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Brief communication (Original)

A nonlinear model for diagnosing malignancy in patients with exudative plural effusion using routine plural fluid findings

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Background: There is a challenge in diagnosing cancer in patients with exudative plural effusion using a noninvasive and accurate method.
Objective: We developed artificial neural network (ANN), as a nonlinear model, to discriminate malignant exudative plural effusion from nonmalignant based on routine pleural fluid findings.
Methods: The plural fluid parameters including total and differential cell counts, total proteins, lactate dehydrogenase (LDH), glucose, adenosine deaminase (ADA), as well as age and sex of 114 patients with exudative plural effusion were applied by models as input. The output was supposed to be the presence or absence of the cancer.
Results: The accuracy, sensitivity and specificity of ANN for predicting malignancy were 89.7%, 86.7%, and 91.7%, respectively. In addition, the neural network significantly outperformed the logistic regression model, as a linear model, (AUC: 0.892 vs. 0.633, respectively, $p < 0.001$).
Conclusion: The ANN is a novel accurate and noninvasive method that can be used clinically to diagnose malignancy in patients with exudative plural effusion.

Keywords: Artificial neural network, exudative plural effusion, malignancy

Pleural effusion is a common clinical problem and can occur as a complication of many different diseases [1]. Treatments vary noticeably and therefore etiological diagnosis is necessary. Cancer is a common cause of exudative pleural effusions [2, 3]. However, the differential diagnosis of malignant pleural effusion, such as pleural empyema and tuberculosis, is often difficult because of the similar biochemical profiles and predominance of lymphocytes in these conditions, especially in early phases of the formation of effusion [4-6].

Several diagnostic tests including cytological, microbiological, and biochemical evaluation of pleural fluid or sputum, and pleural biopsy, are not always helpful, because they have limitations [7-10]. Moreover, pleural fluid measurements of different tumor markers play a limited role in differentiating malignant and nonmalignant pleural effusions, and they should be interpreted in parallel with clinical findings and the results of conventional tests [11, 12]. Even though thoracoscopy or thoracotomy can be used to determine the cause of pleural effusion in these patients, this facility is invasive and not available in most hospitals [13]. Therefore, the development of early, less-invasive and accessible methods with high accuracy is greatly needed.

Previous investigators have used artificial neural networks (ANN) to provide a diagnosis for complex clinical problems. ANN are composed of a large number of highly interconnected processing elements (neurons) working in unison to solve specific problems. The capability of neural networks is because of their special features including nonlinear, adaptive, and parallel processing [14, 15].

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In this research, we developed ANN models, based entirely on pleural fluid findings that can be assessed in most laboratories, in order to discriminate cancer from other causes of pleural effusions.

Material and methods

We included 114 patients with a diagnosis of exudative pleural effusion who was admitted in Masih-Daneshvari hospital (Tehran, Iran) between June 2011 and May 2012. The study was approved by the local ethics committee and all subjects signed written informed consent.

The cause of pleural effusion was diagnosed cancer if the cytology or pleural biopsy specimen revealed underlying malignancy. In inconclusive cases, diagnosis was established by thoracoscopy or video-assisted thoracic surgery (VATS).

Before initiating any treatment, pleural fluid was analyzed for total cell count, differential white cell count, glucose, protein, lactate dehydrogenase (LDH), and adenosine deaminase (ADA). Biochemical measurements were performed using standardized photometric methods and cell counts were obtained by manual microscopy.

The patients were randomly divided into two groups. The first group included the data of 75 patients. This group was used to train and validate the models. The validation set is used to ensure that there is no overfitting in the final result. The second group (39 patients) was used to test the models. The test set provides an independent measure of how well the models can be expected to perform on data not used to train it.

We used ten data including routine analysis of the pleural fluid (ADA, LDH, glucose, protein, white blood cell (WBC), red blood cell (RBC), percentile of polynuclear leukocytes, percentile of lymphocytes), sex and age of patients as inputs of models. The outputs of the models were supposed to be diagnosis of cancer.

Artificial neural network model

We have designed a standard feed-forward ANN (in Matlab 7.4 environment, using its neural network toolbox), including five input neurons, fifteen neurons in a hidden layer, and one output neuron, to predict the cause of pleural effusion (malignant or nonmalignant). The number of the network layers, hidden neurons and the stopping criteria were determined through a trial-and-error process because no commonly accepted theory exists for predetermining the optimal number of neurons in the hidden layer [14, 17]. The default transfer functions for hidden layers and output layer were tansig and purelin, respectively. The newff function was used to create a network object in the training feed-forward network. The default back-propagation training algorithm was Levenberg–Marquardt (trainlm). To simplify the problem for the network, we preprocessed the input and target values and mapped them in to the interval [1]. The ANN was trained 500 times (epochs). The mean standard error was 2.46e-05.

Logistic regression model

A logistic regression model was developed using SPSS for Windows version 16.0. The training and testing datasets were the same as those used in the ANN. Student's *t* test and a Mann–Whitney *U* test were used for independent normally and nonnormally distributed continuous variables, respectively. Nominal variables were analyzed by means of a Chi square test. Accuracy (the number of correct predictions divided by the total predictions), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), likelihood ratio positive (LR+) and likelihood ratio negative (LR") of two models to predict cancer, cause of pleural effusion, were calculated. The discriminating power of these diagnosis models were measured by receiver-operating characteristic (ROC) curves. Significance was defined at the level of $p < 0.05$.

Results

The present study included 114 patients with exudative pleural effusion. Thirty-six patients had malignant pleural effusion (31.6%), of which 21 cases were randomly used in the training set and fifteen in the testing set. The nonmalignant causes of pleural effusion were tuberculosis (n = 27), empyema (n = 16), and others (n = 35). The characterization of patients with malignant and nonmalignant pleural effusions is shown in **Table 1**. The patients with cancer were significantly older ($p < 0.001$), and had higher RBC and lower ADA levels in pleural fluid ($p = 0.004$) than patients with other causes.

According to **Figure 1**, the ANN could diagnose 13 out of 15 patients with cancer and 22 out of 24 nonmalignant ones in a testing set. These amounts were 9 out of 15 and 16 out of 24 in a logistic regression test, respectively. **Table 2** shows the ANN and logistic regression performance in diagnosing the cancer in patients with exudative plural effusion.

Table 1. The characterizations and pleural fluid biomarkers of patients with malignant and nonmalignant pleural effusion

	Malignant pleural effusion (n = 36)	Nonmalignant pleural effusion (n = 78)	*p*
Age (year)	63.56 (12.7)	45.1 (20.7)	<0.001
Sex (male)	22 (61.1)	54 (69.2)	0.393
Red blood cell ($\times 10^3/\mu L$)	181.8 (234.0)	702.4 (167.6)	0.004
White blood cell ($\square 10^3/\mu L$)	1.7 (1.8)	2.7 (4.6)	0.191
Polynuclear leukocytes (%)	19.4 (23.7)	14.6 (24.5)	0.331
Lymphocyte (%)	79.3 (23.2)	84.3 (24.8)	0.314
Glucose (mg/dL)	101.6 (53.2)	95.4 (52.5)	0.557
Protein (mg/dL)	4.2 (1.2)	5.5 (5.8)	0.196
Lactate dehydrogenase (U/L)	713.4 (617.8)	698.8 (514.5)	0.895
ADA	20.6 (10.1)	45.5 (25.7)	<0.001

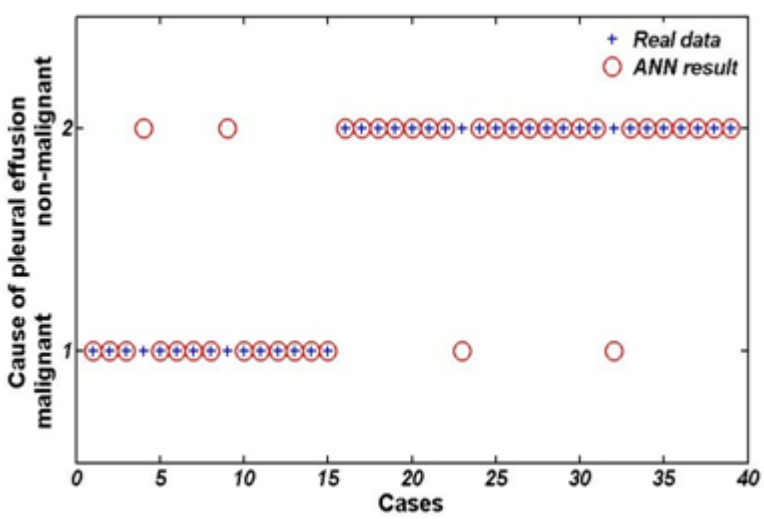

Figure 1. ANN (artificial neural network) test results. The pluses represent the real output and the circles the ANN output. "1" means presence and "2" means absence of the malignancy

Table 2. Comparison of predictive performance of artificial neural network (ANN) and logistic regression (LR) at diagnosing malignant pleural effusion

	ANN	LR
Accuracy (%)	89.7	64.1
Sensitivity (%)	86.7	60.0
Specificity (%)	91.7	66.7
Positive predictive value (%)	86.7	52.9
Negative predictive value (%)	91.7	72.7
Likelihood ratio positive	10.4	1.8
Likelihood ratio negative	0.1	0.6

The ROC curves of the ANN and LR models were shown in **Figure 2**. Results of the comparison of the area under curves (AUC) between two models are shown in **Table 3**. The ANN model significantly outperformed the logistic regression model (AUC: 0.892 vs. 0.633, respectively, $p < 0.001$).

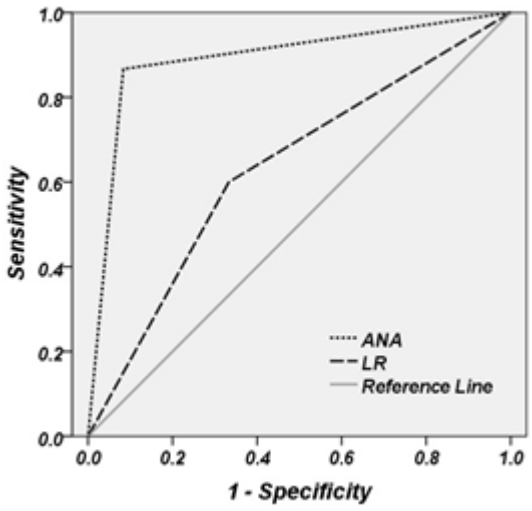

Figure 2. Comparison of receiver operating characteristic (ROC) curves between artificial neural network (ANN) and logistic regression (LR)

Table 3. Comparison of receiver operating characteristic (ROC) curves

	Area under curve	Standard error	95% confidence interval
Artificial neural network	0.892	0.061	0.753–1.000
Logistic regression	0.633	0.093	0.451–0.816

Discussion

The results demonstrated that the ANN could distinguish cancer from other causes of exudative plural effusion with reliable accuracy. Although only three parameters, age, RBC, and ADA levels of plural fluid, were significantly different between malignant and nonmalignant groups, adaptive and parallel processing properties of the ANN enabled it to predict real output using nonlinear interaction between all variables.

Thoracocentesis is the first step in the work-up of every pleural effusion of unknown origin. The diagnosis of cancer in patients with exudative pleural effusion can be obtained through a positive cytology, but its yield varies widely between studies [18]. Sahn and Good [19] reported that patients with malignant pleural effusion confirmed at thoracoscopy, a positive cytology was found in up to 78% of those with pH < 7.30, whereas it was positive in only 51% of those with a pH > 7.30. Moreover, although tumor markers cannot be considered as a definitive diagnosis, they can be helpful in selecting patients for further investigation with more invasive techniques when they are clearly positive [18]. Closed pleural biopsy is less sensitive than cytology in malignant pleural effusions, whereas most of the guidelines recommend the addition of a biopsy procedure when a first cytology is negative [20, 21]. By comparison with needle biopsy, the superiority of thoracoscopy is clear. Results of a study involving patients with malignant pleural effusion showed a positive needle biopsy in 36%, whereas thoracoscopy obtained the diagnosis in 87% [22]. However, thoracoscopy requires hospitalization of the patient, and can have severe complications (such as subcutaneous emphysema, empyema, and air embolism) and contraindications (such as respiratory disorders). Moreover, thoracoscopy is expensive and not available in most hospitals [13, 23-26]. Therefore, developing early, less-invasive, and accessible methods that have high accuracy are greatly needed.

Total and differential cell counts, and biochemical study (including total proteins, LDH, glucose, ADA), are routinely conducted on the pleural fluid samples in hospitals [18]. To our knowledge, there is no study using a mathematical model to diagnose cancer based on pleural fluid biomarkers. Our finding showed that our ANN could accurately diagnose malignancy based on routine laboratory parameters. The accuracy,

sensitivity, and specificity of ANN for predicting cancer was 89.7%, 86.7%, and 91.7%, respectively. By comparison with invasive techniques, diagnostic ability of the ANN as a noninvasive and available method was considerable. According to previous study, an AUC ≥ 0.7 is diagnostically useful [27]. In our study, the ANN model discriminated malignant from nonmalignant plural effusion better than the LR model (AUC = 0.892 vs. 0.633, $p < 0.001$) in the testing set.

The nonlinear and adaptive capability of the neural network made it a satisfactory tool by which to provide a reliable outcome for complex and nonlinear clinical problems. A neural network approach is also preferable in that ANNs are model independent and flexible in being able to use mixes of categorical and continuous variables. The real time use of the ANN is not difficult. The number of hospitals that have an electronic medical record is growing rapidly. Once trained, the ANN could reside in the background of the clinical information systems. The data used by our ANN are standard information routinely collected from patients. Once entered into the electronic record, these data could then be used by the ANN to generate the probability of the predicted outcome. ANN accuracy could also be continuously improved over time because it can constantly be retrained as more patients are added to system. By contrast, the "black box" interpretation is a major obstacle to the acceptance of ANNs as a tool for the medical decision support systems. However, an accurate second opinion is often helpful in medical decision making with or without a detailed understanding of how it works [14, 15].

Some limitations of this study should be addressed. First, the ANN was not tested in real time. It is not clear how physicians will respond if given ANN predicted outcome of BDR. Second, this study was conducted at a single institution. These findings must be corroborated on patients from multiple locations using more samples.

In conclusion, using routine laboratory data from plural fluid, our ANN model was able to diagnose the malignancy in patients with exudative plural effusion. This model is a novel, highly accurate, noninvasive, inexpensive, and available method, which can be used clinically.

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