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The rate of mucosal healing by azathioprine therapy and prediction by artificial systems

INTESTINE

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Original Article

ABSTRACT

Background/Aims: We aimed to assess the effect of azathioprine on mucosal healing in patients with inflammatory bowel diseases (IBD). Artificial neural networks were applied to IBD data for predicting mucosal remission.

Materials and Methods: Two thousand seven hundred patients with IBD were evaluated. According to the computer-based study, data of 129 patients with IBD were used. Artificial neural networks were performed and tested.

Results: Endoscopic mucosal healing was found in 37% patients with IBD. Male gender group showed a negative impact on the efficacy of azathioprine ($p<0.05$). Responder patients with IBD were older than the nonresponder ($p<0.05$) patients. According to this study, the cascade-forward neural network study provides 79.1% correct results. In addition to a 0.16033 training error, mean square error (MSE) was taken at the 16th epoch from the feed-forward back-propagation neural network. This neural structure, used for predicting mucosal remission with azathioprine, was also validated.

Conclusion: Analyzing all parameters within each other to azathioprine therapy were shown that which parameters gave better healing were determined by statistical, and for the most weighted six input parameters, artificial neural network structures were constructed. In this study, feed-forward back-propagation and cascade-forward artificial neural network models were used.

Keywords: Induction, mucosal healing, azathioprine therapy, prediction, artificial systems

INTRODUCTION

In this study, in order to prove the effectiveness of azathioprine (Imuran; Excella GmbH, Feucht, Germany) in the treatment of endoscopic mucosal healing in patients with inflammatory bowel diseases (IBD), active parameters were determined using statistical studies. For these active data [age, age of diagnosis, prior to azathioprine (in months), sex, smoking, and mucosal remission], artificial neural network models were constructed and the structure was attempted to be determined with the best performance (1-6).

Many gastroenterology studies were performed using expert systems, such as externally validating gastronomical score and comparison with artificial neural networks (7), investigating Crohn's disease (CD) using a vacillating genetic algorithm and neural classifier (8), monitoring gastrointestinal motility using neural networks (9), and distinguishing among subtypes of neoplastic colorectal lesions using neural networks (10).

Feed-forward back-propagation classification networks have been often used for medical applications in recent areas, such as classification of lung cancer using neural networks (11) and diagnosis of human brain tumor (12) and image reconstruction by electron magnetic reso-

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nance tomography (13). Cascade-forward networks have been used in the biomedical field as feed-forward back-propagation networks, for instance, in the detection of ischemic stroke (14) and preparation of two-dimensional sequences of corneal images (15).

In this study, feed-forward back-propagation and cascade-forward neural networks were implemented to IBD data to predict the response of the designed graphical interface system and to determine the method that will be more successful in helping the doctor.

This paper will be organized as follows: Section 2 will be constructed as Materials and Methods, which includes algorithms and detailed explanations. In section 3, the results which belong to implemented networks and discussions will be shown. Section 4 includes the appraisal of this study.

MATERIALS AND METHODS

This study investigated which technique would be better for diagnosing azathioprine active ingredient.

Azathioprine is a kind of purine that competitively inhibits the biosynthesis of purine nucleotides. Absorbing azathioprine is metabolized to 6-mercaptopurine. It has many side effects including leucopenia, pancreatitis, malaise, nausea, fever, rash, diarrhea, and hepatitis. These side effects sometimes limit their use in practice. Azathioprine is now a standard therapy for IBD. Clinical trials and meta-analysis have confirmed the influences of azathioprine for IBD in maintenance of therapy. Some patients can be maintained in clinical remission, but the rates of endoscopic mucosal remission are not great. There are less efficacy data for endoscopic mucosal remission by azathioprine in IBD. Moreover, any factor that alters the efficacy of azathioprine is not known yet. In this study, we evaluated patients with IBD administered 2.0–2.5 mg/kg per day of azathioprine of body weight to assess its effectiveness and limitations.

Study design and patients

This study was retrospectively designed. A total cohort of 2700 patients with IBD from 1995 to 2014 was reviewed. Data were collected in the Türkiye Yüksek İhtisas Hospital Inflammatory Bowel Disease clinic for azathioprine treatment only. Hospital study was conducted for the patient at the clinic over a period of at least 6 months. Patients who had started azathioprine therapy at another hospital were excluded. Patients who received azathioprine before for other indications were also excluded. Appropriate patients were at least 18 years old and had IBD for at least 3 months, with a score of 220–450 points on the Crohn's Disease Activity Index (CDAI). Other patients who were excluded were patients with short bowel syndrome, patients who had undergone ostomy surgery, patients with symptomatic strictures, a patient with abscess, patients who had undergone abdominal surgery within 6 months, patients with tuberculosis or other granulomatous infection, patients tested for purified protein skin or patients with a positive chest radiograph.

The patients were regularly followed-up with endoscopic examinations at the clinic. Remission was defined endoscopically with a full lower gastrointestinal endoscopy, showing no inflammation and no mucus, granularity, ulcer, or vascular invisibility. Definition criteria included no need for oral steroids (either prednisolone or budesonide). The continued use of oral 5-aminosalicylic acid compounds was allowed within healing definition. The effect of azathioprine healing was only assessed if treatment had been continued for over 4 months. Patients were excluded to follow-up if there was no endoscopic visit during the azathioprine therapy. Examination of colonoscopy with the degree of disease was involved and not defined by histological evidence of inflammation. Efficacy data was obtained from the last clinical evaluation.

Dosage of azathioprine was increased to 2.5 mg/kg per day using 50-mg tablets (125–250 mg per day). Systemic corticosteroids were started (for patients not receiving the drugs) with adjusted dosage until week 4 (maximum dosage is 40 mg/day). At the end of week 4, the dose was tapered and stopped until week 12.

Evaluation of efficacy and safety

Ileocolonoscopy was evaluated at baseline and week 16 later for each patient who had mucosal ulcers at the first examination and later in some patients. Each colonoscopy was interpreted by one of the experienced endoscopists who were ignorant of the study and the timing of the procedure (in first or at week 16). Corticosteroid-free clinical healing was defined in patients who had not received systemic corticosteroids for a minimum of 4 weeks. Mucosal healing or endoscopic mucosal remission was defined as the absence of mucosal ulceration at week 16 at least in patients with confirmed mucosal ulcers at baseline.

Primary end point

The primary efficacy end point was the rate of corticosteroid-free endoscopic remission at week 16.

Statistical analyses

Statistical analyses were tested with the paired t-test, Mann–Whitney U test, or Wilcoxon W test using Statistical Package for the Social Sciences (SPSS) (IBM, New York, USA).

In light of the medical evaluation, for designing a safety system for doctors, artificial neural networks were used for diagnosis. The topology that belongs to this system is given in Figure 1. A specialist doctor enters the patients' parameters via graphical interface; this helps them to predict whether the azathioprine cure will give mucosal remission or not.

Neural networks

Artificial neural networks are widely used in classification problems. Feed-forward back-propagation artificial neural networks

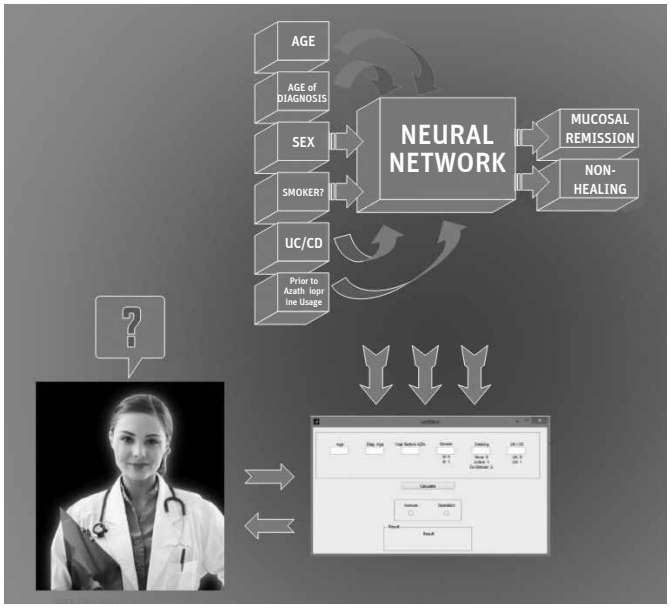

Figure 1. System topology.

include one or more hidden layers. Output layer, which is applied to the activation function, is connected to input layer via hidden layer or layers, for nonlinear structures (16).

The first step in the technical methodology, which related to this study, is about a feed-forward back-propagation network, and the next step consists of a cascade-forward network.

1. Feed-forward back-propagation networks:

The system includes one input, one hidden, and one output layer as shown in Figure 2. Six input parameters are used in the neural system. These include age, age of diagnosis, prior to azathioprine (in months), sex, smoking, and mucosal remission. Further response of the system that belongs to the network will be given in the Results & Discussions part.

For this method, data which came from the hidden layer to the j^{th} (j: [1,6] → ℵ) neuron is calculated by formula (1);

$$H(i)=f(\sum_{i=0}^{5}[I(i)*w(i,j)]+\phi(i)) \quad (1)$$

In the formula above, $H(i)$ is determined as the neuron value of each hidden layer, $I(i)$ is the input value, $w(i, j)$ is the weight value of the j^{th} hidden layer which comes from the i^{th} (i: [1,6] → ℵ) input neuron, $\phi(i)$, is the bias of the i^{th} hidden neuron, and f is the activation function.

For this method, data which came from the output layer to the k^{th} (k: [1,2] → ℵ) neuron is calculated by formula (2);

$$O(k)=f(\sum_{k=0}^{2}[H(j)*w(j,k)]+\phi(k)) \quad (2)$$

In formula (2), $O(k)$ determines the value of each output neuron, $H(k)$ is the hidden layer's value, $w(j, k)$ is the weight value of the k^{th} output layer which comes from the j^{th} (j: [1,6] → ℵ) hidden neuron, $\phi(k)$ is the bias of the k^{th} hidden neuron, and f is shown as the activation function.

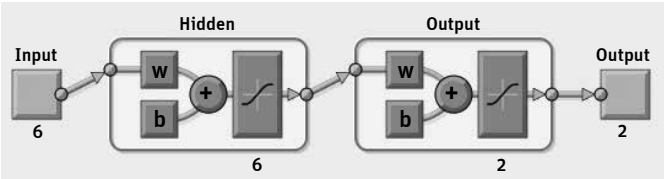

Figure 2. Feed-forward back-propagation network.

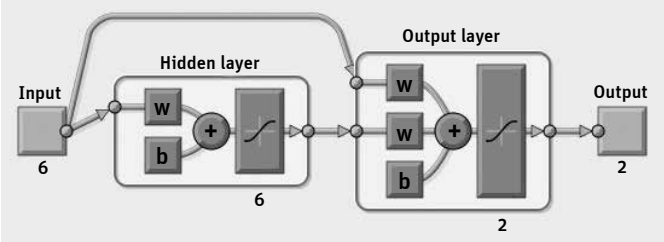

Figure 3. Cascade-forward neural network.

The cascade-forward neural network, another learning network, was been used in the second step for this study. The system which is related to cascade-forward network is shown in Figure 3.

Cascade-forward neural structure is used in the second step, and network parameters for this method are pointed out as follows.

2. Cascade-forward neural network:

Cascade-forward neural networks are similar to feed-forward networks. The difference between them is that there exists a weight connection to hidden and output layers which provides fast learning for input–output relationships. At the same time, the cascade-forward neural networks were used in this study for estimating the mucosal healing. The network was tested with different numbers of neurons in the hidden layer and the best is given in Figure 3.

For this method, data which came from the hidden layer to the j^{th} (j: [1,6] → ℵ) neuron is calculated by formula (1);

Cascade-forward method data which came from the output layer to the k^{th} (k: [1,2] → ℵ) neuron is calculated by formula (3);

$$O(k)=f(\sum_{k=0}^{2}[H(j)*w_j(j,k)]+I(i)*w_i(i,k)]+\phi(k)) \quad (3)$$

In formula (2), $O(k)$ determines the value of the each output neuron, $H(k)$ is the hidden layer's value, $w_j(j, k)$ is the weight value of the k^{th} output layer which comes from the j^{th} (j: [1,6] → ℵ) hidden neuron, $w_i(i, k)$ is the weight value of the k^{th} output layer which comes from the i^{th} (j: [1,6] → ℵ) input neuron, $\phi(k)$ is the bias of the k^{th} hidden neuron, and f is shown as the activation function.

This computer-based study includes six input parameters and two output parameters. Input and output parameters can be seen in Table 1. This study aims to find the best structure

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Table 1. Parameters used in tests

Input	Input	Input	Input	Input	Input	Output	Output
Age	Age of the Diagnosis	Prior to azathioprine (in months)	Usage Of Smoke	Sex	UC-CD	Mucosal Remission	Mucosal Non-Healing

UC: ulcerative colitis CD: Crohn's disease

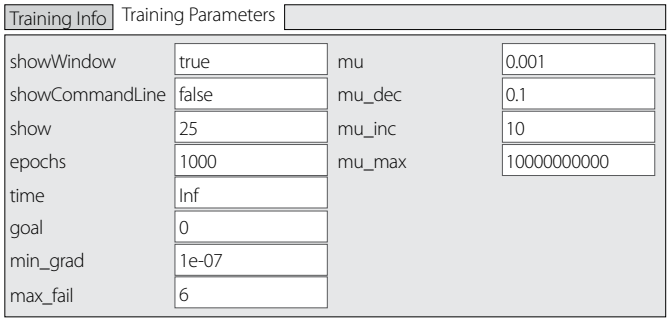

Figure 4. Training parameters.

for predicting mucosal remission or not for patients with IBD. Achieving this classification, feed-forward back-propagation and cascade-forward neural network structures were used.

Constructed network system's learning steps were defined in three stages as follows and the same learning parameters were used in both networks.
Gradient descent adaptive learning rate with back-propagation algorithm was applied to train the networks. Data division was randomly separated for training, validation, and test sets, and mean square error (MSE) performance criteria was selected.

i) Back-propagation: Scaled conjugate back-propagation is selected for supervised learning which finds the optimum weights. As long as the training process differences between output and target are compared, error is obtained. The error can be reduced and then, back-propagated using updating weights based on an iterative back-propagation learning rule. Training process is stopped when determined error rate is reached. For all inputs applied to the trained network, learning process will be concluded.

ii) Scaled conjugate gradient: There are many back-propagation optimization techniques that can be performed. Steepest descent (17), Newton's method (18), and conjugate gradient (19) are the most popular techniques. In this paper, scaled conjugate gradient algorithm was used for training the neural networks.

iii) Learning rate: Learning rate is defined as the degree of the updating weights and biases for each iteration (18). Adjusting the learning rate is really important for networks. Because the learning rate is too small, iteration process takes a long time. In contrast, if the learning rate selected is too large, weights change fast; therefore, the algorithm will be unstable. Avoiding this problem is the use of an adaptive learning rate in which the step size is chosen as large as possible while keeping the learning stable.

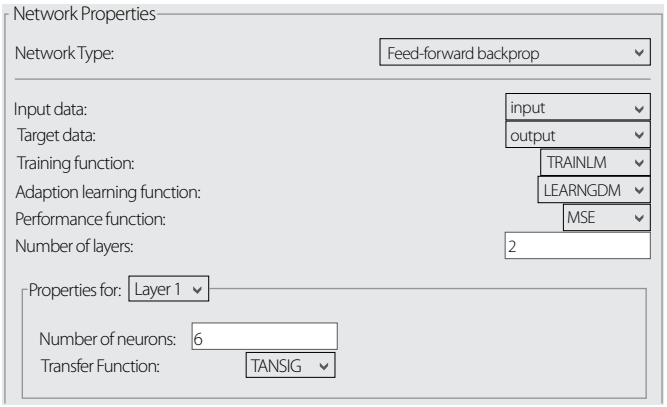

Figure 5. Network properties.

The initial value of learning rate was set to 0.01, as shown in Figure 4. In addition, a maximum 1000 iteration process was determined for avoiding an infinite loop.

Updating parameters are generally executed using online or offline (batch) training. In the online training, the network weights are changed after each step. Conversely, in the offline training, the weights are updated only after all the patterns are presented to the network.

Both networks' training were carried out for a total of 129 IBD data. Eighty percent (103 patients) were selected as training data, 10% (13 patients) as validation data, and 10% (13 patients) as the test data, which were distributed randomly.

Both artificial neural networks' (feed-forward back-propagation network and cascade–forward network) performance criteria was selected as MSE and various hidden layer sizes were evolved for obtaining minimum validation value, which was 0.24526, and a six-hidden-layer cascade-forward neural network was constructed (Figure 2,3). Transfer function was selected as a tangent-sigmoid (Figure 5).

For faster and easy usage of evaluating network's results, the doctor could enter the patient's parameters using graphical interface; therefore, the doctor could predict azathioprine usage (Figure 6). As a result of this interface, the doctor could make the prognosis effectively, and unnecessary drug usage can be reduced.

RESULTS

Patient demographics

A total cohort of 2700 patients with IBD, from 1995 to 2014, at the IBD clinic in Ankara, Türkiye Yüksek Ihtisas Hospital was re-

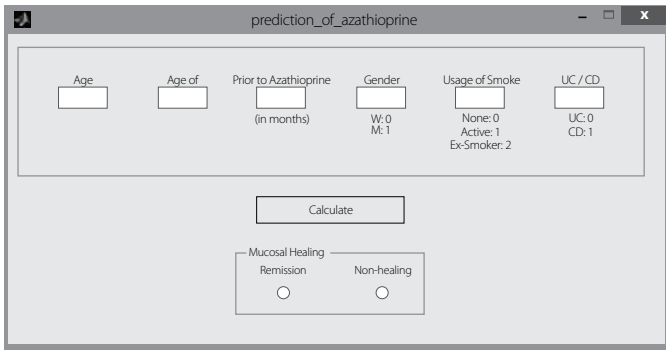

Figure 6. GUI for predicting system.

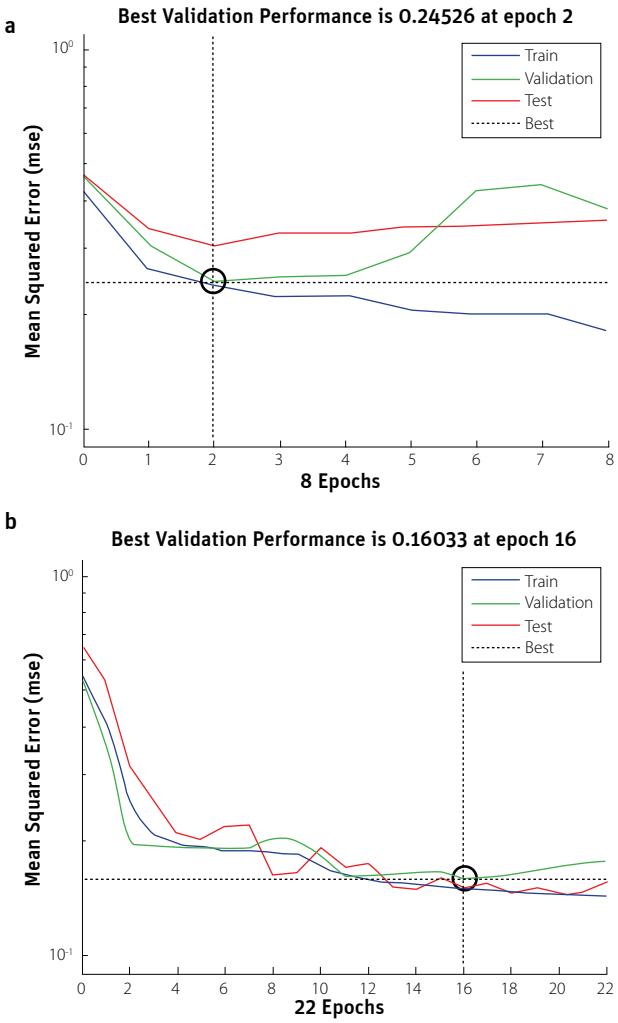

Figure 7. a, b. Performance criteria of the network. Feed-forward back-propagation network **(a)** Cascade forward network **(b).**

viewed from the database. Of the 2700 patients with IBD, there were 702 patients with CD and 1998 with ulcerative colitis (UC).

A total of 129 patients treated with azathioprine for IBD who met the enrollment criteria were selected from a total cohort. The mean age at IBD diagnosis of patients treated with azathioprine was 37 years (range: 11–72) with a male to female ratio of 2:1. The mean period between IBD diagnosis and azathioprine administration was 39.8 months (range: 0–264). The average duration of treatment was 31.5±24.7 months (range: 4-113) in the study.

Remission rates at IBD

We found that 37% patients were steroid-free and had an endoscopic mucosal remission after at least week 16 of azathioprine therapy. Of these patients with endoscopic mucosal remission, 44% (20 patients) were in the UC group, whereas 33% (25 patients) were in the CD group. These patients with endoscopic mucosal remission remained on endoscopic remission during the follow-up, up to 113 months in some cases.

Azathioprine therapy reduced the number of surgical interventions in patients with IBD ($p<0.05$). Male gender had a negative impact on the efficacy of azathioprine ($p<0.05$). Patients with IBD remission were older than the nonresponder group ($p<0.05$).

Remission rates at CD

Of the 53 azathioprine naive non-operated patients with CD, 34% (18 patients) were steroid-free and had endoscopic mucosal remission at least for 16 weeks of azathioprine therapy compared with 32% (7 patients) in operated patients ($p>0.05$). There was no difference between responders and nonresponders for smoking rates, INH use, and appendectomy existence as shown in Table 2 (a) and (b). Azathioprine therapy reduced the necessity for undergoing a surgery in patients with CD. There was no difference for the endoscopic mucosal remission rates in CD group based on the gender.

In this study, MATLAB (Mathworks, MA, USA) was used for six input parameters [age, age of diagnosis, prior to azathioprine (in months), sex, smoking, and mucosal remission] of 103 patients and performed by feed-forward back-propagation algorithm and cascade-forward network. As a first step, MSE curve showed the performance parameters of educational learning (Figure 7). MSE curve, which belongs to feed-forward with an educational learning curve, was performed with a 0.24526 error (Figure 7a). In the advanced cascade network, there was a 0.16033 training error (Figure 7b). The cascade-forward network is found to provide a better learning of approximately 34.6%.

Then, both of the networks were investigated in the area of classification performances, and they are presented in Figure 8. In determining the classification success of their feed-forward back-propagation network test parameters, when the confusion matrix was examined (Figure 8a), it was found that there is a total of 58.1% correct classification. Class 1 (mucosal healing) has remained at 11.6%. Class 2 (with no mucosal healing) for this rate has also remained at 46.5%. Figure 8 shows the areas under the receiver operating characteristic curves for the examined Class 1 and Class 2 with a determined rate of 64.2% and 52.7%, respectively.

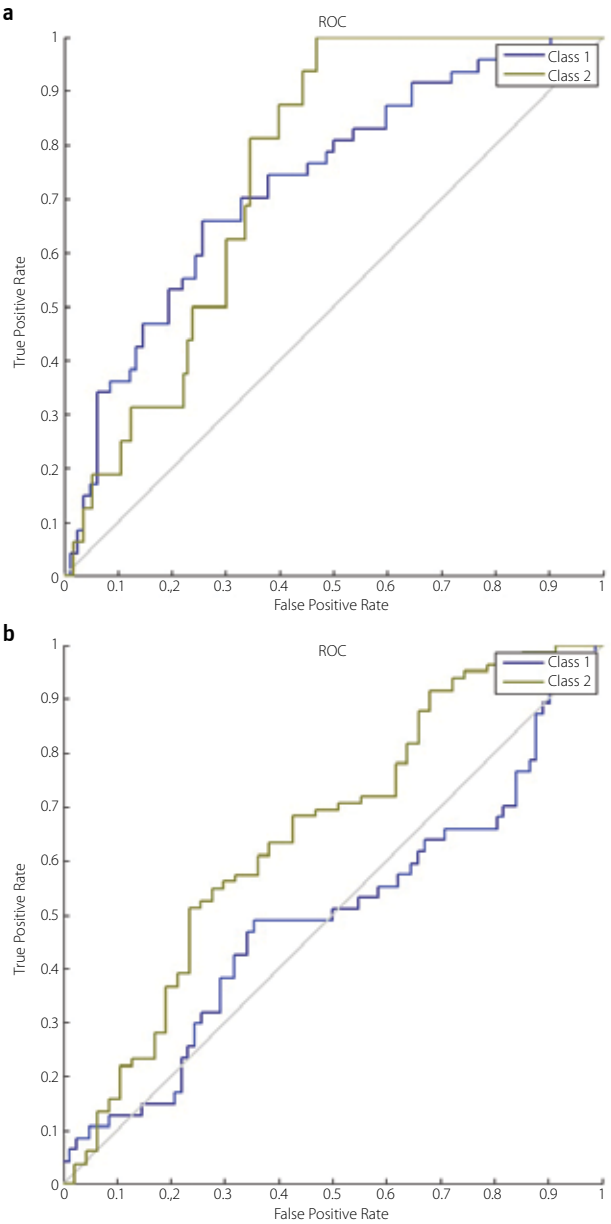

Figure 8. a, b. Receiver operating characteristics. Feed-forward back-propagation network **(a)** Cascade forward network **(b).**

Table 2. Confusion matrix for network test. Feed-forward back-propagation network, cascade-forward network

			Confusion Matrix	
Output Class	Class 1	15 (11.6%)	22 (17.1%)	40.5% 59.5%
	Class 2	32 (24.8%)	60 (46.5%)	65.2% 34.8%
		31.9% 68.1%	73.2% 26.8%	58.1% 41.9%
		Class 1	Class 2	TOTAL
			Target Class	
			Confusion Matrix	
Output Class	Class 1	98 (76.0%)	10 (17.1%)	90.7% 9.3%
	Class 2	17 (13.2%)	4 (3.1%)	19% 81%
		85.2% 14.8%	28.6% 71.4%	79.1% 20.9%
		Class 1	Class 2	TOTAL
			Target Class	

When determining the success of the cascade network classification with analysis of the confusion matrix (Figure 8b), it was found to have a total of 79.1% correct classification. Class 1 (mucosal healing) has remained at 76%. When this analysis offers the information to the accuracy of ROC analysis curve, the area under the curve is determined as 88.3%, under the feed-forward back-propagation network were identified, respectively, and the result is 81.6% (Figure 8b).

DISCUSSION

In this study, with 129 patients with IBD on azathioprine active ingredient, parameters were investigated to examine the improvement of the disease. The statistical significance of these parameters was examined corresponding to the input parameters and advanced cascade feed-forward neural network structure, and the results were analyzed. For the artificial neural network, the total number of samples is 120, 80% of this is used for the training of the network and 10% is used for validation. According to this ratio, 103 patient samples were used for learning, 13 samples were used for validating, and 13 samples were used for testing the network.

A system that can predict the response of patients with gastric mucosal structure, who can be cured completely, with the six input parameters given in this artificial neural network structure created for changing 129 patients with IBD, between the ages of 20 and 75, has been developed. Input parameters of age and age at diagnosis were normalized to enhance the system performance to prior periods of azathioprine. In order to create a system to help doctors to diagnose, offline feed-forward artificial neural network structure is developed, and also, using the structure, an interface that predicts the inflammatory mucosal healing or not was performed. This structure was tested and the success rate was found to be 79.1%.

When the success that was tested is evaluated by specialist doctors, these parameters provide faster and more successful patient assessment. Looking at the results of the network, specialist doctors would see quick results for patients who have been identified. In these studies, the success of widely used expert systems in medical parameters demonstrated that it could be an accurate and a fast algorithm for patient diagnosis.

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