Mathematical modeling of the in-stent restenosis risk of patients with coronary heart disease

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ABSTRACT

Aims: This article presents the mathematical modeling of the in-stent restenosis risk of patients with coronary heart disease, which is also known as ischemic heart disease. **Methods:** The mathematical model was developed based on an artificial neural network and regression analysis. **Results:** The results identified increased in-stent restenosis risk in patients with the following genotypes: [Hp 1-2; Gc 1-2; Tf CB; C's SS], [Hp 2-2; Gc 1-1; Tf CC; C's FF], [Hp 2-2; Gc 1-2; Tf CB; C's SS], [Hp 2-2; Gc 1-1; Tf CC; C's SS]. **Conclusion:** The coefficients of determination of ANN (0.21) and linear regression (0.11) were calculated. The resulting values of the coefficient of determination were <0.5, suggesting that the simulation was unacceptable. Analysis revealed that the presence or absence of restenosis was possible with the same set of phenotypes

KEY WORDS: Artificial neural network, Ischemic heart disease, Mathematical modeling, Prognostication, Regression analysis, Restenosis

INTRODUCTION

Coronary heart disease (CHD) caused by stenosing coronary atherosclerosis is one of the major causes of mortality and disability among people in developed countries.

New diagnostic and treatment methods for clinical cardiology have been introduced in recent years. Among them, percutaneous intracoronary troops (PCI), particularly intracoronary stenting, have been recognized as the leading approach. Literature review indicated that the introduction of the coronary stenting of coronary arteries had not achieved the desired result because the incidence of restenosis within the stents remains high.[1,2]

One of the causes of restenosis is the stent itself. Its metal base assumes a foreign body, which triggers an inflammatory response and ultimately initiates the development of restenosis. The implantation of drug-coated stents has significantly reduced the incidence of restenosis. Nonetheless, restenosis after PCI still cannot be completely eliminated. Stents covered with appropriate medicines cannot be widely adopted because of their high cost. Therefore, modern cardiology studies have focus on elucidating the mechanisms of restenosis development after PCI.

The factors that predispose to restenosis development were identified. The key roles of cytokines, angiotensin II, thrombin, and endothelin in the initiation of pathomorphological processes in the surgical intervention zone were established. The significant role of the high level of inflammatory processes and the non-intima formation activity in the genesis of coronary vehicle restenosis after PCI allowed for the identification of the influence of the genetic factors in the development of CHD and the formation of individual mechanisms of restenosis initiation.

Recent works have emphasized the development and comparison of new methods for diagnosing cardiac restenosis in various stent locations, as well as the effect of stent materials on the accuracy of diagnosis.[3,4] Most studies have been directed toward the development of materials and coatings of stents that can reduce the probability of restenosis development.[5,6]

The following list presents the disadvantages posited by a number of recent works on the development of mathematical models for predicting heart vehicle restenosis.[7-9]:

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1. The model cannot quantitatively define the probability of restenosis development probability (patent RU # 2395091, published: 20.07.2010, patent RU # 2349919 published: 20.03.2009).
2. The gender factor is hardly considered (patent RU # 2410019, published: 27.01.2011).
3. An insufficiently high reliability exists between the forecasts, as communication was absent between the value of restenosis and the probability of restenosis development in a stent (patent RU # 2308884, published: 10.07.2012).

Thus, one of the main factors preventing the development of various human diseases, including cardiovascular, and further effective treatment is the application of the latest scientific achievements not only in the field of medicine but also in the field of system analysis and mathematical modeling. The idea of using e-health and telemedicine in medical practice has become widespread.[10] The construction of reliable predictive mathematical models of the emergence of diseases and the course of the disease as the basis of telemedicine technologies will allow us to obtain a formal description of the procedure for diagnosing and obtaining the best results for recovery.

In our previous works, we determined and analyzed the dependence of the progress of heart vehicle restenosis in biochemical blood data.[11,12]

MATERIALS AND METHODS

This article used two types of mathematical models: Artificial neural networks (ANNs) and regression mathematical models.

ANN is a mathematical model, including its software or hardware implementation, that is based on the principle of the organization and functioning of biological neural networks, that is, the nerve cell networks of a living organism.[13]

Regression (or regression analysis) is a statistic method for determining the effects of one or more independent variables x_1, x_2, x_p on the dependent variable y.[13]

One of the most common regression models is linear regression, which is the model of the dependence of one (explained and dependent) variable y on another or several other variables (factors, regressors, and independent variables) x with a linear dependence function.[13]

The coefficient of determination was used to compare the results of the two models. This coefficient is typically used to calculate the nonlinear relationship among variables. If the coefficient of determination tended to one, the dependence of the variable x on the variable y was stronger.[14]

Main Part

This article showed the modeling of restenosis based on genetic markers. Previous studies in this direction showed the correlation between restenosis and the following genetic markers (input data):

- Haptoglobin (Hp)
- Group-specific component (Gc)
- Transferrin (Tf)
- Citrate synthase (C's).

The phenotypes in the Hp and Gc system are of three types: 1-1, 1-2, and 2-2. The Tf system has the CC and CB phenotypes. The C's system has three kinds of phenotypes: SS, FS, and FF.

The output data were the predicted values of restenosis.

Given that the mathematical models of ANN and linear regression do not accept text data types, the data were encoded as in Table 1.

The mathematical model of ANN was projected with the help of the neural network toolbox, which is a Matlab extension package that contains the tools for designing, modeling, developing, and visualizing neural networks.[15]

After the input data were encoded, the input (the set of encoded phenotypes of gene markers) and target data (the presence or absence of restenosis) were input using the NNTool. The NNTool is a graphical interface that allows the creation, training, simulation, importing, and exporting of neural networks and data without the need to access the command window of the Matlab system.[14]

The neural network was formed and trained, as shown in Figure 1. Input refers to the set of encoded phenotypes of genetic markers (input data). Target refers to the presence or absence of restenosis (target data). Output refers to the predicted restenosis value (output data). Error refers to the array of network errors.

The mathematical model of linear regression was developed in Microsoft Excel ("Regression" add-on). The model had the following form:

Table 1: Encoding input data

Phenotypes	Phenotypes code in model
Hp 1−1	1
Hp 1-2	2
Hp 2-2	3
Gc 1-1	4
Gc 1-2	5
Gc 2-2	6
Tf CB	7
Tf CC	8
C's SS	9
C's FS	10
C's FF	11

Table 2: Patients with the same set of phenotypes and presence or absence of restenosis

Input data	Presence of restenosis	Absence of restenosis	Prognosis of restenosis
[Hp 2-2;Gc 1-2;Tf CC; C's SS]	9	3	0,21
[Hp 2-2;Gc 1-1;Tf CC; C's FS]	3	2	0,49
[Hp 1-2;Gc 1-1;Tf CC; C's SS]	12	3	0,19
[Hp 1-2;Gc 1-2;Tf CC; C's SS]	16	2	0,03
[Hp 2-2;Gc 2-2;Tf CC; C's SS]	4	1	0,1
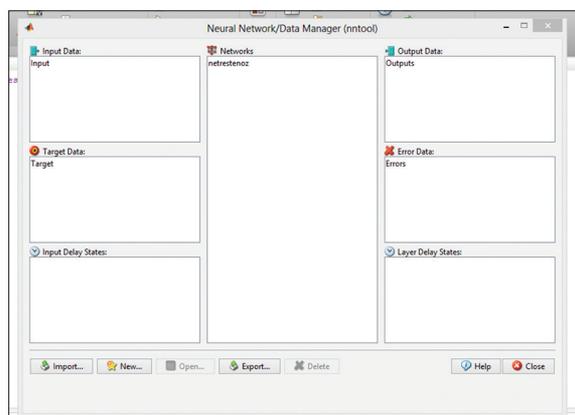
Figure 1: TSimulation of a neural network in NNTool

$$Y = a_0 + a_1x_1 + a_2x_2 + a_3x_3 + a_4x_4$$

where y is absence or presence of restenosis in a patient (1; 0); a_0, a_1, a_2, a_3, and a_4 are the regression parameters (coefficients); x_1, x_2, x_3, and x_4 represent the phenotypes of Hp, Gc, Tf, and C's.

The model was analyzed using student's *t*-tests. The calculated values of the student's test were compared using a table of values from the student's t-distribution. ($t = 1,9847$; $P = 0.95$). The input variables x_1, x_2, and x_4 were excluded from next iteration of modeling, because the values of the t-statistics of these variables were less than the table. In the second iteration, x_3 corresponded to the student's test.

Thus, the mathematical model of linear regression had the following form:

$$Y = 6.979 - 0.854x_3$$

CONCLUSION

The coefficients of determination of ANN (0.21) and linear regression (0.11) were calculated. The resulting values of the coefficient of determination were <0.5, suggesting that the simulation was unacceptable. Analysis revealed that the presence or absence of restenosis was possible with the same set of phenotypes [Table 2].

To obtain acceptable simulation results, the input data from Table 2 were removed from the next simulation. As a result of repeated modeling, new models of ANN and linear regression were developed:

$$Y = 7.4615 - 0.923x_3$$

The coefficient of determination of the ANN model became equal to 0.73, and the linear regression model became 0.47. Thus, the ANN model of in-stent restenosis risk of patients with CHD provided more acceptable predictive results for prognosis. The results of the simulation were applicable to patients with the following genotypes:

- [Hp 1-1; Gc 1-1; Tf CC; C's FF]
- [Hp 1-1; Gc 1-1; Tf CC; C's SS]
- [Hp 1-1; Gc 1-2; Tf CC; C's SS]
- [Hp 1-1; Gc 2-2; Tf CC; C's SS]
- [Hp 1-2; Gc 1-1; Tf CC; C's FS]
- [Hp 1-2; Gc 1-2; Tf CB; C's SS]
- [Hp 1-2; Gc 2-2; Tf CC; C's FS]
- [Hp 2-2; Gc 1-1; Tf CC; C's FF]
- [Hp 2-2; Gc 1-1; Tf CC; C's SS]
- [Hp 2-2; Gc 1-2; Tf CB; C's SS]
- [Hp 2-2; Gc 1-2; Tf CC; C's FS]
- [Hp 2-2; Gc 2-2; Tf CC; C's FS]

Moreover, increased in-stent restenosis risk was identified in patients with the following genotypes: [Hp 1-2; Gc 1-2; Tf CB; C's SS], [Hp 2-2; Gc 1-1; Tf CC; C's FF], [Hp 2-2; Gc 1-2; Tf CB; C's SS], [Hp 2-2; Gc 1-1; Tf CC; C's SS].

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