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Factors associated with survival of tuberculosis patients in Southeast Iran: comparison of stepwise cox regression, survival tree, and random survival forest

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Abstract

Background Understanding the factors associated with survival of tuberculosis (TB) patients is crucial for effective control and prevention efforts. This study aimed to identify the survival factors of TB patients in Iran.

Method A historical cohort study was conducted using data from the Iranshahr (Southeast Iran) Tuberculosis Control Program. Stepwise Cox regression, survival tree analysis, and Random Survival Forest (RSF) models were employed to identify survival predictors. The C-index was used for model comparison.

Result Of the 3429 TB patients (2016–2021), 292 (8.5%) died. Stepwise Cox regression revealed that positive smears after 2 and 3 months of treatment significantly increased mortality risk [HR: 15.44 and HR: 38.28, respectively]. Other factors contributing to a higher risk of death included being a prisoner [HR: 3.8], chest pain [HR: 1.35], and older age [HR: 1.01] ($P < 0.05$). In contrast, having extrapulmonary TB [HR: 0.16], nationality (Afghan or Pakistani) [HR: 0.36], and increased weight [HR: 0.98] reduced the risk of death ($P < 0.05$). RSF analysis identified a positive smear after two months as the most critical variable, followed by age, smear results after three months, weight, and TB type. The stepwise Cox model demonstrated a higher C-index than the RSF model.

Conclusion This study highlights key factors associated with the TB patient survival in the region, urging health policymakers to focus on early diagnosis and treatment optimization, especially for high-risk groups.

Keywords Tuberculosis, Survival model, Random survival forest, Cox regression

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Introduction

Besides being curable in most cases, tuberculosis is a preventable disease. Still, it regained the very undesirable top position of leading killer by any single infectious agent, occupied by COVID-19 for the last three years in 2023. Meanwhile, TB now kills almost a factor of two more than HIV/AIDS. More than 10 million people continue to develop TB every year, with this number having risen since 2021 [1].

In 2023, the battle against TB remained fundamental, with the highest numbers coming from the WHO regions of Southeast Asia, Africa, and the Western Pacific, which accounted for 45%, 24%, and 17%, respectively. An alarmingly smaller percentage was recorded within the Eastern Mediterranean, the Americas, and Europe at 8.6%, 3.2%, and 2.1%, respectively. The 30 countries with the most significant challenges in terms of TB accounted for a staggering 87% of all estimated new cases globally. Of these, only eight countries accounted for more than two-thirds of the global total: India, 26%; Indonesia, 10%; China, 6.8%; the Philippines, 6.8%; Pakistan, 6.3%; Nigeria, 4.6%; Bangladesh, 3.5%; and the Democratic Republic of Congo, 3.1%. As is clear, the top five countries alone contributed an astonishing 56% of the total cases, which speaks volumes about the urgent need for focused public health interventions and resources in these areas [1]. In 2022, the incidence of pulmonary TB with positive sputum smear in Iran was 4.6 cases per 100,000 people, a 17-fold reduction since 1964. Sistan Baluchistan and Golestan provinces had the highest rates, with Sistan Baluchistan reporting an incidence of 37.63% [2].

Studies have identified several risk factors for mortality in TB patients, including male gender, old age, smoking, alcohol consumption, low socioeconomic status, malnutrition, multidrug resistance (MDR), diabetes, low initial weight, extrapulmonary TB, patient category, hepatitis, delayed diagnosis, treatment, and HIV status. These risk factors have been found in studies from China, Malaysia, the UK, and India. These risk factors may vary across populations and settings. Identifying and addressing them can aid TB control efforts and reduce mortality [3–10].

The healthcare system in Iran consists of both public and private providers, with the Ministry of Health and Medical Education central to policy-making and service delivery. However, significant regional disparities exist, particularly in underprivileged areas like Sistan and Baluchistan province [11, 12]. This region confronts considerable challenges, including inadequate healthcare infrastructure, a shortage of medical professionals, and socioeconomic difficulties that worsen health inequalities. As a result, it experiences higher rates of TB incidence and mortality compared to other regions in the country. Understanding this context highlights the need

to address these disparities to improve health outcomes, aligning these findings with broader global health challenges [12, 13]. Iranshahr University of Medical Sciences, located in southeast Sistan and Baluchistan province (the highest TB incidence in Iran), covers 14 counties and serves a population of 1.3 million, with an overall TB incidence of 39.3 per 100,000 in 2022. Numerous global and Iranian studies have examined TB patient survival using various methods [10, 14–18]. This study aims to explore TB survival and related factors in the Baluchistan area, comparing Stepwise Cox regression, survival trees, and Random Survival Forest models.

Method

Study population

This historical cohort study used data from the Iranian National Tuberculosis Control Program, focusing on Iranshahr (southeast Iran, Figure. 1) from 2016 to 2021. Individuals suspected of having TB (persistent cough, unexplained weight loss, night sweats, fever) are referred to specialized TB centers. Iran's surveillance system, following World Health Organization (WHO) guidelines, helps healthcare providers identify and treat TB cases effectively [19].

The tuberculosis control program has been an integral part of Iran's healthcare system for many years, characterized by a structured and interconnected framework [20]. When a patient shows tuberculosis symptoms, the associate and physician work together to document the case at the health center, assessing the type, progression, and treatment classification according to the National Tuberculosis Control Handbook. The prescribing physician determines medication dosages based on established protocols. In rural areas, a Behvarz (health worker) oversees medication intake, while in urban settings, a trained assistant takes on this role. Nurses and doctors also examine individuals near smear-positive TB patients to monitor for potential cases. This protocol applies to smear-negative or extrapulmonary TB, which may be diagnosed by other laboratories; these patients are then referred to a tuberculosis specialist. If a patient refuses to visit the health center after a tuberculosis diagnosis, a standardized file is completed per national guidelines, and key information is recorded in an online database for municipal TB patient registration [21].

Variable's measurement

The Iranian National Tuberculosis Control Program collects a comprehensive set of information on confirmed TB patients. This includes the patient's age at diagnosis, gender (male or female), nationality (Iranian or foreigner), and region of residence (urban or rural). Prison history (yes or no) and patient weight (in kilograms) are recorded, alongside the specific treatment regimen,

which may vary depending on factors such as drug resistance, co-infections, or prior treatments. The results of smear microscopy, a diagnostic test used to detect TB bacteria in sputum samples, categorize patients as smear-positive or smear-negative, which is critical for understanding transmission risk and monitoring treatment. Chest CT scans, used to assess the extent of pulmonary TB, are also collected. The study distinguishes between new, recurrent, or treatment failure cases and classifies TB type as either pulmonary or extrapulmonary. Additionally, the time from the initiation of symptoms to diagnosis and the time from diagnosis to the start of treatment are recorded, as is information on whether the patient was hospitalized. Finally, the patient's outcome is classified as cure, treatment failure, or death [22].

Statistical analysis

To avoid bias, the first step in the analysis was to exclude variables with more than 20% missing values, which is a common practice in data analysis [23].

Cox regression model

The stepwise variable selection method was applied to finalize the Cox regression model. This method uses the Akaike Information Criterion (AIC) to identify the most important variables by sequentially adding or removing them. The Cox regression model operates under the proportional hazards (PH) assumption, which posits that the hazard ratio (the relative risk of an event occurring) remains constant over time for different groups. This means that the impact of each covariate on the hazard rate is assumed to be consistent throughout the study period [24].

Survival tree algorithm

This is a non-parametric method used in survival analysis to create a decision tree model that predicts the survival outcome of an event. The algorithm is used to overcome the instability and overfitting problems of single trees [25]. In this model, the specific split points for continuous variables like weight or age are determined through statistical methods that assess the effectiveness of potential splits. These methods include the log-rank test statistic, which evaluates differences in survival distributions across subgroups, and exponential log-likelihood loss, which measures how accurately the model predicts outcomes [26, 27].

Random survival forest (RSF) algorithm

RSF is a non-parametric machine learning algorithm used to analyze right-censored survival data. It has significant clinical applications, providing objective assessments of variable interactions and ranking their importance automatically. The algorithm uses bootstrap samples from the

original dataset, generating a survival tree for each sample. On average, 37% of the data is excluded from each sample, known as Out-Of-Bag (OOB) data. The Cumulative Hazard Function (CHF) is calculated for each tree, and an ensemble CHF is created by averaging all the trees. The prediction error of the ensemble CHF is then determined using the OOB data. RSF is widely applied in healthcare to predict outcomes, identify disease risk factors, and develop personalized treatment plans. It is also used in finance, engineering, and environmental science [28, 29].

The Cox model is a semi-parametric approach for survival analysis that aims to evaluate the impact of independent variables on the time to a specific event. This model assumes that the hazard ratio influenced by the variables remains constant over time. The significant variables in this model are identified based on their linear relationship with the relative hazard. In contrast, the Random Survival Forest (RSF) model is a non-parametric method that does not rely on the proportional hazard assumption. It can capture complex, nonlinear relationships and interactions among variables. RSF uses an ensemble of decision trees that operate collectively to model survival data [30].

To compare the survival models in this study, the C-index was used, a metric for predictive accuracy where 1 indicates perfect prediction and 0.5 represents random chance [31]. A higher C-index indicates better model accuracy. In addition, t-tests, Chi-square tests, and Fisher's exact tests were applied to compare survivors and non-survivors, with a p-value less than 0.05 considered statistically significant.

Results

Data from 3,429 TB patients in the Baluchistan region of Iran (2016–2021) showed that 292 patients (8.5%) died. Among these, 178 (61%) were men, and the rest were women. Table 1 presents a comparison of the descriptive information for TB patients based on their survival status. The mean age of those who died was 53.87 ± 22.83 years, and their mean weight was 43.4 ± 12.5 kg. In contrast, survivors had a mean age of 43.79 ± 22.25 years and a mean weight of 46.7 ± 21.4 kg, with both differences being statistically significant ($P < 0.05$). The Kaplan–Meier survival curve for the entire population is shown in Fig. 2.

The conditional survival tree of TB patients, displayed in Fig. 3, identifies the most critical factors influencing patient survival. The first key variable is the positive smear result after two months of treatment. Following this, having pulmonary TB and a negative smear result after three months had the most significant effects on survival. Patients with the highest survival rates had negative smear results after two months, no chest pain, and

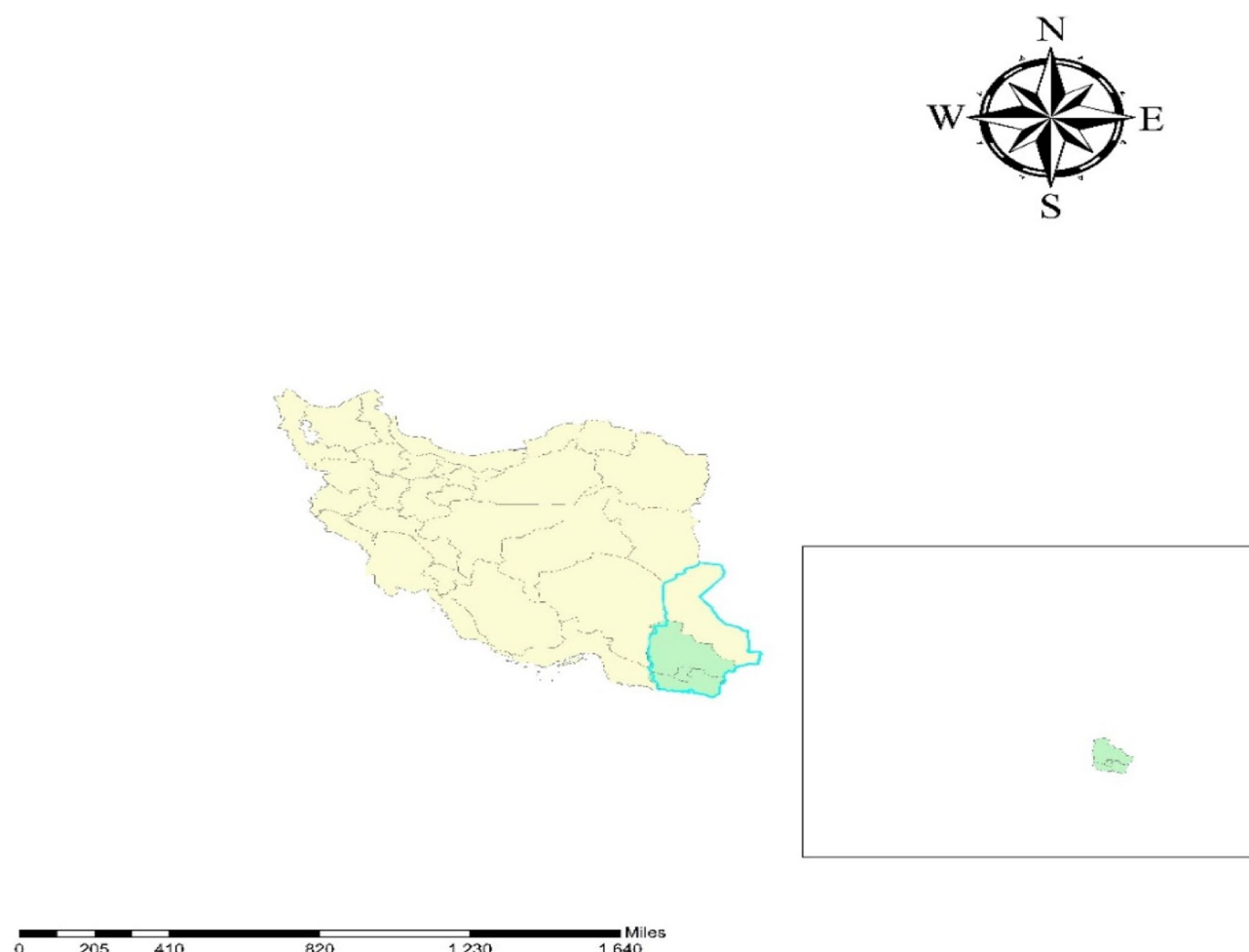


Figure. 1 Shows the location of the study area

negative smear results before treatment. The lowest survival rates were observed in patients with positive smear results after two months of treatment, pulmonary TB, positive smear results after three months, and those aged over 65.

Stepwise cox regression with proportional hazards

The Cox regression results are presented in Table 2, with the last column showing the p-value for the proportional hazard assumption. Since all values are greater than 0.05, the assumption is valid for all variables. Based on the stepwise Cox regression, variables such as place of residence, time from symptom onset to diagnosis, time from diagnosis to treatment, hospitalization, and new case status were removed from the model. The gender variable was also found to be non-significant.

Key findings include a 15.44 times higher hazard of death for patients with a positive smear result after two months of treatment [HR: 15.44, CI: 11.37–20.97, $P < 0.001$], and a 38 times higher hazard for those with a positive smear after three months [HR: 38.28, CI:

9.48–154.67, $P < 0.001$], compared to patients with negative smear results. Tuberculosis patients in prison had three times the hazard of death compared to non-prisoners [HR: 3.85, CI: 1.69–8.80, $P < 0.001$]. In contrast, having extrapulmonary tuberculosis lowered the hazard of death by 83% compared to pulmonary TB [HR: 0.169, CI: 0.11–0.25, $P < 0.001$], while chest pain increased the risk of death by 35% [HR: 1.35, CI: 1.04–1.75, $P = 0.02$]. Foreign TB patients (from Afghanistan and Pakistan) had a 64% lower hazard of death compared to Iranians [HR: 0.36, CI: 0.13–0.97, $P = 0.04$].

Each unit increase in weight reduced the hazard of death by 2% [HR: 0.98, CI: 0.98–0.99, $P < 0.001$], while each additional year of age increased the hazard of death by 1% [HR: 1.015, CI: 1.01–1.02, $P < 0.001$]. The full results for other variables are presented in Table 2.

Random survival forest (RSF)

The most important variable identified by the Random Survival Forest (RSF) model in predicting survival was a positive smear result after two months of treatment,

Table 1 Characteristics of tuberculosis patients based on final status in South Iran from 2016–2021

Variables	Group	Final Status of TB patients		p-value
		Survived N (%)	Dead N (%)	
Sex	Male	1533(48.9%)	178(61%)	< 0.001 ^a
	Female	1604(51.1%)	114(39%)	
Prison	No	3101(98.9%)	286(97.9%)	0.166 ^b
	Yes	36(1.1%)	6(2.1%)	
Nationality	Iranian	3052(97.3%)	288(98.6%)	0.168 ^a
	Not Iranian	85(2.7%)	4(1.4%)	
Region of residence	City	1199(38.2%)	112(38.4%)	0.964 ^a
	Village	1938(61.8%)	180(61.6%)	
Treatment group	Treat1	2886(92%)	253(86.6%)	0.002 ^a
	Treat2	251(8%)	39(13.4%)	
Type of TB	Pulmonary	2537(80.9%)	260(89%)	0.001 ^a
	Extra pulmonary	600(19.1%)	32(11%)	
smear result before treatment	Negative	772(24.6%)	91(31.2%)	0.014 ^a
	Positive	2365(75.4%)	201(68.8%)	
Chest CT imaging	Aggressive	2180(69.5%)	203(69.5%)	0.992 ^a
	No aggressive	957(30.5%)	89(30.5%)	
Smear result after 2-month treatment	Negative	2308(73.6%)	54(18.5%)	< 0.001 ^a
	Positive	829(26.4%)	238(81.5%)	
Smear result after 3-month treatment	Negative	175(5.6%)	2(0.7%)	< 0.001 ^a
	Positive	2962(94.4%)	290(99.3%)	
hospitalization	No	2186(69.7%)	138(47.3%)	< 0.001 ^a
	Yes	951(30.3%)	154(52.7%)	
Age (years)	-	Mean ± SD	Mean ± SD	< 0.01 ^c
		43.79 ± 22.25	53.87 ± 22.83	
Weight (kg)	-	46.7 ± 21.4	43.4 ± 12.5	< 0.01 ^c

Hist: History of; Dis: Disease;

^a Chi-square, ^b Fisher's exact test, ^c Two samples t-test

followed by age, a positive smear result after three months, weight, and the type of tuberculosis (pulmonary or extrapulmonary). Other factors, such as nationality, urbanization, new or recurrent cases, treatment failure, and time from diagnosis to treatment, were found to be less significant (Fig. 4).

The conditional survival tree of TB patients (Fig. 3) also highlighted the positive smear result after two months as the most critical factor influencing patient survival. In the order of variable importance, having pulmonary TB and a negative smear result after three months were the next most significant factors. Patients with the highest survival rates had negative smear results after two months, no chest pain, and negative smear results before treatment. In contrast, the lowest survival rates were observed in patients with positive smear results after two months, pulmonary TB, positive smear results after three months, and those aged over 65.

Comparison of stepwise cox regression model and random survival forest

The Concordance index (C-Index) was used to compare the performance of the stepwise Cox regression model and the Random Survival Forest (RSF) model, as shown in Fig. 5. The C-index ranges from 0 to 1: a C-index of 1.0 indicates perfect concordance, meaning that all pairs are correctly ranked. A C-index of 0.5 suggests no discrimination ability, akin to random predictions. Values below 0.5 indicate worse-than-random predictions.

Both models produced C-Index values higher than the reference value of 0.5, indicating good predictive performance. However, the stepwise Cox regression model demonstrated higher C-Index values compared to the RSF model, suggesting a better overall fit. Despite this, the RSF model accounted for more variables in its predictions. In both models, the two most influential variables affecting patient survival were the positive smear result after two months of treatment and patient age.

Discussion

This study aimed to identify factors associated with tuberculosis (TB) patient survival in the Sistan and Baluchistan region of southern Iran using Cox regression and Random Forest models. By employing both methods, we enhanced the robustness of the analysis, cross-validating the findings and providing a comprehensive understanding of survival-related factors. The Cox regression model highlighted several variables significantly impacting survival, including positive smear results after two and three months, pulmonary TB, chest pain, Iranian nationality, weight, age, and incarceration. The Random Forest model identified positive smear results after two months, age, positive smear results after three months, weight, and TB type (pulmonary or extrapulmonary) as key predictors.

These findings align with previous studies, such as those by Moosazadeh et al., which revealed that smear-positive patients of advanced age have lower survival rates compared to their younger counterparts, despite successfully completing treatment [32, 33]. Delayed diagnosis, comorbidities, and weakened immunity may contribute to higher mortality among older patients, suggesting that age-specific interventions are crucial for improving outcomes [34–37]. These findings highlight the importance of considering age as a key factor in TB management and suggest that tailored interventions are needed to improve outcomes for older patients [38]. Our study further supports the idea that weight loss negatively impacts TB prognosis, consistent with previous research [39]. Weight loss in TB patients is often caused by malnutrition and loss of appetite, which can lead to secondary immunodeficiency and increased susceptibility to infections [34, 35]. Weight loss can also indicate more severe disease, making it an important factor in

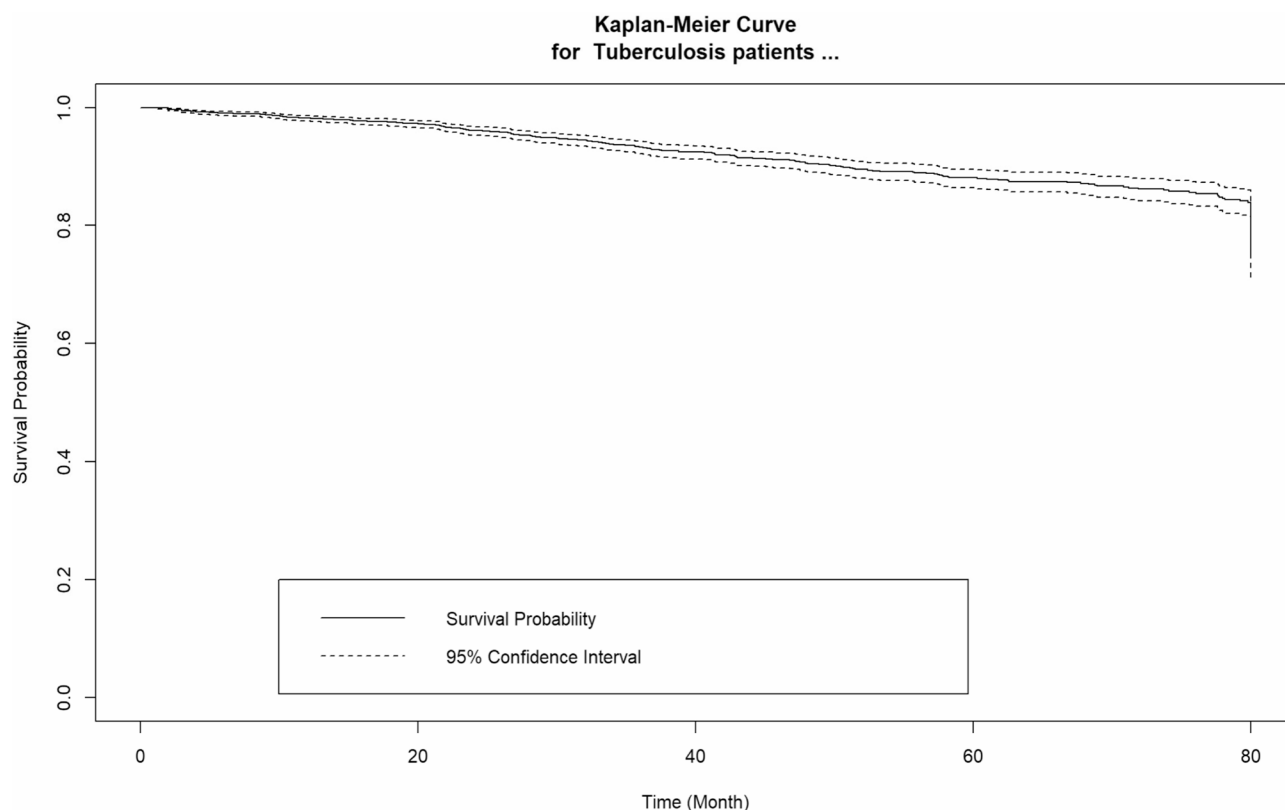


Fig. 2 The Kaplan - Meier curve of the whole TB patients

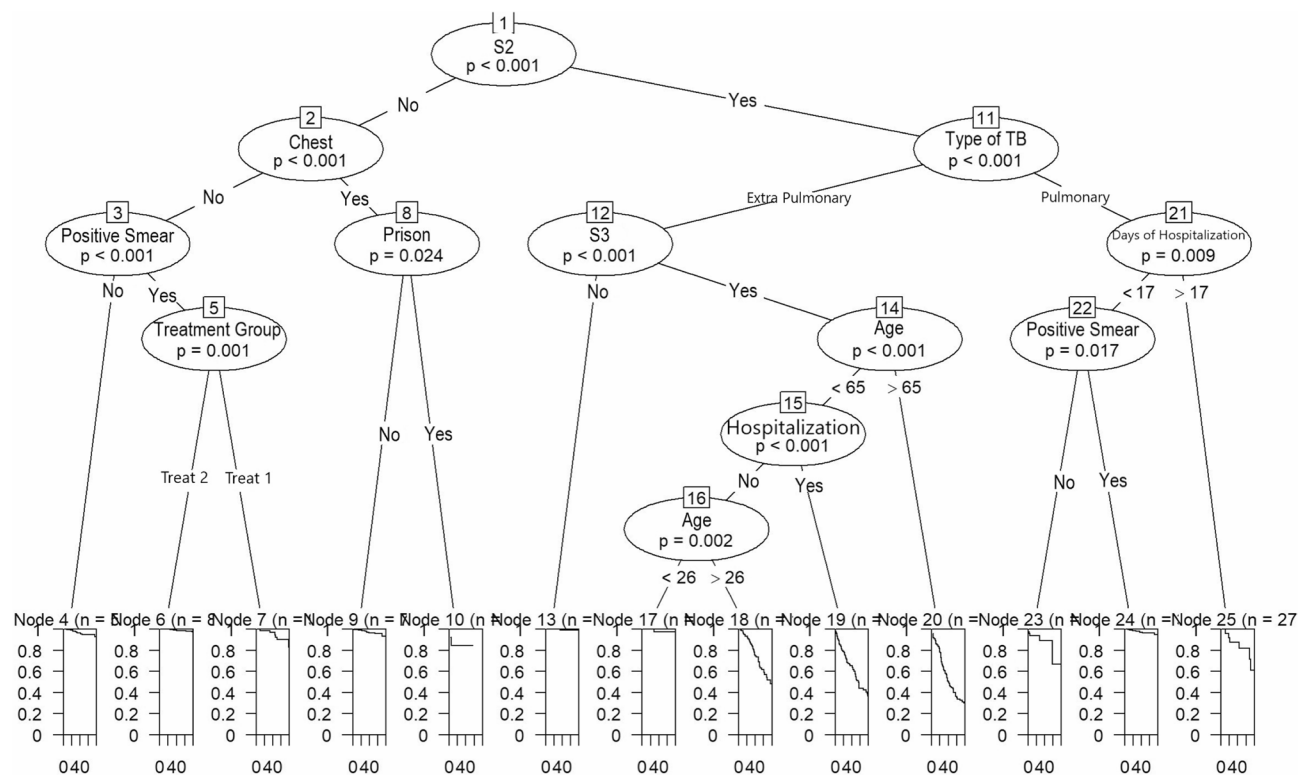


Fig. 3 Conditional survival tree of TB patients in southeast Iran (S2: Smear result after 2-month treatment; Chest: Chest CT imaging; Positive Smear: Positive Smear result before treatment; Treat 1: New Case; Treat 2: Recurrence/Failure Case; S2: Smear result after 3-month treatment;)

Table 2 Summary of Stepwise Cox regression for modeling the TB patients in the Southeast of Iran

Factor	Coefficient	S.E.	HR*	95%CI for HR		p-value	p-value of PH**
				Lower	upper		
Sex	reference	-	-	-	-	0.073	0.18
Female	-0.221	0.123	0.801	0.628	1.020		
Male							
Prison	reference	-	-	-	-	< 0.001	0.90
No	1.348	0.421	3.852	1.686	8.798		
Yes							
Age	0.015	0.002	1.015	1.010	1.020	< 0.001	0.44
Nationality	reference	-	-	-	-	0.042	0.30
Iranian	-1.032	0.509	0.356	0.131	0.966		
Not Iranian							
Weight	-0.016	0.004	0.984	0.975	0.992	< 0.001	0.20
Treatment group	reference	-	-	-	-	0.003	0.77
New case	0.505	0.175	1.658	1.175	2.338		
Recurrence/failure case							
Type	reference	-	-	-	-	< 0.001	0.61
Pulmonary	-1.778	0.199	0.169	0.114	0.249		
Extra pulmonary							
Chest	reference	-	-	-	-	0.02	0.18
Aggressive	0.301	0.132	1.351	1.042	1.751		
No aggressive							
Smear positive after 2 months of treatment	reference	-	-	-	-	< 0.001	0.58
Negative	2.736	0.156	15.43	11.368	20.96		
Positive							
Smear positive after 3 months of treatment	reference	-	-	-	-	< 0.001	0.29
Negative	3.645	0.712	38.28	9.476	154.66		
Positive							
hospitalization No	reference	-	-	1.320	-	< 0.001	0.32
Yes	0.515	0.121	1.674		2.123		
Model						< 0.001	0.57

*Hazard Ratio

**Proportional Hazard

TB prognosis [38, 40, 41]. Previous research has shown that patients with positive sputum smears after two and three months of treatment, as well as those with a positive smear at the end of the second month, have lower survival rates [33, 42]. These facts are corroborated by the results of our study, which indicated that patients who still showed positive smear results even after two or three months of treatment had a significantly higher risk of mortality. This could be due to either drug resistance or immune dysfunction and thus reflects the urgent need for timely intervention and appropriate treatment strategies [43–47]. Additionally, pulmonary TB has been recognized as a significant predictor of lower survival, consistent with the findings of Kazempour et al. [48]. Our study also found that chest pain was linked to lower survival, echoing earlier studies that associated symptoms and disease severity with worse outcomes [47].

Due to the significant amount of missing data on HIV status and drug resistance in this study, we are unable to assess the association between HIV and drug-resistant TB concerning the survival outcomes of TB patients. However, previous studies have established this

association. HIV infection further elevates the mortality risk for individuals with tuberculosis (TB), primarily because those co-infected with HIV often develop a more severe, disseminated form of the disease [49, 50]. Additionally, drug-resistant TB, including both multi-drug-resistant and extensively drug-resistant strains, is associated with poorer outcomes, such as longer treatment durations, higher rates of treatment failure, and an overall increased risk of recurrence [51]. Moreover, incarcerated TB patients exhibited lower survival rates, consistent with past studies conducted in prisons in developing countries, which identified tuberculosis as the leading cause of death [52, 53]. Incarcerated patients face unique challenges, including late diagnosis, inadequate treatment, high rates of HIV co-infection, intravenous drug use, and poor nutrition, which likely worsen outcomes [53, 54].

The present study showed a higher mortality rate among Iranian patients compared to immigrant patients, which contrasts with some reports indicating poorer outcomes among immigrants. Several factors may contribute to this finding and warrant further investigation. For

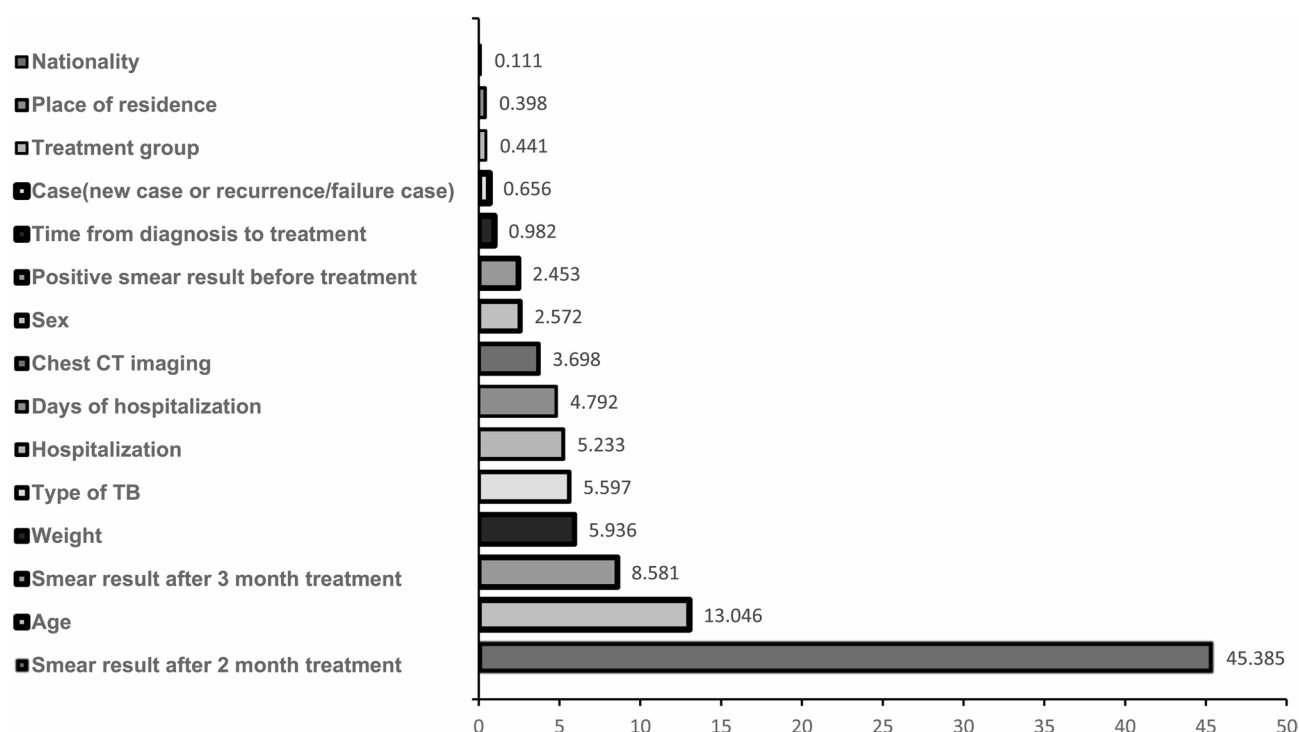


Fig. 4 Random Survival Forest (RSF) algorithm for Variable's importance in survival of TB patients

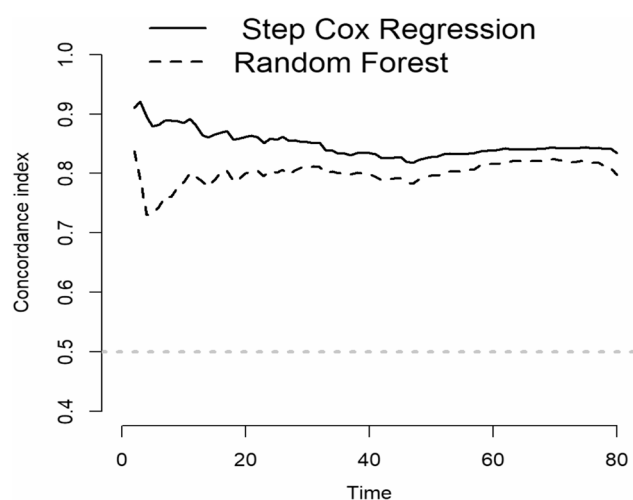


Fig. 5 C-index for comparison Stepwise Cox Regression and Random Survival Forests for modeling the survival of Tb patients in southeast Iran. The C-index ranges from 0 to 1: a C-index of 1.0 indicates perfect concordance, meaning that all pairs are correctly ranked. A C-index of 0.5 suggests no discrimination ability, akin to random predictions. Values below 0.5 indicate worse-than-random predictions

instance, most Afghan migrants to the Islamic Republic of Iran are young, healthy men seeking work, often leaving families behind. This demographic trend may explain the observed age difference, as age is a critical determinant of TB mortality; older patients generally experience worse outcomes due to comorbidities, delayed diagnosis, and immunosuppression [9, 32]. Additionally, the

“healthy worker effect” may also play a role. This phenomenon refers to the fact that migrants are often a self-selected group of healthier and more physically capable individuals who are better suited for work. Those with significant illness or disability are less likely to migrate. This selection bias toward healthier individuals could contribute to the lower TB mortality observed among the immigrant population in this study [55, 56]. Another potential explanation lies in genetic factors. While speculative, Iranian patients may possess distinct genetic characteristics influencing TB progression. Previous studies have shown that genetic variation can impact TB susceptibility and disease progression [57, 58]. Future research should explore the role of genetic variation across populations in shaping clinical outcomes.

Additionally, inequalities in access to healthcare may play a role. Immigrant populations often face barriers such as language challenges, lack of documentation, and fear of deportation, which delay diagnosis and treatment [59, 60]. However, in this context, severely ill Afghan patients may return home to Afghanistan for treatment alongside their families, potentially skewing outcomes. Conversely, Iranian patients, despite better access to health services, may experience higher mortality due to factors such as advanced age, severe illness at presentation, or chronic comorbidities. Future studies should examine comparative access to healthcare and its impact on TB outcomes between Iranian and immigrant populations to better understand these disparities.

Limitations of the study

Several significant limitations must be considered when interpreting the findings of this study. The absence of crucial information on key predictors, such as HIV status and drug resistance, may bias the association between tuberculosis and survival outcomes. Additionally, right-censoring in survival analysis complicates the understanding of mortality rates, particularly if those lost to follow-up differ systematically from those who remain in the study.

Conclusion

In conclusion, this study identifies several factors significantly associated with mortality in tuberculosis (TB) patients, including age, weight loss, prolonged sputum positivity, TB type, chest pain, incarceration, and Iranian nationality. Targeted interventions addressing these factors could improve TB patient outcomes. Early and optimized management is critical, particularly for older patients and those with weakened immunity. Preventing malnutrition and weight loss should be prioritized to maintain immune function. Although Iranian nationality was linked to higher mortality, the underlying causes require further investigation.

Overall, this study provides valuable insights into the determinants of TB patient survival in the region. By addressing these factors, healthcare providers can develop more effective strategies for prompt diagnosis, optimized treatment, and mortality reduction, especially for high-risk groups. Improved management of vulnerable patients could significantly enhance survival outcomes.

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Authors' contributions

MSH and MT: providing the main idea of study and methodology, SN and FR, AZ and JD: developing the idea and writing the manuscript, MSH, MT, MKH, and N B: revising the final manuscript. All authors approved the final version of the manuscript that is submitted.

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Data availability

Data can be inquired from the corresponding author.

Declarations

Ethics approval and consent to participate

This study was performed according to the ethical guidelines expressed in the Declaration of Helsinki and the Strengthening of the Reporting of Observational Studies in Epidemiology (STORB) guideline. The study was also approved by the Research Ethics Committee of Fasa University of Medical Sciences (ID:402042).

This is a retrospective cohort study and informed consent was waived by the Research Ethics Committee of Fasa University of Medical Sciences [ID: IR.FUMS.REC.1402.066].

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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