematic review of risk factors for death in adults during and after tuberculosis treatment. Int J Tuberc Lung Dis. 2011;15(7):871–885.
27. Sreeramareddy CT, Qin ZZ, Satyanarayana S, et al. Delays in diagnosis and treatment of pulmonary tuberculosis in India: a systematic review. Int J Tuberc Lung Dis. 2014;18(3):255–266.
28. Needham DM, Foster SD, Tomlinson G, et al. Socio-economic, gender and health services factors affecting diagnostic delay for tuberculosis patients in urban Zambia. Trop Med Int Health. 2001;6(4):256–259.
29. Hussen A, Biadgilign S, Tessema F, et al. Treatment delay among pulmonary tuberculosis patients in pastoralist communities in Bale Zone, Southeast Ethiopia. BMC Res Notes. 2012;5(1):320.
30. Türkkani MH, Özdemir T, Ç Ö. Determination of related factors about diagnostic and treatment delays in patients with smear-positive pulmonary tuberculosis in Turkey. Turk J Med Sci. 2020;50(5):1371–1379.
31. World Health Organization. Epidemiology. Global Tuberculosis Control 2016. Epidemiology, Strategy, Financing. Geneva: WHO Report; 2016 cited 2021 May 12. https://apps.who.int/iris/bitstream/10665/250441/1/9789241565394-eng.pdf
32. Kurtaran B, Nazik S, Ulu A, et al. HIV enfeksiyonu ve tüberküloz birlikteliğinin değerlendirilmesi. Mediterr J Infec Microbes Antimicrob 2015;4:4. (in Turkish.