**Health Science Monitor**
2024; 3(1): 39-47
Published online (http://hsm.umsu.ac.ir)

Original Article

# Evaluation of the time-dependent effects of factors influencing the hazard of disease recurrence in tuberculosis patients

**Mehdi Kazempour Dizaji [1,2*], Mohammad Varahram [1], Atefe Abedini [3], Rahim Roozbahani [4], Ali Zare [2], Payam Tabarsi[4], Majid Marjani [4], Afshin Moniri [4], Niloufar Alizadeh Kolahdozi [2], Mohammadreza Madani [3], Parvaneh Baghaei Shiva [4]**

[1] *Mycobacteriology Research Center (MRC), National Research Institute of Tuberculosis and Lung Disease (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran*

[2] *Department of Biostatistics, National Research Institute of Tuberculosis and Lung Disease (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran*

[3] *Chronic Respiratory Diseases Research Center, National Research Institute of Tuberculosis and Lung Disease (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran*

[4] *Clinical Tuberculosis and Epidemiology Research Center, National Research Institute of Tuberculosis and Lung Disease (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran*

***Corresponding author:** Mehdi Kazempour Dizaji, **Address**: Mycobacteriology Research Center (MRC), National Research Institute of Tuberculosis and Lung Disease (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran
**Email**: mkazempour@sbmu.ac.ir, **Tel**: +98-21 27122080

## Abstract

***Background & Aims*:** There are variables whose influence on the risk of tuberculosis (TB) recurrence change over time. Therefore, this study aimed to assess the time-dependent effects of these variables on the hazard of TB recurrence.

***Materials & Methods*:** In this historical cohort study, data were collected from 4,564 TB patients who were referred to the TB research center of Dr. Masih Daneshvari Hospital, Tehran, from 2005 to 2015, in order to evaluate factors affecting the hazard of TB recurrence in terms of time dependency or time constancy. Data were analyzed in STATA 14 software using a statistical test based on Schoenfeld residuals, the time-dependent effects method, and the time-varying effects model (considering time function as f (t) = t).

***Results*:** The results showed that only the impact of the variables of drug adverse effects and passive smoker were inconstant over time and had time-dependent effects, and they also influenced the hazard of TB recurrence. Also, the effect of the two mentioned variables on the hazard of TB recurrence displayed a decreasing and increasing trend with time, respectively.

***Conclusion*:** Using the time-varying effects model in the study of the hazard of TB recurrence allows evaluating the time-dependent effects of the studied variables and also can differentiate them from the time-independent variables.

***Keywords*:** Recurrence, Time-dependent effects, Time-varying effects model, Tuberculosis

**Received 25 December 2022; accepted for publication 01 February 2023**

## Introduction

Recurrence of tuberculosis (TB) is the reappearance of this disease in a person who appears to be cured. Patients who take their medicine on a daily basis and complete their treatment plan have a very low chance of recurrence. Therefore, these patients do not need follow-up after ending the treatment period (1-2). Recurrence of the disease often occurs within the first few years after the treatment ending and is generally accompanied by clinical symptoms; hence, patients should be treated in shortest time possible following symptoms recurrence (1,3). Clinical trials have shown that the quality of care provided for patients and the treatments considered by physicians have a significant impact on the recurrence of TB.

TB recurrence can generally be classified into three categories: relapse (patients who have previously been cured but have recently presented with positive sputum), treatment failure (patients who have positive sputum after five months of taking medication or have become positive after being negative during this period of treatment), and absence of treatment (patients who have stopped taking their medication) (1,4). The main causes of TB recurrence are incomplete treatment, misdiagnosis, voluntary discharge, nosocomial infection, temporary discharge, and disease complications (5-7). However, there is a wide range of individual, demographic and clinical characteristics of patients that can be effective in the disease recurrence and the failure of treatment strategies (1-4, 8). Despite comprehensive research on TB and its recurrence, the mentioned causes have received little attention (2-3, 9).

The effect of variables on the risk of TB recurrence are divided into two categories in terms of changes over time, constant (time-independent) and inconstant (time-dependent) variables. In most studies related to TB recurrence, data analysis has been designed assuming that the effects of the influencing factors are constant over time (10-12, 6). In the absence of this assumption for some variables, the estimates obtained from the study are erroneous. Researchers have paid more attention to the impact of the time-independent variables on TB recurrence due to its simplicity in the clinical interpretention (12). However, it should be noted that the lack of attention to the time-dependent effects of the studied variables can create a clinically incomplete understanding of the mechanism of the hazard of TB recurrence (13-15). Failure to consider the time-dependent variables related to TB recurrence will not only lead to inaccurate inferences about TB but also deprive researchers of the possibility of careful studying the behavior of time-dependent effects of related variables in the recurrence of TB (13-15).

Various statistical methods have been designed to study the effect of variables on different events such as TB recurrence. The Cox regression model is one of the most common of these statistical approaches (1, 8, 16-18). Another method is time-varying effects model, a generalization of the Cox regression model, which studies the time-dependent effects of the studied variables (15, 19-20). The model time-varying effects allows researchers not only to study the time-dependent effects of the studied variables but also to distinguish time-independent from time-dependent variables (13, 15, 20). In this method, by creating a series of interactive factors that includes the interaction between the desired variables and a function of time could fit a model for time-dependent variables (this function f (t) can be in the form of $\ln(t), \sqrt{t}, t, \ldots$) (15, 19, 20).

Studying the time-dependent effects for the hazard of TB recurrence can accurately reveal the time dependence, as well as how risk factors influence it. For instance, suppose the AIDS variable has an incremental effect on the TB recurrence over time. According to the fixed effects model, there is no obvious difference in the risk of TB recurrence between a patient who has had AIDS for one year and a patient who has had AIDS for five years in terms of the risk of TB recurrence. In this model, no relationship exists between the variables AIDS and time, and it is not the same as the time-dependent effects model. Based on this model, a patient with a five-year history of AIDS is more likely to have TB recurrence than a patient with a one-year history of AIDS. As a result, to better understand TB recurrence and the influence of related factors, the effects of factors related to the hazard of TB recurrence overtime must be taken into consideration. Thus, the present study was aimed to evaluate the time-dependent effects of factors affecting the hazard of disease recurrence in TB patients who referred to the Tuberculosis and Lung Diseases Research Center of Dr. Masih Daneshvari Hospital, Tehran, Iran.

.

## Materials & Methods

This retrospective cohort study was conducted in Dr. Masih Daneshvari Hospital from 2005 to 2015. The data of this study were obtained from the medical records of 4,564 TB patients who referred to and were treated by the National Institute of TB and Lung Disease Research Center of this hospital. These patients were studied after treatment and recovery, and the disease recurrence was considered the study event based on sputum culture and the clinical physician's opinion. Patients' information was collected to follow their status until the disease recurrence. The last follow-up of the patients who were discharged without a history of recurrence was carried out through a telephone contact. Patients without disease recurrence until the end of the study and after that (no information was available about them) and patients whose information was complete until the end of the study and indicated no disease recurrence were censored.

In the present study, the impact of factors such as gender, age, marital status, education level, residency area, nationality, family size, medicine adverse effects, smoking, exposure to secondhand smoke (passive smoker), history of drug use, contact with a TB patient, imprisonment, pulmonary and extra-pulmonary TB, diabetic mellitus, HIV-positive, and comorbidities was assessed for the hazard of TB recurrence in terms of time dependency or time constancy. All the data were analyzed in STATA 14 software using a statistical test based on Schoenfeld residuals, the time-dependent effects method, and the time-varying effects model (considering time function as f (t) = t). A level of 5% was considered as statistically significant.

## Results

This study was performed on 4,564 TB patients, of which 166 (3.64%) patients experienced a recurrence of the disease as the desired event after treatment during the study, and 4,398 (96.36%) patients were considered as censored. According to our findings, the majority of the patients were married and illiterate, lived in urban areas, and were Iranian nationals. A small percentage of patients had a history of smoking, drug use, contact with TB patient, imprisonment, and cigarette smoke.

As per the results of the study, most of the patients had pulmonary TB, with only a small percentage having extra-pulmonary TB. In addition, a small percentage of patients in this study had a history of diabetes, AIDS, and comorbidities such as cancer, liver disorders, and so on. Furthermore, the patients' conditions were almost the same in terms of gender variables and medicines adverse effects during the study. The findings of this study also revealed that the age distribution of patients, with an average of about 52 years, was almost similar. The variable household number, with an average of about four people, was also the same (Table 1).

**Table 1.** Descriptive analysis of individual, demographic and clinical variables of TB patients

| Factors | Category | N (%) | Mean (SD) |
|---|---|---|---|
| Gender | Female<br>Male | 2282 (50.00)<br>2282 (50.00) | |
| Age | - | - | 51.78 (21.47) |
| Marital Status | Single<br>Married<br>Widow<br>Divorced | 914 (20.04)<br>2933 (64.32)<br>606 (13.29)<br>107 (2.35) | |
| Education | Illiterate | 2119 (46.46) | |

| Factors | Category | N (%) | Mean (SD) |
|---|---|---|---|
| | Primary | 914 (20.04) | |
| | Secondary | 743 (16.29) | |
| | High School | 558 (12.23) | |
| | Higher education | 227 (4.98) | |
| Residency area | Rural | 790 (17.33) | |
| | Urban | 3768 (82.67) | |
| Nationality | Iranian | 3623 (79.38) | |
| | Non-Iranian | 941 (20.62) | |
| Family size | - | - | 3.81 (2.10) |
| Adverse effect | No | 2241 (49.10) | |
| | Yes | 2323 (50.90) | |
| Smoker | No | 3239 (71.64) | |
| | Yes | 1282 (28.36) | |
| Passives smoker | No | 3953 (90.13) | |
| | Yes | 433 (9.87) | |
| Drug user | No | 3585 (79.26) | |
| | Yes | 938 (20.74) | |
| TB contact | No | 3706 (81.20) | |
| | Yes | 858 (18.80) | |
| Imprisoned | No | 4212 (92.29) | |
| | Yes | 352 (7.71) | |
| Pulmonary TB | No | 426 (9.34) | |
| | Yes | 4135 (90.66) | |
| Extra-pulmonary | No | 3816 (83.67) | |
| | Yes | 745 (16.33) | |
| Diabetic mellitus | No | 3712 (81.33) | |
| | Yes | 852 (18.67) | |
| HIV positive | No | 4317 (94.59) | |
| | Yes | 247 (5.41) | |
| Co morbidities | No | 3259 (71.41) | |
| | Yes | 1305 (28.59) | |

In the present study, a Schoenfeld residuals test was used to evaluate and detect variables with constant-over-time effects and with time-varying effects. Based on the results of this test, only the variables of drug adverse effect and exposure to cigarette smoke (passives smoker) had time-dependent effects among the study variables, while the effect of other variables was not time-dependent (Table 2). In addition, studying the results of the time-varying effects model, which is one of the generalizations of the Cox model in the absence of the assumption of fixed effects, showed that only variables of drug adverse effect and passives smoker were among the factors affecting the hazard of TB recurrence. The results of this model also exhibited that the variables drug adverse effects (β = -0.34) and passives smoker (β = -0 / 72) had a decreasing effect on the hazard of TB recurrence. However, the effects of these variables on the hazard of disease recurrence were inconstant over time and based on the function varied with time. According to the time-varying effects model, the drug adverse effects showed a decreasing trend (β = -0/20), and the effect of the passive smoker variable indicated an increasing trend (β = 0.08) on the hazard of TB recurrence. The results of this model reflected that the variables drug adverse and passive smoker effects decreased and increased the hazard of TB recurrence by exp (-0/34 + (-0/20 × t) and exp (-0/72 + (-0/08 × t) per unit time, respectively. The variables drug adverse effects and cigarette smoke exposure reduced the hazard of TB recurrence by 0.26 times and 0.72 times in the first five years and by 0.58 times and 0.53 times in the first year after treatment, respectively. As a result, the effects of the two above-mentioned variables, i.e. cigarette smoke exposure and drug adverse effects, compared to the initial times after treatment showed an increasing and decreasing trend, respectively, over time (Table 3). To better understand the effect of time-dependent changes in both aforesaid variables on the hazard of TB recurrence, we plotted these changes for each variable. According to Figure 1, while both variables reduced the hazard of TB recurrence, the trend of their effect was different.

**Table 2.** Assessment of time-dependent or time-fixed effects of variables for hazard of recurrence in TB patients

| Factor | Estimation | P-value |
|---|---|---|
| Gender | 0.11 | 0.24 |
| Age | 0.04 | 0.61 |
| Marital status | 0.01 | 0.88 |
| Education | -0.15 | 0.14 |
| Residency area | -0.11 | 0.26 |
| Nationality | -0.05 | 0.68 |
| Family size | -0.01 | 0.92 |
| Adverse effect | -0.22 | 0.03 |
| Smoker | 0.02 | 0.62 |
| Passives smoker | 0.46 | < 0.005 |
| Drug user | 0.05 | 0.60 |
| TB contact | 0.15 | 0.12 |
| Imprisoned | -0.16 | 0.07 |
| Pulmonary TB | 0.05 | 0.67 |
| Extra-Pulmonary | -0.10 | 0.34 |
| Diabetic mellitus | -0.12 | 0.17 |
| HIV positive | 0.08 | 0.47 |
| Comorbidities | -0.09 | 0.33 |

**Table 3.** Results of time-varying effect model for assessing the effect different factors on the hazard of recurrence in TB patients.

| Factor | Category | $\beta$(SE) | P-value | 95% Confidence interval |
|---|---|---|---|---|
| Time-fixed effects | | | | |
| Gender | Male/female | -0.11 (0.22) | 0.62 | (-0.54, 0.32) |
| Age | - | 0.00 (0.01) | 0.90 | (-0.01, 0.01) |
| Marital status | Married/single<br>Widow/single<br>Divorced/single | -0.27 (0.26)<br>-0.60 (0.41)<br>0.50 (0.39) | 0.29<br>0.14<br>0.19 | (-0.78, 0.23)<br>(-1.40, 0.20)<br>(-0.2 , 1.27) |
| Education | Primary/illiterate<br>Secondary/illiterate<br>High School/illiterate<br>Higher education/ Illiterate | 0.11 (0.23)<br>0.17 (0.27)<br>-0.27 (0.33)<br>-0.35 (0.47) | 0.63<br>0.54<br>0.41<br>0.46 | (-0.34, 0.57)<br>(-0.36, 0.70)<br>(-0.92, 0.37)<br>(-1.27, 0.57) |
| Residency area | Urban/rural | 0.05 (0.23) | 0.82 | (-0.40, 0.51) |
| Nationality | Non-Iranian/Iranian | 0.32 (0.28) | 0.25 | (-0.22, 0.86) |
| Family size | - | 0.03 (0.04) | 0.51 | (-0.05, 0.11) |
| Adverse effect | Yes/no | -0.34 (0.24) | 0.15 | (-0.81, 0.12) |
| Smoker | Yes/no | 0.45 (0.25) | 0.07 | (-0.04, 0.94) |
| Passives smoker | Yes/no | -0.72 (0.46) | 0.12 | (-1.62, 0.19) |
| Drug user | Yes/no | 0.37 (0.26) | 0.15 | (-0.14, 0.87) |
| TB contact | Yes/no | -0.04 (0.21) | 0.85 | (-0.45, 0.37) |
| Imprisoned | Yes/no | -0.66 (0.43) | 0.13 | (-1.51, 0.19) |
| Pulmonary TB | Yes/no | -0.10 (0.53) | 0.85 | (-1.14, 0.94) |
| Extra-pulmonary TB | Yes/no | -0.80 (0.43) | 0.06 | (-1.64, 0.03) |
| Diabetic mellitus | Yes/no | -0.05 (0.24) | 0.82 | (-0.53, 0.42) |
| HIV positive | Yes/no | -0.10 (0.36) | 0.77 | (-0.82, 0.61) |
| Co morbidities | Yes/no | -0.01 (0.21) | 0.95 | (-0.43, 0.40) |
| Time-dependent effects | | | | |

| | | | | |
|---|---|---|---|---|
| Adverse effect | Yes/no | -0.20 (0.08) | 0.01 | (-0.35, -0.04) |
| Passives smoker | Yes/no | 0.08 (0.03) | 0.02 | (0.01, 0.14) |
| Imprisoned | Yes/no | 0.24 (0.12) | 0.06 | (-0.01, 0.48) |

Variables in time-dependent effect part interacted with f (t) =t

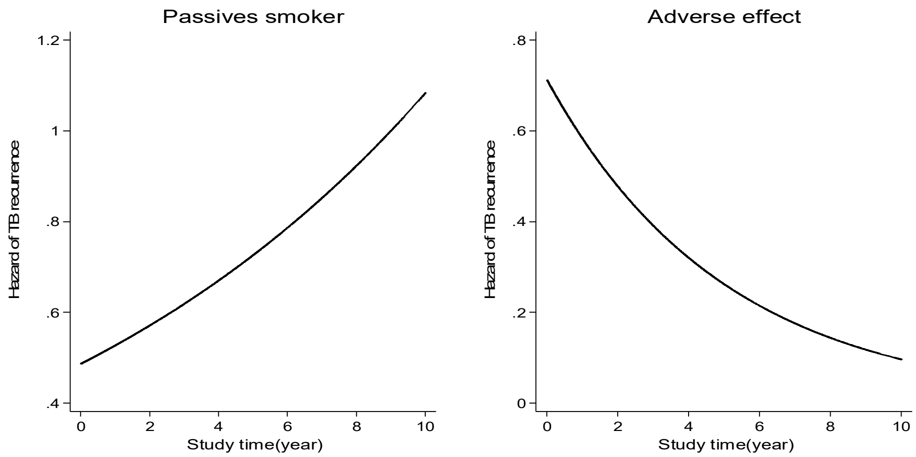


**Fig. 1.** Trend of time-dependent effects of adverse effect and passive smoker on the hazard of TB recurrence

## Discussion

In many studies that assess the factors influencing the time until the occurrence of a particular event, such as TB recurrence, it is assumed that the effect of variables on the hazard of disease recurrence is constant over time and does not change during the study period. According to this hypothesis, if the results show that some variables affect the hazard of TB recurrence, this effect is constant over time and does not change. In other words, no dependence is considered between the desired variables and time. This assumption is correct when the studied variables have constant effects on time, and their effect on the hazard of TB recurrence is not time-dependent. However, if the effect of these variables is not constant over time and, for example, shows an increasing or decreasing trend over time, it is clear that ignoring this issue can lead to an incomplete and ambiguous understanding of the effect of factors influencing the hazard of TB recurrence.

Despite numerous studies conducted on TB so far, there is no comprehensive information on how factors affect TB recurrence (1-4, 8). The failure to pay attention to time-dependent effects, as well as the use of time-fixed effects models because they are easier to interpret clinically; it has obscured the mechanism of factors affecting the hazard of TB recurrence (1-4, 7, 16, 21, 22). In addition, the misunderstanding of how factors influence the hazard of TB recurrence has made the recurrence issue a public health problem in TB control (8, 23, 24). Unfortunately, most statistical models are designed on the assumption that the effects of the variables being studied are constant, making it impossible to study and evaluate how variables affect events like TB recurrence over time (13, 15, 17, 25). Time-varying effects model is a method considered for studying the time-dependent effects of the studied variables (15, 19-20). This model can identify variables with variable effects over time and allows researchers to evaluate the process of changing the effects of these variables over time (13, 15, 20).

Based on the time-varying effects model, we designed and performed this study to investigate the time-dependent effects of factors influencing the hazard of TB recurrence. According to the results, only drug adverse effects and cigarette smoke exposure had time-dependent effects among a wide range of individual, demographic, and clinical variables. The Schoenfeld residuals test indicated that the effects of these variables on the hazard of TB recurrence did not remain constant over time and changed throughout the study (Table 2). The results of time-varying effects model also revealed that only the two above-mentioned variables were effective on the hazard of TB recurrence (Table 3). Moreover, both variables reduced the risk of TB recurrence, but the process of changing their effects varied with time. For patients with drug adverse effects and cigarette smoke exposure, TB was less likely to recur than in other patients. However, as shown in Figure 1, this trend decreased during the study period for the former variable and increased for the second variable. In this regard, the variable drug adverse effects reduced the hazard of TB recurrence by 0.58 times in the first year, by 0.26 times in the fifth year, and about 10.10 times in the 10th year after treatment. For the cigarette smoke exposure variable, these changes were different. The study findings revealed that secondhand smoke exposure reduced the hazard of TB recurrence by approximately 53.5 times in the first year and 0.72 times in the fifth year after treatment, but increased the hazard of TB recurrence by 1.08 times in the 10th year after treatment.

The findings of this study demonstrated that the variable drug adverse effects always reduced the hazard of TB recurrence, with only the severity of this reduction decreased over time. While the variable cigarette smoke exposure reduced the hazard of TB recurrence in the short term, it had a devastating effect on the patient and increased the hazard of TB recurrence in the long term. Thus, if researchers study the two above-mentioned variables without considering the time-varying effects, they could only conclude that these variables influence the hazard for TB recurrence as reducing or increasing factors; however, they are unable to assess how these variables affect the hazard for the recurrence of TB (13-15). This problem exists in most studies on TB and the factors influencing events such as recurrence, death, and so on. Hence, researchers should consider the possibility of assessing the trend of the variables' impacts with time-dependent effects in these studies, in addition to identifying and separating variables with fixed and variable effects with time. Because researchers are ignoring the time-dependent effects of the studied variables, many clinical aspects associated with TB patients are out of reach.

## Conclusion

The use of the time-varying effects model in the study of TB recurrence not only allows researchers to assess the time-dependent effects of the studied variables but also allows them to differentiate variables with fixed and time-varying effects. As a result, this model can provide a better understanding of the mechanism of variable effect in order to control and reduce the incidence.


## Acknowledgments

None declared.

## Conflict of interest

The authors have no conflict of interest in this study.

## Funding/support

None declared.


## Data availability

The raw data supporting the conclusions of this article are available from the authors upon reasonable request.

## Ethical statement

This research was conducted in accordance with ethical principles.

## References


1. Sevim T, Doganay M, Kilic A, Aksoz S, Aygun G, Karsligil T, et al. Treatment outcome of relapse and

defaulter pulmonary tuberculosis patients. Int J Tuberc Lung Dis. 2002 Apr;6(4):320-5.

2. Farley JE, Ram M, Pan W, Waldman S, Cassell GH, Chaisson RE, et al. Outcomes of multi-drug resistant tuberculosis (MDR-TB) among a cohort of South African patients with high HIV prevalence. PLoS One. 2011 Jul 6;6(7):e20436. https://doi.org/10.1371/journal.pone.0020436
3. Pietersen E, Ignatius E, Streicher EM, Mastrapa B, Padanilam X, Pooran A, et al. Long-term outcomes of patients with extensively drug-resistant tuberculosis in South Africa: a cohort study. Lancet. 2014 Apr 5;383(9924):1230-9. https://doi.org/10.1016/S0140-6736(13)62675-6
4. Salaniponi FML, Nyirenda TE, Kemp JR, Squire SB, Godfrey-Faussett P, Harries AD. Characteristics, management and outcome of patients with recurrent tuberculosis under routine programme conditions in Malawi. Int J Tuberc Lung Dis. 2003 Oct;7(10):948-52.
5. World Health Organization. Global tuberculosis control: WHO report 2010. Geneva: World Health Organization; 2010.
6. Quy HT, Lan NTN, Borgdorff MW, Grosset J, Linh PD, Tung LB, et al. Drug resistance among failure and relapse cases of tuberculosis: is the standard re-treatment regimen adequate? Int J Tuberc Lung Dis. 2003 Jul;7(7):631-6.
7. World Health Organization. Anti-tuberculosis drug resistance in the world: third global report. Geneva: World Health Organization; 2004.
8. World Health Organization. Tuberculosis Fact sheet N°104 [Internet]. Geneva: World Health Organization; 2015.
9. Kazempour-Dizaji M, Bahrampour A, Nasehi M, Tabarsi P, Mansouri D. Estimation of Ten-Year Survival of Patients with Pulmonary Tuberculosis Based on the Competing Risks Model in Iran. Tanaffos. 2016;15(1):37-44.
10. World Health Organization. Global tuberculosis report. Geneva: World Health Organization; 2015. 204 p.
11. Diacon AH, Pym A, Grobusch MP, de los Rios JM, Gotuzzo E, Vasilyeva I, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. N Engl J Med. 2014 Aug 21;371(8):723-32. https://doi.org/10.1056/NEJMoa1313865
12. Mansoori SD, Asefzadeh S, Nasseri-Moghaddam S, Kamalzadeh N. Comparative study of initial and acquired drug resistance in pulmonary tuberculosis. Rev Int Serv Sante Forces Armees. 2003;76(1):45-9.
13. Mirsaeidi SM, Tabarsi P, Baghaei P, Ebrahimi G, Mansouri D, Masjedi MR, et al. Treatment of multiple drug-resistant tuberculosis (MDR-TB) in Iran. Int J Infect Dis. 2005 Nov;9(6):317-22. https://doi.org/10.1016/j.ijid.2004.09.012
14. Wright A, Zignol M. Anti-tuberculosis drug resistance in the world: fourth global report: the world health organization/international union against tuberculosis and lung disease (who/union) global project on anti-tuberculosis drug resistance surveillance, 2002-2007. Geneva: World Health Organization; 2008.
15. Mirsaeidi MS, Tabarsi P, Ebrahimi G, Mansouri SD, Masjedi MR, Velayati AA. Trends of drug resistant Mycobacterium tuberculosis in a tertiary tuberculosis center in Iran. Saudi Med J. 2007 Apr;28(4):544-50.
16. Akl A, Ismail AM, Ghoneim MA. Prediction of graft survival of living-donor kidney transplantation: nomograms or artificial neural networks? Transplantation. 2008 Nov 15;86(9):1401-6. https://doi.org/10.1097/TP.0b013e31818b221f
17. Corbett EL, Marston B, Churchyard GJ, De Cock KM. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. Arch Intern Med. 2003 May 12;163(9):1009-21. https://doi.org/10.1001/archinte.163.9.1009
18. World Health Organization. Global tuberculosis control: surveillance, planning, financing. Geneva: World Health Organization; 2008.
19. Velayati AA, Masjedi MR, Farnia P, Tabarsi P, Ghanavi J, Ziazarifi AH, et al. Emergence of new forms of totally drug-resistant tuberculosis bacilli: super extensively drug-resistant tuberculosis or totally drug-resistant strains in Iran. Chest. 2009 Aug;136(2):420-5. https://doi.org/10.1378/chest.08-2427
20. Leprosy AKSV. Tuberculosis situation in Iran 2015. Tehran: Infectious Diseases Management Center -

Ministry of Health, Treatment and Medical Education; 2015.

21. Chi C-L, Street WN, Wolberg WH. Application of artificial neural network-based survival analysis on two breast cancer datasets. AMIA Annu Symp Proc. 2007 Oct 11:130-4.
22. Yegnanarayana B. Artificial neural networks. New Delhi: PHI Learning Pvt. Ltd.; 2009.
23. LaFaro RJ, Ahmed M, Baribeau Y, Mackenzie GS, Martin TD, Engoren M, et al. Neural network prediction of ICU length of stay following cardiac surgery based on pre-incision variables. PLoS One. 2015 Dec 22;10(12):e0145395. https://doi.org/10.1371/journal.pone.0145395
24. World Health Organization. Global tuberculosis control: epidemiology, strategy, financing: WHO report 2009. Geneva: World Health Organization; 2009.
25. World Health Organization. TB/HIV: a clinical manual. 2nd ed. Geneva: World Health Organization; 2004.