Health Science Monitor
2023; 2(2): 90-98
Published online (http://hsm.umsu.ac.ir)

Original Article

Prediction of multidrug-resistant tuberculosis in tuberculosis patients using perceptron artificial neural networks model

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

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

[4] *Chronic Respiratory Diseases 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**: +9821 27122080

Abstract

***Background & Aims*:** Diagnosis and treatment of patients with multidrug-resistant tuberculosis (MDR-TB) are very important. Hence, it is necessary to predict and diagnose these patients based on individual, demographic and clinical characteristics before starting treatment. This study aimed to predict MDR-TB in TB patients using the perceptron artificial neural networks (ANNs) model.

***Materials & Methods*:** This retrospective cohort study was conducted on 1,050 TB patients who have been treated in Masih Daneshvari Hospital, Tehran, Iran from 2005 to 2015. Data on personal and demographic information, as well as medical data such as drug therapy, final outcome of treatment, and the diagnosis of MDR-TB, were collected from the patients' medical records.

***Results*:** The results of this study indicated that the predictive power of MDR-TB for both training and testing groups was 85% and 80%, respectively. Also, the variables of marital status, education, drug use, being imprisoned, extrapulmonary TB, history of comorbidities, AIDS, patients' age, and family size were identified as very effective factors. However, variables of residence, smoking history, contact with a TB person, pulmonary TB, drug side effects, nationality, and diabetes were found as effective factors in predicting the development of MDR-TB.

***Conclusion*:** Application of the perceptron ANNs model in the study of MDR-TB is able to create new horizons in the diagnosis of these patients due to high predictive accuracy.

***Keywords*:** Artificial neural networks, Perceptron, Tuberculosis, Multidrug-resistant tuberculosis.

Received 15 December 2022; accepted for publication 02 January 2023

Introduction

Today, tuberculosis (TB) disease remains one of the world's major health issues, despite the discovery of the disease agents, vaccines, and effective medications. The basis of treatment for TB relies on drug therapy (1-2). Without treatment, 25% of patients will die within two years, 50% within five years, and 25% will recover spontaneously (5-3). With drug therapy based on antibiotic susceptibility testing for each individual, 8% of patients die during treatment, 90% recover, and only 2% have a positive sputum smear at the end of treatment and are considered patients with multidrug-resistant tuberculosis (MDR-TB) (2-3). The development of MDR-TB is the result of inappropriate or single-drug therapy due to incorrect prescription or incomplete use of the drug by the patient. Anti-TB-resistant strains are caused by a point mutation in the Mycobacterium gene that occurs sparingly but predictably.

The MDR-TB is divided into two types, primary and secondary. The primary type occurs in a person who has no previous history of anti-TB treatment, but the second type occurs as a result of inappropriate treatment. Low initial resistance and resistance to isoniazid are more common in North America and Europe (6). In the U.S., although the primary resistance to isoniazid has remained stable at 7% to 8% in recent years, the rate of MDR-TB has dropped from 2.5% to 1%. Globally, MDR-TB has become a major problem in some areas, especially in Russia and regions of Asia (6). The World Health Organization (WHO) estimated the prevalence of MDR-TB to be about 4.6% in the Eastern Mediterranean region. The MDR-TB prevalence was rated for 85.9% in Uzbekistan and up to 84.8% in Azerbaijan. According to some reports, the prevalence of MDR-TB was estimated at about 5% in Iran, and approximately 78% of Iranian patients with a previous history of TB treatment cases had at least one drug resistance (7).

Due to the problems in the diagnosis and treatment of patients with MDR-TB, prediction and diagnosis of these patients before starting treatment based on individual, demographic and clinical characteristics are of great importance. Despite the promising reports that have been published in recent years about TB treatment in Iran and the world, the spread of MDR-TB continues to pose a serious challenge to TB control worldwide. Many methods are available in order to predict and diagnose patients with MDR-TB based on individual demographic and clinical characteristics of patients, but the study design based on these methods due to low flexibility and limitations are unable to accurately predict patients.

Currently, treatment approaches have improved and patients' quality of life has ameliorated; thus, the use of modern methods, as opposed to outdated methods that cannot reliably predict disease status, has often been suggested (8-9). The model of perceptron artificial neural networks (ANNs), whose application has increased in recent decades, is one of the methods designed to predict and diagnose patients. Due to their high prediction accuracy, perceptron ANN models are superior tools in many applications related to complex processes and are widely used in various fields of medical sciences such as diagnosis, treatment, and prediction. The term ANN refers to a family of models inspired by human brain studies and is like a processor with a natural desire to store experimental knowledge and make it usable. The ANN is similar to the human brain in two ways, one is that knowledge is acquired through the learning process by the network, and the other is that knowledge is stored using the power of communication between neurons, known as synaptic weights. The neuron is the smallest processing unit in an ANN. These neurons are present in different layers of the ANN, such as the input, hidden, and output layers, and are connected by synaptic weights. One of the most widely used ANNs is perceptron. This network is a kind of ANN that is based on a computational unit called perceptron. The most common type of this ANN is a three-layer perceptron, which is shown in Figure 1.

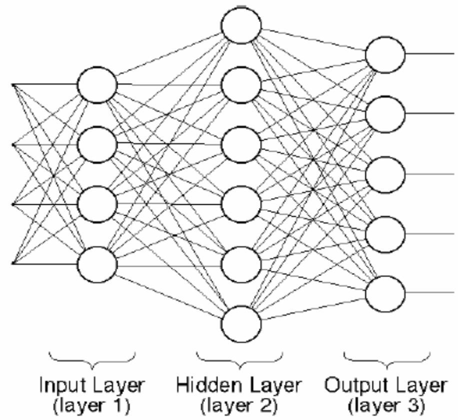

Fig. 1. Schematic of a three-layer perceptron ANN.

The perceptron ANNs evaluate information in two phases: training and testing. By receiving a random sample of data that is usually more than 50% of the information, network training learns how to relate data and variables studied, and after training for each input, provide appropriate output. After completing the training phase, the network performance and predictive power will be tested with the remaining observations. In the model of ANNs, there is no limit to the type of data studied; therefore, these models are able to present replies logically and plausible with missing data and data with a heavy censoring rate, as well as data with bias. Perceptron ANNs can be one of the best strategies to study health data. The application of the perceptron ANN model, due to the high flexibility and accuracy of prediction is able to create new horizons in the diagnosis of patients with MDR-TB. Hence, this study was aimed to predict MDR-TB by using the perceptron ANN model in TB patients who had been treated in Masih Daneshvari Hospital, Tehran, Iran.

Materials & Methods

This retrospective cohort study has been performed at Dr. Masih Daneshvari Hospital, Tehran, Iran from 2005 to 2015. The data of this study were obtained from the medical records of 1,050 TB patients who referred to and were treated by the National Institute of TB and Lung Disease Research of the mentioned hospital. Diagnosis of MDR-TB for these patients was made through information recorded in patients' medical records, as well as the clinical examination of patients. Patients whose latest information showed that they did not have MDR-TB, and later, no information was available about them, as well as patients whose information was complete and did not have MDR-TB by the end of this study, were considered as patients without TB resistance.

In this study, the effects of gender, age, marital status, education, place of residence, nationality, family size, the adverse effect of drug, smoking, passive smoker, the drug user, contact to a patient with TB, imprisoned, pulmonary TB, extrapulmonary TB, diabetic mellitus, AIDS, and comorbidities were evaluated on the diagnosis and prognosis of MDR-TB. Also, a three-layer perceptron ANN was applied to predict the prevalence of MDR-TB in TB patients. According to the variables studied, 39 neurons were considered for the input layer and two neurons for the output layer. Also, the appropriate number of hidden or middle layer neurons was evaluated and determined during data analysis for the perceptron ANN.

The effect of variables on the prediction and diagnosis of patients with MDR-TB in the model of perceptron ANN was also presented by the importance index and normalized importance. All analyzes were performed using SPSS19 software. The hyperbolic tangent activation function was used for the middle or hidden layer, and the Soft-Max activation function was used for the output layer.

Results

This study was performed on 1,050 TB patients, of which 137 (13.05%) were diagnosed with MDR-TB, and 913 (86.95%) patients were considered as patients without TB resistance. To predict and diagnose patients with MDR-TB, the patients' individual, demographic, and clinical data sets as input layer variables and the status of MDR-TB were examined as output layer variables in the perceptron ANN model (Table 1).

Table 1. Individual, demographic and clinical variables of tuberculosis patients and number of neurons for input and output layers in perceptron artificial neural networks model

Layers	Variables	Category	Number of neurons
Output	Multidrug-resistant tuberculosis	No Yes	2
Input	Gender	Female Male	2
Input	Age	-	1
Input	Marital Status	Single Married Widow Divorced	4
Input	Education	Illiterate Primary Secondary High school Higher education	5
Input	Residency area	Rural Urban	2
Input	Nationality	Iranian Non-Iranian	2
Input	Family size	-	1
Input	Adverse effect	No Yes	2
Input	Smoker	No Yes	2
Input	Passives smoker	No Yes	2
Input	Drug user	No Yes	2
Input	TB contact	No Yes	2
Input	Imprisoned	No Yes	2
Input	Pulmonary TB	No Yes	2
Input	Extrapulmonary	No Yes	2
Input	Diabetic mellitus	No Yes	2
Input	HIV-positive	No Yes	2
Input	Comorbidities	No Yes	2

In addition, 70% of the patients were randomly assigned to the training group and 30% to the study group to predict patients with MDR-TB using the perceptron ANN model. A collection of perceptron ANNs with different numbers of neurons was examined for the hidden layer to decide the best model structure and determine the number of neurons appropriate for the hidden layer based on the training sample. These models were compared using indicators such as entropy error, the percentage incorrect prediction, and area below the ROC curve. According to these findings, the best structure of the perceptron ANN model with 39 neurons for the input layer, 25 neurons for the hidden layer, and 2 neurons for the output layer was selected with the lowest entropy error, the percentage incorrect prediction as well as the highest area under the ROC curve among others (Table 2).

Table 2. Best structure for perceptron artificial neural networks model based on varing the number of neruns in hidden layer

Perceptron ANNs structure (Input/hidden/output)	Entropy error	Percent incorrect predictions	Area under the ROC curve
39/5/2	119.32	16.1	0.57
39/6/2	112.61	16.1	0.65
39/7/2	122.76	16.1	0.59
39/8/2	125.21	16.1	0.49
39/9/2	118.07	16.5	0.60
39/10/2	115.31	16.1	0.64
39/11/2	119.59	16.1	0.60
39/12/2	١١٦.88	16.1	0.64
39/13/2	110.74	16.5	0.68
39/14/2	115.44	16.1	0.62
39/15/2	129.03	16.1	0.46
39/16/2	117.81	16.1	0.59
39/17/2	114.82	16.1	0.66
39/18/2	128.18	16.5	0.54
39/19/2	104.63	15.8	0.70
39/20/2	126.50	16.5	0.56
39/21/2	105.17	16.1	0.71
39/22/2	115.26	15.4	0.66
39/23/2	116.06	16.8	0.67
39/24/2	108.03	16.1	0.70
39/25/2	104.23	15.0	0.71

Results are based on training sample

According to the results of this model, the correct predictive power of patients with MDR-TB for both training and testing samples was 85% and 80%, respectively. This model showed 15% and 20% errors in predicting the incidence of MDR-TB in patients with TB based on training and testing samples, respectively. The importance of the individual, demographic, and clinical factors in the prediction of MDR-TB in TB patients was assessed using a scale based on the normalized importance index. Variables with a normalized importance index of more than 60% were considered very effective factors, variables with a normalized importance index of 20% to 60% as effective factors, and variables with a normalized importance index of less than 20% as ineffective factors. Therefore, based on this scale, the results of the perceptron ANN model for selecting important variables in predicting MDR-TB showed that the variables of marital status, education, drug use, imprisoned being, extrapulmonary TB, history of comorbidities, AIDS, age of patients, and family size had the greatest effect on the prediction of MDR-TB and were among the most effective factors in the diagnosis and prognosis of MDR-TB. Also, the variables of residence, smoking, and history of contact with a person with TB, pulmonary TB, and adverse effect of drug, nationality, and diabetes were identified as the effective factors, and the variables of the patient's gender and passives smoker were among the least effective factors in the prediction of MDR-TB in TB patients (Table 3).

Table 3. Importance of the effect of individual, demographic and clinical variables based on perceptron artificial neural networks model

Variables	Importance	Normalized importance%
Gender	0.020	19.7
Age	0.099	100
Marital status	0.069	69.2
Education	0.079	79.7
Residency area	0.039	39
Nationality	0.026	26.1
Family size	0.074	74.9
Adverse effect	0.041	40.8
Smoker	0.040	40.3
Passives smoker	0.015	15.2
Drug user	0.077	77.6
TB contact	0.037	36.9
Imprisoned	0.066	66.2
Pulmonary TB	0.020	20.2
Extrapulmonary TB	0.072	72.7
Diabetic Mellitus	0.057	57.6
HIV Positive	0.079	79.2
Comorbidities	0.090	90.7

Moreover, to better understand the importance of the factors affecting the prediction of MDR-TB in patients with TB, information on the normalized importance and importance indices have been marked graphically (from the most to the least impact; Figure 2).

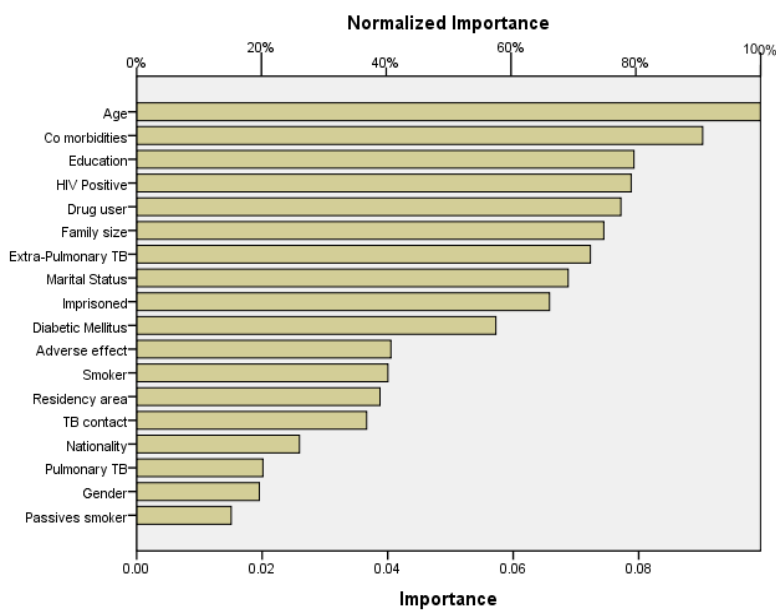

Fig. 2. Effect of individual, demographic and clinical variables on the prediction of MDR patients based on normalized importance and importance index.

Discussion

In many chronic infectious diseases, such as TB, the issue of diagnosis and treatment of patients is of great importance. Despite the effective drugs and treatment mechanisms that have been introduced in recent years to treat TB, the problem of MDR-TB has caused the failure of treatment for this disease. According to various studies, part of this failure is related to the patient and part to the treatment. However, some studies have identified factors such as incomplete treatment of the disease, misdiagnosis, voluntary discharge, and temporary discharge as the causes of MDR-TB and treatment failure strategies (10-12). However, the cause of MDR-TB should not be considered in terms of treatment alone. Various studies have shown that approximately 70% to 85% of patients with a history of previous treatment with anti-TB drugs had at least one drug resistance (13). Studies have also shown that the cause of MDR-TB and the failure of TB treatment strategies can be related to individual, demographic and clinical characteristics of patients, not just their treatment (10-11,14-15).

Despite studies conducted on MDR-TB so far, researchers do not have comprehensive information about the role of individual, demographic and clinical characteristics of patients with this type of TB. This problem can be due to the difficulties in the diagnosis and treatment of patients with MDR-TB and due to the low incidence of this type of TB. However, individual, demographic, and clinical characteristics of TB patients may play a significant role in MDR-TB diagnosis and prognosis. Understanding which characteristics of the TB patient can be effective in diagnosing and predicting MDR-TB will be helpful in treating TB patients. For instance, AIDS and drug use have been shown to play a significant role in the development of MDR-TB. Therefore, clinically, patients with AIDS and addicts have a higher chance of developing MDR-TB than other patients. As a result, physicians can have a higher predictive power before starting anti-TB treatments with the view that these patients are more likely to develop MDR-TB and also prescribe anti-TB therapies more effectively for these patients.

There are a variety of statistical methods for diagnosing and predicting MDR-TB, as well as understanding the significance of individual, demographic, and clinical characteristics in predicting these patients, but these methods may not be able to make accurate predictions in patients with MDR-TB due to limitations in patients' data structure, information, and characteristics. Therefore, for the current study, a perceptron ANN model was designed and implemented as a new method with high flexibility and accuracy in predicting patients' data structure, information, and characteristics. This perceptron ANN model with 39 neurons in the input layer, 25 neurons in the latent layer, and 2 neurons in the output layer was applied for the diagnosis and prediction of MDR-TB in TB patients. Based on the results of this model, the correct predictive power of MDR-TB patients for both training and testing samples was 85% and 80%, respectively, which is considered a high degree of accuracy in prediction. In other words, this model was able to accurately predict and diagnose MDR-TB for 85 and 80 patients out of every 100 TB patients in the training and testing samples, respectively. Various studies have also shown that perceptron ANNs have higher predictive power compared to a range of conventional statistical methods (16-22). In this study, in addition to determining the effect of different variables on the diagnosis and prediction of MDR-TB, the order of their importance was also assessed graphically based on the indicators of importance and normalized importance. One of the advantages of using ANN models is presenting the order of importance of the effective factors in the prediction of MDR-TB in patients with TB. This is particularly critical in community-based health policy and prevention.

In the present study, the variables of marital status, education, drug use, imprisoned being, extrapulmonary TB, history of comorbidities, AIDS, patients’ age, and family size with a normalized importance index of above 60% had the greatest impact on the prediction of MDR-TB in TB patients. Also, the variables of residence, smoking, and history of contact with a person with TB, pulmonary TB, and adverse effect of drug, nationality, and diabetes with a normalized importance index between 20% and 60% was introduced as the effective factors in predicting the disease of MDR-TB. The findings of this study can be used to supplement previous research in terms of diagnosing and predicting MDR-TB. Several studies have shown that when diagnosing and predicting MDR-TB, researchers and physicians paid less attention to the individual, demographic, and clinical characteristics of patients. Treatment problems were found to be effective in developing MDR-TB in the majority of these studies (2,5,23).

The authors of this article hope that with the results of this study, physicians will be able to predict which patients are more likely to develop MDR-TB than others before starting treatment for TB patients. The findings of this study showed that individual, demographic and clinical characteristics (such as old age of patients, history of other diseases (e.g. cancer, liver disorders, hyperthyroidism, heart disease, etc.)), the low level of education (especially illiterate patients with primary and secondary education), AIDS, history of drug use, number of household members (households one to five), extrapulmonary TB, marital status of patients (married patients, and widowed and separated patients) and having a history of being a prisoner were highly effective in predicting the development of MDR-TB. Therefore, in order to control and treat MDR-TB, clinicians should pay more attention to the characteristics of patients in the treatment of TB patients since the results of this study showed the individual, demographic and clinical characteristics of TB patients in addition to the way they are treated affect the risk of developing MDR-TB.

Conclusion

The use of the perceptron ANN model in the study of patients with MDR-TB due to high prediction accuracy and insensitivity to the data structure, information, and characteristics of patients is able to open new horizons in the diagnosis, prediction, and control of MDR-TB.

Acknowledgments

None declared.

Conflict of interest

The authors have no conflict of interest in this study.

Funding/support

The Shahid Beheshti University of Medical Sciences financially supported this study.

Data availability

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

References

1. Organization WH. Tuberculosis Fact sheet N°104 [Internet]. 2016 [cited 2023 Apr 15]. Available from: https://www.who.int/news-room/fact-sheets/detail/tuberculosis
2. Organization WH. Global tuberculosis control: WHO report 2010 [Internet]. World Health Organization; 2010 [cited 2023 Apr 15]. Available from: https://apps.who.int/iris/handle/10665/44425
3. Rom WN, Garay S, editors. Tuberculosis Boston. New York, Toronto, London: Little, Brown and Company; 1996.
4. Mansoori S, Aghazadeh M, Asmar M, Masjedi MR, Velayati AA. Comparative study of initial and acquired drug resistance in pulmonary tuberculosis. Revue internationale des services de santé des forces armées. 2003;76(1):45-9.
5. Mirsaeidi SM, Tabarsi P, Khoshnood K, Mansouri D, Masjedi MR, Velayati AA. Treatment of multiple drug-resistant tuberculosis (MDR-TB) in Iran. International journal of infectious diseases. 2005;9(6):317-22.
6. Organization WH. Anti-tuberculosis drug resistance in the world: third global report [Internet]. 2004 [cited 2023 Apr 15]. Available from: https://apps.who.int/iris/handle/10665/42910

7. 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 Journal. 2009;136(2):420-5.
8. Kay JW, Titterington DM, editors. Statistics and neural networks: advances at the interface. Oxford University Press on Demand; 1999.
9. Warner B, Misra M. Understanding neural networks as statistical tools. The American Statistician. 1996;50(4):284-93.
10. Sevim T, Doganay M, Bakir M, Kilic A, Kayacan O, Kocagoz T, et al. Treatment outcome of relapse and defaulter pulmonary tuberculosis patients. The International Journal of Tuberculosis and Lung Disease. 2002;6(4):320-5.
11. Salaniponi FM-L, Nyirenda TEH, Kemp JRHJr., Squire SBHJr., Godfrey-Faussett PHJr., Harries ADHJr… Characteristics, management and outcome of patients with recurrent tuberculosis under routine programme conditions in Malawi. The International Journal of Tuberculosis and Lung Disease. 2003;7(10):948-52.
12. Quy HTTJr., Lan NTNJr., Borgdorff MWJr., Grosset JHJr., Linh PDJr., Tung LBHJr., et al… Drug resistance among failure and relapse cases of tuberculosis: is the standard re-treatment regimen adequate? The International Journal of Tuberculosis and Lung Disease. 2003;7(7):631-6.
13. Mirsaeidi MS, Tabarsi P, Farnia P, Ebrahimi G, Morris MW, Masjedi MR, et al. Trends of drug resistant Mycobacterium tuberculosis in a tertiary tuberculosis center in Iran. Saudi medical journal. 2007;28(4):544-7.
14. Kritski AL, Marques MJ, Rabahi MF, Vieira MA, Werneck-Barroso E, Carvalho CE, et al. Retreatment tuberculosis cases: factors associated with drug resistance and adverse outcomes. CHEST Journal. 1997;111(5):1162-7.
15. Zignol M, Hosseini MS, Wright A, Weezenbeek CL, Nunn P, Watt CJ, et al. Patients with previously treated tuberculosis no longer neglected. Clinical infectious diseases. 2007;44(1):61-4.
16. Sargent DJ. Comparison of artificial neural networks with other statistical approaches: results from medical data sets. Cancer: Interdisciplinary International Journal of the American Cancer Society. 2001;91(S8):1636-42.
17. Chi C-L, Street WN, Wolberg WH. Application of artificial neural network-based survival analysis on two breast cancer datasets. In: AMIA Annual Symposium Proceedings [Internet]. American Medical Informatics Association; 2007 [cited 2023 Apr 15]. p. 130-4. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2655849/
18. Ahmed FE. Artificial neural networks for diagnosis and survival prediction in colon cancer. Molecular cancer. 2005;4(1):29.
19. Akl A, Ismail AM, Ghoneim MA. Prediction of graft survival of living-donor kidney transplantation: nomograms or artificial neural networks? Transplantation. 2008;86(10):1401-6.
20. Tsai P-FJ, Lee T-CJ, Chen J-HJ, Yen D-CJ. Length of hospital stay prediction at the admission stage for cardiology patients using artificial neural network. Journal of healthcare engineering [Internet]. 2016 [cited 2023 Apr 15];2016:1-10. Available from: https://www.hindawi.com/journals/jhe/2016/7035463/
21. LaFaro RJ, Stansbury LG, Scalea TM, Bartlett ST, Rabin J. Neural network prediction of ICU length of stay following cardiac surgery based on pre-incision variables. PLoS One. 2015;10(12):e0145395.
22. Yegnanarayana B. Artificial neural networks. New Delhi: PHI Learning; 2009.
23. Kazempour-Dizaji M, Ghafari A, Ghahramani S, Tabatabaei SM, Holakouie-Naieni K. Estimation of Ten-Year Survival of Patients with Pulmonary Tuberculosis Based on the Competing Risks Model in Iran. Tanaffos. 2016;15(1):37-43.