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Original article

The amputation and survival of patients with diabetic foot based on establishment of prediction model

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ABSTRACT

Objective: The objective of this paper is to study the establishment of predictive models and the amputation and survival of patients with diabetic foot.
Methods: A total of 200 inpatients with diabetic foot were selected as the research subject in this study. The amputation and survival status of diabetic foot patients were followed up by telephone. The relevant indicators were screened by cluster analysis. The predictive model was established respectively based on proportional hazard regression analysis, back propagation neural network (BPNN) and BPNN based on genetic algorithm optimization, and the reliability of the three prediction models (PM) was evaluated and compared.
Results: The risk factors for amputation were severe ulcer disease, glycosylated hemoglobin and low-density lipoprotein cholesterol. The risk factors for death were cerebrovascular disease, severe ulcer disease and peripheral arterial disease. In case that the outcome was amputation, the PM of BPNN and the PM of BPNN based on genetic algorithm optimization have obviously higher AUC (area under the receiver operating characteristic curve) than the PM of proportional hazard regression analysis, and the difference was statistically significant ($P < 0.05$). Among the three PMs, the PM based on BPNN had the highest AUC, sensitivity and specificity (SAS). In case that the outcome was death, the PM of BPNN and the PM of BPNN based on genetic algorithm optimization had almost the same AUC, and were obviously higher than the PM based on proportional hazard regression analysis. The difference was statistically significant ($P < 0.05$). The PM based on BPNN and the BPNN based on genetic algorithm optimization had higher SAS than the PM based on COX regression analysis.
Conclusion: The PM of BPNN and BPNN based on genetic algorithm optimization have better prediction effect than the PM based on proportional hazard regression analysis. It can be used for amputation and survival analysis of diabetic foot patients.

1. Introduction

Diabetic foot (DF) refers to diabetic neuropathy, including peripheral nerve sensory disorder, vegetative nerve damage, lower limb vascular disease, skin microvascular disease or bacterial infection causing foot pain, foot ulcer and foot gangrene (Uğurlar et al., 2017). Diabetic foot is usually the result of the synergistic effect of three risk factors of ischemia, neuropathy and infection, and its etiology is the distal nerve abnormalities of lower extremities and peripheral vascular lesions of lower extremities caused by diabetes. Patients do not spontaneously develop ulcers (Clokie et al., 2017; Zelen et al., 2017). The onset of diabetic foot usually occurs at the distal end of the limb, and then develops toward the proximal end (Hartmann et al., 2017). Patients' subjective feelings of pain, temperature and light touch will gradually weaken, and the internal muscle atrophy of the foot will be manifested as claw toe deformity, loss of skin functions such as perspiration, temperature and blood flow regulation, resulting in decreased flexibility of local tissues, forming thick cocoon and cracking (Lin et al., 2017; Martín et al., 2017). Many diabetic foot patients begin with

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sensory neuropathy, autonomic neuropathy and motor neuropathy. Sensory neuropathy combined with excessive mechanical stress is a major initiating factor for foot ulcers and infections, while repeated stress applied to a specific sensory loss area can lead to inflammation and tissue damage (Rastogi et al., 2017; He et al., 2017). Lesions of the autonomic nervous system will cause patients to lose the skin's ability to regulate perspiration, temperature and blood flow, thus reducing the flexibility of local tissues, forming thick cocoons and cracking and breaking. After the skin and soft tissues are damaged, exogenous bacteria are easy to invade the body and cause infection (Almobarak et al., 2017; Takeshi et al., 2018). Motor neuropathy causes contracture of the internal muscle of the foot, which forms an ulcer that is difficult to heal (Tang et al., 2017). Without effective treatment, major vital organs of patients will be damaged. Even if amputation occurs, the function of these organs will be less restored, and many patients will die of cardiovascular or renal failure (Robles et al., 2017).

Currently, the treatment of diabetic foot mainly includes wound management, blood glucose control, supportive treatment, anti-infection and maintaining the stability of internal environment (Vibha et al., 2018). Treatment methods are limited, so it is particularly important to establish PMs for early risk assessment of diabetic foot patients. Disease PM is to establish a prediction mathematical model to predict the incidence probability of individuals in a specific time in the future, or to evaluate risk factors based on a certain number of patients and disease characteristics to classify high-risk groups. Several studies have shown that the establishment of disease PM has an early warning effect on diseases and can effectively reduce the incidence. Currently, most risk PMs of diabetic foot evaluate risk factors through multivariate COX regression, multivariate Logistic regression and multivariate linear regression based on statistical regression analysis, but such PMs have many limitations that lead to poor fitting effect. In addition, artificial NN can also be used for the analysis of risk factors. The PM established by artificial NN has the advantages of self-learning, self-adaptation and self-organization, with good simulation function. However, such PMs of diabetic foot are rare at present.

To sum up, the traditional PM has many shortcomings, and the prediction effect is not good. Therefore, inpatients with diabetic foot were taken as the research object. A PM was established. Through the establishment of three different PMs, it was analyzed which one is more advantageous. After the study, it was found that the PM based on BPNN and genetic algorithm optimization BPNN had better prediction effect. The PM can be used to predict the amputation and survival status of diabetic foot patients in advance, as well as to understand the related risk factors of diabetic foot amputation, which is of great reference and guidance significance for clinical prevention and treatment of diabetic foot.

2. Materials and methods

2.1. Research objects

200 inpatients diagnosed with diabetic foot in XXX hospital (January 2018 – July 2018) were selected, including 99 males and 101 females, aged 40–85 years old, with an average age of 62.14 years. This study was reviewed and approved by the ethics committee of the hospital, and all patients signed the relevant informed consent.

Inclusion criteria: those whose clinical symptoms met the diagnostic criteria for diabetic foot: the skin of the foot was obviously pale after lifting the lower limb for 30–60 s, and the middle part of the limb was purplish red after sagging. If the filling time of the vein (the time when the skin of the foot turns from pale to rosy) is more than 15 s, the blood supply to the lower limb is obviously insufficient. The popliteal and dorsal arteries can be palpated in the popliteal fossa (the fossa behind the knee) and on the back of the foot; peripheral neuropathy; weakness of lower limbs walking, calf gastrocnemius distension pain, especially intermittent claudication; electrocardiogram and coronary examination were performed in all patients; patients with good clinical compliance; those with perfect clinical data.

Exclusion criteria: patients without ECG and coronary artery examination; patients without obvious symptoms; patients with incomplete clinical data.

2.2. Indicator analysis of amputation and survival status of diabetic foot patients

Follow-up of amputation and survival status of diabetic foot patients: follow-up by telephone, record the patient's amputation and survival status, including large amputation and small amputation. The large amputation means that the part above the ankle joint of the lower extremity is cut off, and the part of the lower amputation is below the ankle joint of the lower extremity. Survival status is the patient's three-year survival status, and death needs to be related to the death of the diabetic foot.

Screening of relevant indicators: Through cluster analysis, 69 biochemical indicators of five categories: nutritional index, coagulation index, inflammation index, liver function index and renal function index were screened, and the meaningful indexes with Euclidean distance less than 2 were selected. 12 indexes were selected, including: platelet (PLT), white blood cells (WBC), blood urea nitrogen (BUN), serum creatinine (Cr), hemoglobin (Hb), apolipoprotein A1 (ApoA1), alkaline phosphatase (ALP) Glycated hemoglobin (HbA1c), hypersensitive C-reactive protein (hs-CRP), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and platelet distribution width (PDW). Combined with clinical data and complications, 33 variables were obtained.

Selection of training sets and test sets: 160 patients were randomly selected as training sets to construct a PM in 200 patients, and the remaining 40 patients were used as test sets to test the performance of the PM.

2.3. Establishing a PM based on COX regression (proportional risk regression) analysis

Rationale: COX regression is a semiparametric regression, which takes survival outcomes and survival time as dependent variables, and analyzes the effects of multiple factors on survival, to study the relationship between variables and observed result, that is survival function (cumulative survival rate).

Establishing a PM based on COX regression analysis: predictive agreement rate = (true positive + true negative)/total number of cases $\times$ 100%. The predictive agreement rate of the training set was calculated, and then the prognostic index (PI) was calculated based on the COX regression result, that is, the individual's risk. If the prognostic index is larger, the higher the risk, the worse the prognosis. If the prognostic index is smaller, the lower the risk, the better the prognosis. The cut-off value of the prognostic index was selected according to the highest predictive rate and substituted into the training set data. If the prognostic index is greater than the cut-off value, it is 1, that is, the outcome event occurs. If the prognostic index is less than the cut-off value, it is 0, that is, the outcome event does not occur. Through multivariate COX regression analysis, three variables were selected as independent risk factors for amputation and death, and the PMs were as follows:

Table 1
The results of single-factor COX regression analysis with outcomes for amputation.

Variables	B	SE	HR	P Value
Platelet	0.004	0.003	1.035	0.002
Hemoglobin	−0.021	0.006	1.002	0.042
Apolipoprotein A1	−1.523	0.601	0.245	0.005
Total white cell count	0.072	0.039	1.113	0.021
Alkaline phosphatase	0.003	0.002	1.035	0.049
Severe ulcer	1.812	0.503	6.105	0.001
Glycosylated hemoglobin	0.184	0.088	1.194	0.017
Low density lipoprotein cholesterol	0.057	0.083	1.077	0.049
High density lipoprotein cholesterol	1.125	0.571	3.089	0.040
Dorsal artery pulsation				0.007
Dorsal artery pulsation (weak)	−0.694	0.391	0.506	0.048
Dorsal artery pulsation (normal)	−0.987	0.553	0.417	0.047
Hypersensitive C-reactive protein				0.009
Hypersensitive C-reactive protein (<1 mg/L)	−2.154	0.998	0.112	0.017
Hypersensitive C-reactive protein (1.0–3.0 mg/L)	−1.004	0.507	0.334	0.022

Table 2
The results of single-factor COX regression analysis with outcomes for death.

Variables	B	SE	HR	P Value
Gangrene	0.715	0.338	2.055	0.035
Coronary heart disease	0.956	0.368	2.642	0.004
Diabetes course	0.051	0.029	1.057	0.019
Hemoglobin	−0.024	0.006	1.009	0.004
Total white cell count	0.061	0.036	1.068	0.041
Alkaline phosphatase	0.005	0.002	1.015	0.011
Cerebrovascular disease	1.145	0.345	2.993	0.001
Apolipoprotein A1	1.000	0.524	0.384	0.043
Severe ulcer	0.958	0.359	2.430	0.009
Peripheral arterial disease	1.584	0.537	5.005	0.002
Dorsal artery pulsation				0.026
Dorsal artery pulsation (weak)	−0.501	0.411	0.598	0.049
Dorsal artery pulsation (normal)	−2.005	0.792	0.156	0.007
Hypersensitive C-reactive protein				0.008
Hypersensitive C-reactive protein (<1 mg/L)	−0.991	0.558	0.392	0.047
Hypersensitive C-reactive protein (1.0–3.0 mg/L)	−1.304	0.507	0.332	0.007

Table 3
The results of multi-factor COX regression analysis with outcomes for amputation and death.

Outcome	Variables	B	SE	HR	P Value	95% CI
Amputation	Severe ulcer	1.602	0.517	4.837	0.001	1.756–12.755
	glycosylated hemoglobin	0.247	0.092	1.311	0.003	1.081–1.501
	low density lipoprotein cholesterol	0.132	0.069	1.157	0.025	1.008–1.281
Death	Cerebrovascular disease	1.120	0.513	3.118	0.019	1.122–8.201
	Severe ulcer	1.369	0.663	3.902	0.027	1.066–13.900
	Peripheral arterial disease	0.992	0.563	2.688	0.049	0.903–8.003

$$h(t,x) = h_0(t)exp(\beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3) \quad (1)$$

In the equation, h (t, x) is the dependent variable, the risk function of the observed subject with variable X at time t, and X is the covariate, β is the partial regression coefficient of the independent variable.

2.4. Establishing a PM based on BPNN

Rationale: BPNN is a multi-layer feedforward NN trained according to the error back propagation algorithm. It uses the gradient search technique to minimize the error mean square error between the actual output value and the expected output value of the network.

The PM of amputation outcome: network initialization was first performed, and the input layer, hidden layer, and output layer were set. The three amputation risk factors obtained by multivariate COX regression analysis were substituted into the training set as the input layer. The hidden layer was 4 nodes, the transfer function was trainlm, and the output layer was 2 categorical variables, namely no amputation and amputation. The transfer function was purelin and the learning rate was 0.001. The data was normalized so that the indicators were of the same order of magnitude, the equation is as follows:

$$X_1 = (X_1 - X_{min})/(X_{max} - X_{min})$$

The PM of death outcome: network initialization was first performed, and the input layer, hidden layer, and output layer were set. The three death risk factors obtained by multivariate COX regression analysis were substituted into the training set as the input layer. The hidden layer was 2 nodes, the transfer function was trainlm, and the output layer was 2 categorical variables, namely death and survival. The transfer function was purelin and the learning rate was 0.001. The data was normalized so that the indicators were of the same order of magnitude.

Table 4
Predictive performance comparison results for three predictive models with outcome for amputation and death.

Outcome	Model	AUC	Sensitivity (%)	Specificity (%)
Amputation	The PM based on COX regression analysis	0.557	19.05	94.74
	The PM based on BPNN	0.924	100.00	81.82
	The PM of BPNN based on genetic algorithm optimization	0.891	100.00	78.95
Death	The PM based on COX regression analysis	0.635	26.32	89.47
	The PM based on BPNN	0.712	73.91	70.59
	The PM of BPNN based on genetic algorithm optimization	0.712	73.91	70.59

2.5. Establishing a PM of BPNN based on genetic algorithm optimization

Rationale: Genetic algorithm (GA) is a method to simulate the natural evolution of Darwin's biological evolution theory and the biological evolution process of genetic mechanism to search for optimal solutions.

The PM of BPNN based on genetic algorithm optimization was established. Firstly, the structure of the model was determined. The PM was built based on BPNN, and then the model was optimized by genetic algorithm. Population initialization: the individual was coded by real number coding. It consists of four parts: the threshold of the hidden layer, the threshold of the output layer, the connection weight between the input layer and the hidden layer, and the connection weight between the hidden layer and the output layer. The fitness function is as below:

$$F = k\left(\sum_{i=1}^{n} \mathrm{abs}(y_i - o_i)\right) \tag{2}$$

In the equation, k is the coefficient, n is the number of network output nodes, y_i is the expected output of the i-th node, and o_i is the predicted output of the i-th node. The smaller the fitness value F, the better. The selection operation was performed by the roulette method based on the fitness value, and then the cross operation was performed by the real number intersection method, and finally the mutation operation was performed.

2.6. Reliability assessment of three PM

Calculation of predicted values: The predicted values of the three PMs for the prognosis of diabetic foot patients were calculated and compared. In the PM based on COX regression analysis,

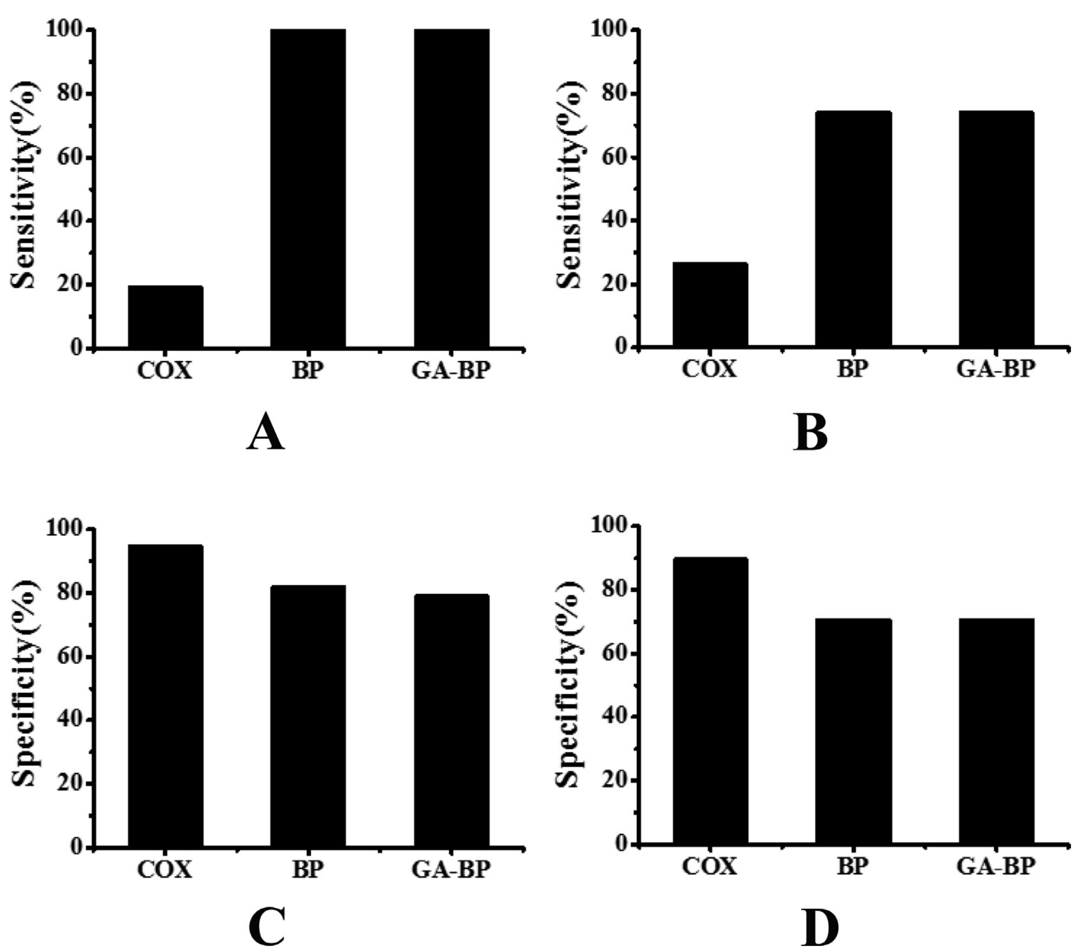

Fig. 1. Comparison of SAS of the three predictive models of amputation and death (A is the sensitivity comparison of the three predictive models with outcomes for amputation; B is the sensitivity comparison of the three predictive models with outcomes for death; C is the specificity comparison of the three predictive models with outcomes for amputation; D is the specificity comparison of three predictive models with outcome for death).

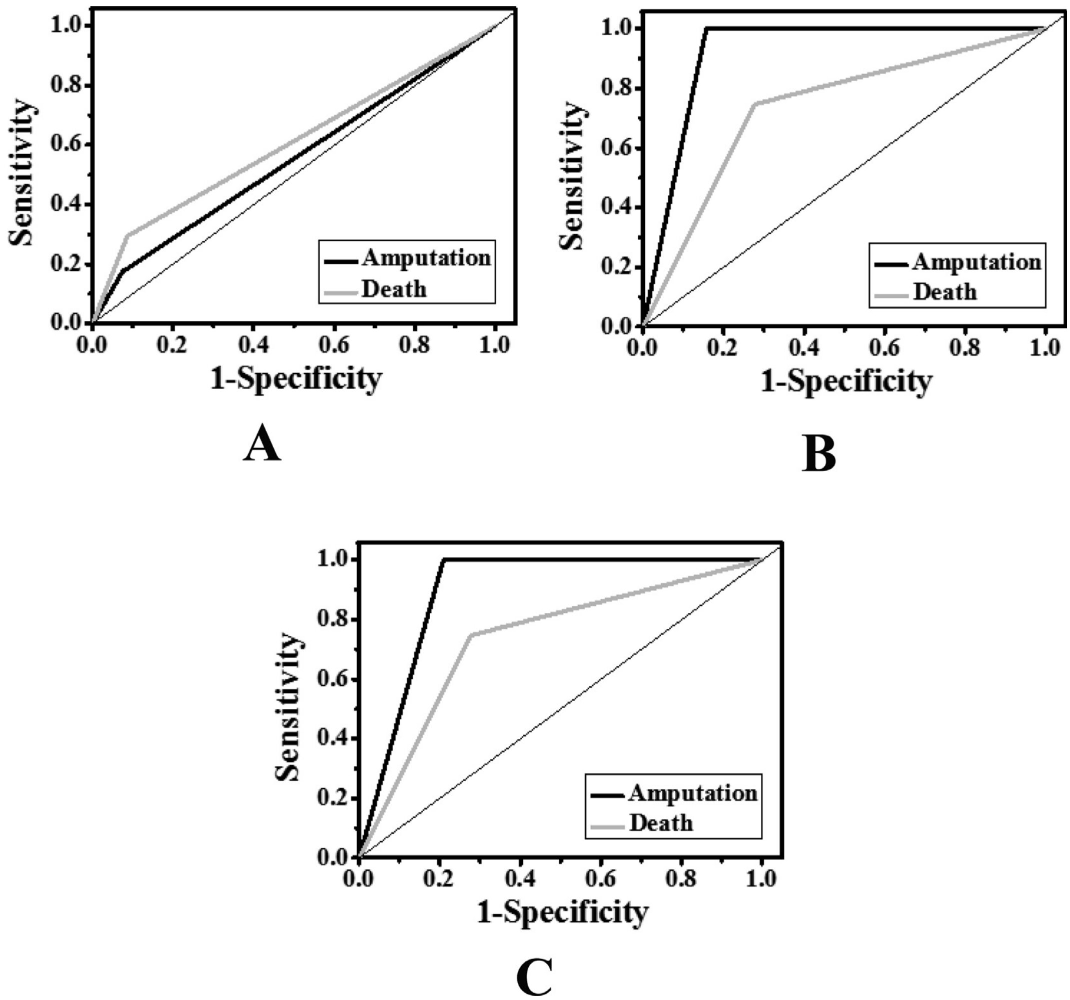

Fig. 2. The ROC curves of three predictive model with outcome for amputation and death (A is a PM based on COX regression analysis; B is a PM based on BPNN; C is a PM based on BPNN optimized by genetic algorithm).

the covariate coefficients were substituted into the test set to calculate the prognostic index and the cut-off value. In the PM based on the BPNN and the PM of BPNN based on genetic algorithm optimization, the test set was substituted into the trained network model to obtain the predicted binary variable.

Assessment of predictive performance: the SAS of the three predictive models were calculated and compared. The receiver operating characteristic curve (ROC curve) of the three models was plotted and the area under curve (AUC) was calculated. If AUC < 0.5, it indicates that the PM does not meet the actual situation. If AUC = 0.5, it indicates that the PM has no predictive ability. If AUC > 0.5, it indicates that the PM has predictive ability, and the larger the AUC, the higher the accuracy of its prediction.

2.7. Statistical method

In the experiment, the SPSS 22.0 statistics software was used for statistical analysis of the data; all quantitative data were submitted to normal distribution test and homogeneity test of variance, and were expressed as the mean number ± standard deviation (x ± s). The One-way ANOVA was used for comparison between groups; if the normal distribution and variance were consistent, the LSD method was used; otherwise, the SNK-q test was used. Pearson correlation analysis was used to analyze the correlations between two parameters, $P < 0.05$ indicated the statistical significance of the difference.

3. Results and discussion

3.1. Analysis of risk factors for diabetic foot amputation and death

The results of single-factor COX regression analysis with outcomes for amputation are shown in Table 1. There were 11 variables with statistical significance ($P < 0.05$), which were platelet, hemoglobin, apolipoprotein A1, total white blood cell count, alkaline phosphatase, and severe ulcer conditions, glycated hemoglobin, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, dorsal artery pulsation, and hypersensitive C-reactive protein. The multivariate COX model analysis results are shown in Table 3. The risk factors for amputation in patients are severe ulcer conditions, glycated hemoglobin and low-density lipoprotein cholesterol.

The results of single-factor COX regression analysis with outcomes for death as shown in Table 2 showed that there were 12 variables with statistical significance ($P < 0.05$), namely gangrene, coronary heart disease, diabetes course, hemoglobin, total white blood cell count, alkaline phosphatase, cerebrovascular disease, apolipoprotein A1, severe ulcer condition, peripheral arterial disease, dorsal artery pulsation and hypersensitive C-reactive protein. The multivariate COX model analysis results are shown in Table 3. The risk factors for death in patients are cerebrovascular disease, severe ulcer disease, and peripheral arterial disease.

3.2. Comparison of reliability assessment results of three PM

The predictive performance of the three predictive models is shown in Table 4. The SAS of the three predictive models with outcomes for amputation and death are shown in Fig. 1. The ROC curves of the three predictive models with outcomes for amputation and death are shown in Fig. 2. For cases with outcome of amputation, the PM based on COX regression analysis had an AUC of 0.557, a sensitivity of 19.05%, and a specificity of 94.74%. The PM based on BPNN had an AUC of 0.924, a sensitivity of 100.00%, and a specificity of 81.82%. The PM of BPNN based on genetic algorithm optimization had an AUC of 0.891, a sensitivity of 100.00%, and a specificity of 78.95%. It can be concluded that the PM of BPNN and BPNN based on genetic algorithm optimization had higher AUC than the PM based on COX regression analysis, and the difference was statistically significant ($P < 0.05$). Among the three PMs, the PM based on BPNN had the highest AUC, SAS.

For cases with outcome of death, the PM based on COX regression analysis had an AUC of 0.635, a sensitivity of 26.32%, and a specificity of 89.47%. The PM based on BPNN had an AUC of 0.712, a sensitivity of 73.91%, and a specificity of 70.59%. The PM of BPNN based on genetic algorithm optimization had an AUC of 0.712, a sensitivity of 73.91%, and a specificity of 70.59%. It can be concluded that the PM of BPNN and the PM of BPNN based on genetic algorithm optimization had almost the same AUC, and were obviously higher than the PM based on COX regression analysis. The difference was of great significance ($P < 0.05$). The PM based on BPNN and the BPNN based on genetic algorithm optimization had higher SAS than the PM based on COX regression analysis.

4. Conclusion

The progress of diabetic foot is the comprehensive effect of many factors. Severe ulcer is significant for amputation and death of diabetic foot. Clinical treatment should focus on prevention and treatment. At the same time, attention should be paid to the complications of peripheral artery disease and cerebrovascular diseases, and the biochemical indicators such as glycosylated hemoglobin and low-density lipoprotein cholesterol should be strictly controlled, so as to improve the quality of life of patients. Ulcer severity was a significant independent risk factor in the analysis of amputation outcomes. As ulcer grade deepens, patient limb has appeared ischemic. Gangrene and amputation are inevitable. Low-density lipoprotein cholesterol (LDL-C) is also an independent risk factor for diabetic foot amputations. When its concentration is increased in the blood, it will lead to abnormal deposition in the arterial wall of the heart and blood vessels, and then develop into atherosclerotic plaque, which will lead to the blockage of the corresponding blood vessels. Finally, it can cause peripheral artery obstructive disease and eventually lead to amputation. At the time of death, the severity of foot ulcer was also associated with the death of the patient, with a lower survival rate in the severe ulcer group. It can be concluded that the PM based on BPNN and the BPNN optimized by genetic algorithm are generally superior to the PM based on COX regression analysis. These two models have high reliability in the prediction of amputation and survival conditions of diabetic foot patients. The experimental results have reached the expected effect. In the past, the PM established by scholars based on artificial NN has a good simulation function, which is also consistent with the results of this study.

Therefore, a forecast model researching patients with diabetic foot amputation and survival condition was established in this article, the PM based on BPNN and BPNN based on genetic algorithm optimization of forecasting model prediction effect are better than the PM based on proportional hazards regression analysis, which can be used in patients with diabetic foot amputation and survival condition analysis. Although the BPNN model and the BPNN model optimized by genetic algorithm have many advantages, they also have some disadvantages. For example, at present, there is no explicit formula to require the sample size of BPNN model and there is no effective quantitative analysis method to indicate the accuracy, credibility and computational complexity of genetic algorithm, which need to be further discussed and improved in future studies. In addition, the small amount of sample data collected in the research process leads to a certain degree of deviation in the results. Therefore, in the later research process, the data capacity will be further increased, making the obtained results more valuable for reference.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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