Study of Aided Diagnosis of Hepatic Carcinoma Based on Artificial Neural Network Combined with Tumor Marker Group

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Abstract

To develop a computer-aided diagnostic scheme by using an artificial neural network (ANN) combined with tumor markers for diagnosis of hepatic carcinoma (HCC) as a clinical assistant method. 140 serum samples (50 malignant, 40 benign and 50 normal) were analyzed for α-fetoprotein (AFP), carbohydrate antigen 125 (CA125), carcinoembryonic antigen (CEA), sialic acid (SA) and calcium (Ca). The five tumor marker values were then used as ANN inputs data. The result of ANN was compared with that of discriminant analysis by receiver operating characteristic (ROC) curve (AUC) analysis. The diagnostic accuracy of ANN and discriminant analysis among all samples of the test group was 95.5% and 79.3%, respectively. Analysis of multiple tumor markers based on ANN may be a better choice than the traditional statistical methods for differentiating HCC from benign or normal.

Keywords: Artificial neural network, Tumor marker, Hepatic carcinoma

I. Introduction

HCC is one of the most common cancers in the world, and its mortality rate is next to cancer of the stomach and esophagus and resides the 3rd [1]. For a long time, HCC has been the second leading cause of cancer death in china. In recent years, the incidence and mortality rate have been increasing [2]. For the lack of typical symptoms of HCC in early stage, it is easy to neglect, and easy to confuse with other gastrointestinal diseases. The diagnosis of HCC usually occurs at later stages in the disease when there are few effective treatment options and the prognosis for patients with HCC is very poor. Currently

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serum AFP combined with ultrasound imaging is applied to achieve the monitoring of high-risk groups in clinic. HCC can be diagnosed in sub-clinical stage. But now people rely too much on liver cancer diagnostic imaging. AFP is a specific indicator for diagnosis of HCC, but the specificity of its individual value is not adequate for effective screening. Related literature reported that the positive rate of AFP was from 60% to 80% [3]. There is also defective in ultrasound. Multiple serum markers might be utilized to improve sensitivity. Over the years, a large number of markers for HCC have been reported to complement AFP [4]. However, tumor markers cannot solve the problem because it contains multi-parameter which cannot be efficiently analyzed by general statistics analysis methods. Methods based on ANN appear to be suited for this task.

ANN analysis as a statistical modeling tool has demonstrated the ability to assimilate information from multiple sources and detect subtle and complex patterns. It is a statistical model whose mathematical structure reproduces the biological organization of neural cells for simulation of the learning dynamics of the brain. This model solves the problems of uncertain or ambiguous medical information more effectively. There have been a large number of reports on the use of ANN for clinical diagnosis [5]. The ANN based computer-aided diagnostic scheme of HCC has become one of the most active parts in the recent medical research. Application of intelligent diagnosis system based on the ANN is used to automatic detection and classification for cancer and to improve the accuracy of detection and classification [6].

In this paper, chemiluminescence immunoassay and spectrophotometry were separately used to detect the serum α-fetoprotein (AFP), carbohydrate antigen 125 (CA125), carcinoembryonic Antigen (CEA), sialic acid (SA) and calcium (Ca) in three groups. ANN technology can be applied to extract effective features and improve the diagnostic accuracy of HCC.

2. Subject and Methods

2.1 Study population

A total of 140 serum samples were obtained from the First Affiliated Hospital of Zhengzhou University. The collection included 50 specimens from patients with HCC, 40 specimens from patients with benign conditions and 50 normal individuals. All benign and malignant patients were confirmed by pathology, and normal subjects were confirmed by checkup centers. The 50 patients with HCC (age range was 25~81 years old, average 55.73±12.30 years, 41 of males, 9 of females) were obtained including 42 patients with primary HCC and 8 patients with secondary HCC (34 hepatocellular carcinoma, 10 intrahepatic cholangiocarcinoma and 6 mixed hepatocarcinoma ). The 40 patients with benign liver disease (age range was 26~70 years old, average 46.15±12.45 years, 26 of males, 14 of females) were enrolled. There are 50 health cases in normal group (age range was 23~60 years old, average 42.18±11.45 years, 23 of males and 27 of females).

2.2 Sample preparation and tumor marker measurements

All blood samples were collected in the fasting state, laid at room temperature for 30 minutes and centrifuged for 3 minutes at 3000 r/min. the abstracted serum samples were stored at −80 ℃ and thawed immediately prior to assay. AFP, CA125 and CEA were detected by chemiluminescence immunoassay. SA was determined by spectrophotometry. Ca was detected by calcium assay kit (Azo-end method of arsenic III).
2.3 ANN model derivation

Three-layer, feed-forward ANN with back-propagation (BP) algorithm were implemented. The 140 samples were allocated randomly into training set (100 samples) and test set (40 samples). The model was developed by training set. Then, the samples of test set were used to validate the quality of model. The training and testing of the ANN were performed by means of Sigmoid transfer function. The five tumor marker values in 35 cases with HCC, 30 patients with benign liver disease and 35 normal cases were used as input data. Network parameter settings were 5 nodes as input layer, 15 nodes as hidden layer, 1 node as output layer, 0.001 as target error, 0.7 as learning rate, 0.95 as momentum factor. The value equal to 0.9 was HCC, equal to 0.5 was benign and equal to 0.1 was normal.

The marker values were preprocessed numerically before being used as inputs to the ANN. It involved logarithmic transformation and a “physiologically based” normalization step. In this step, marker values were truncated to within a range most relevant to the differentiation of patients before normalization.

2.4 Data Analysis

The final results of test set which were forecasted by BP network compared with the results of discriminant analysis which was according to SPSS12.0 by using of AUC. The level of test was 0.05.

3. Results

3.1 The detecting results of serum tumor marker

In table I, descriptive statistics of the five tumor markers were listed. The concentration value of SA followed Gaussian distributions and was expressed by Mean±SD, while other tumor markers showed skew distribution and was expressed by median and interquartile range.

3.2 Discriminant analysis model and Prediction Results

In this study, the variables available for inclusion in the model were AFP, CEA, CA125, SA and Ca. The discriminant function was derived based on the known measurements (The expected value in three groups was 1, 2 and 3) and the characteristic of variables, then the discriminant functions were used to decide which class the cases belonged to. The accurate rate was obtained through comparing the classification of original data and the classification of discriminant function. In the process of modeling, the log-in not systematic full-model method and fisher function factor were chose. The results of discriminant analysis were as follows.

In table II, the first three lines were the number of results judged by discriminant functions, while the rest three lines were the corresponding percentage. The accurate rate was 79.3% for three groups by discriminant analysis model.

3.3 Development of artificial neural network model

BP neural network was applied to develop the diagnostic model by training set according to the setting error. The expected results were achieved after 3000 iterations and then stopped the training. Then the model was validated by test set. The sensitivity of HCC was 93.3%, the specificity was 96.0%, the
accuracy was 95.5%, the positive predictive value (PPV) was 93.75% and the negative predictive value (NPV) was 96.2%.

3.4 Comparisons of Discriminant Analysis and ANN

Table III shows the prediction results contrast of BP network and discriminant analysis. Figure 1 shows the ROC curves. The accuracy rates of prediction according to the ANN and discriminant analysis equation were 94.3% and 79.3%, the area under the ROC curve were 0.986(95%CI: 0.968~1.005) and 0.842(95%CI: 0.774~0.910), respectively.

TABLE I Testing results for AFP, CEA, CA125, SA, and Ca

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>AFP (μg/L)</th>
<th>CA125 (U/ml)</th>
<th>CEA (ng/ml)</th>
<th>SA (mg/L)</th>
<th>Ca (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>50</td>
<td>1.80</td>
<td>10.90</td>
<td>9.45</td>
<td>805.44</td>
<td>119.84</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.76b</td>
<td>5.40</td>
<td>2.78</td>
<td>±93.10</td>
<td>30.76</td>
</tr>
<tr>
<td>Benign</td>
<td>40</td>
<td>0.86</td>
<td>6.45</td>
<td>0.51</td>
<td>829.17</td>
<td>97.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.39</td>
<td>3.89</td>
<td>0.55</td>
<td>±97.32</td>
<td>5.09</td>
</tr>
<tr>
<td>HCC</td>
<td>50</td>
<td>22.86m</td>
<td>39.18m</td>
<td>0.32n</td>
<td>833.96±</td>
<td>103.40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>439.30</td>
<td>49.82</td>
<td>0.61</td>
<td>148.73b</td>
<td>37.44m</td>
</tr>
</tbody>
</table>

Table III Comparison of results in test set by BP and discriminant analysis

<table>
<thead>
<tr>
<th>Assessment index</th>
<th>ANN model</th>
<th>Discriminant analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%)a</td>
<td>96.0</td>
<td>46.0</td>
</tr>
<tr>
<td>Specificity (%)a</td>
<td>98.9</td>
<td>98.9</td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td>94.3</td>
<td>79.3</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>98.0</td>
<td>95.8</td>
</tr>
<tr>
<td>NPV (%)</td>
<td>97.8</td>
<td>76.7</td>
</tr>
<tr>
<td>AUC</td>
<td>0.986b</td>
<td>0.842</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.968~1.005</td>
<td>0.774~0.910</td>
</tr>
</tbody>
</table>

aThe sensitivity and specificity were calculated according to HCC, bP<0.05 for difference in area under ROC curve between ANN and discriminant analysis.
4. Discussion

4.1 The diagnostic value of HCC with tumor markers

AFP was first identified in human fetus serum by Bergstralad and Czar in 1956 [7]. It is a molecular 70,000 glycoprotein, produced at high levels by the fetal liver, transcriptionally repressed after birth. AFP is a specific indicator and is the most common serological marker used in HCC [8]. AFP level of 20μg/L is considered as a level that prompts further testing. A systematic review reported that sensitivity of AFP levels higher than 20μg/L ranged from 41% to 65%, while specificity ranged from 80% to 94% [9]. The positive rate of AFP was 60% in this research. This indicated that the sensitivity and specificity of single marker for diagnosis of primary HCC were not high. It was also reported that 40% of patients with early primary HCC and 15%~20% of those with advanced primary HCC, serum AFP were normal. CA 125, a high molecular weight mucin, was first detected with a radioimmunoassay in patients with advanced ovarian cancer [10]. Later, it was found in a wide variety of tumors and was regarded as a relatively broad spectrum tumor marker. Increased serum CA125 levels are correlated with the severity of liver damage. By ELISA, the positive rate of AFP was 76.0%, the positive rate of CA125 in all patients and AFP positive group was 68.7% and 42.9% [11]. The positive rate of CA125 tested by electrochemiluminescence assay was 59.57% [12]. In short, CA125 is one of the indexes which reflect the severity of liver damage in cirrhosis patients, and it is also a sign that cirrhosis produce canceration.

CEA was a nonspecific tumor-associated antigens which was first extracted from colon cancer by Gold and Freedom Man. Previous studies reported that CEA was a tumor marker of colon carcinoma. Later studies revealed CEA still express highly in liver and gastric cancer, and had higher sensitivity for malignant tumor of enteron developed from the embryonic endodermal layer. The rate of positive diagnosis of HCC was over 50% [13]. SA is a vital component of glycoprotein and glycolipids in cell membranes. The serum concentration of SA is at a normal level when cell metabolism is normal. If it is abnormal metabolism, especially advanced malignant tumor, the serum SA level is significantly elevated. A series of reports suggested that serum SA could be regarded as a sensitive marker in early diagnosing of HCC. It has been reported that the sensitivity, specificity, PPV, NPV and accuracy of SA assay to diagnose HCC were 70%, 88.3%, 75%, 85.5% and 82.2%, respectively [14]. But it is not a specific
marker for HCC, and should be combined with other tumor markers for identifying HCC. Liver plays an adjustment role in Ca metabolism. The serum Ca level was reduced after serious disease and cancer of the liver from lack of Ca uptake as a result of the decreased process of vitamin D hydroxylation. It was reported that the level of calcitonin was increased in Patients with HCC and the level decreased after operation. This showed that HCC could produce calcitonin. Experiment showed that the serum Ca, especially free Ca, was correlated to the severity of liver dysfunction [15].

According to this study, AFP was the most specific indicator in these five tumor markers, and this showed that it was a relatively sensitive and specific marker in diagnosis of HCC. Moreover, CA125 and Ca were the relative specific indicators of HCC. Combined detection of AFP, Ca and CA125 might be useful for assisted diagnosis of HCC. The sensitivity and specificity of other two indicators were not elevated and were useful mainly in the tumor markers with union tests.

4.2 The prediction of HCC by ANN model

With the thorough study of ANN and the swift development of computer application technology, the theory of ANN gradually became mature, and in recent years has been used in many fields. It also gradually obtained the development in the application of medical field. ANN is different from traditional statistics. According to ANN, the basic data may not be followed Gaussian distribution, and has certain fault tolerance. These advantages bring considerable convenience to the popularity of ANN. Conventional methods combined with multiple markers might be utilized to improve sensitivity, but specificity has inevitably been reduced. ANN might improve sensitivity using multiple markers without sacrificing specificity.

The established ANN model in this article had sensitivity of 93.3%, specificity of 96.0%, accuracy of 95.5%, PPV of 93.75% and NPV of 96.2%. The results of this study were superior to detection of tumor marker alone and combined detection of tumor markers [16-19]. Moreover, the ANN model accomplished not only the differential diagnosis of HCC with benign and normal but also the differential diagnosis of benign disease and normal. This is a matter of the utmost importance to screening the high risk people. These results indicated that ANN in combination with multiple markers can realize the assisted diagnosis of liver cancer.

4.3 Comparisons of ANN Model and Discriminant analysis

The sensitivity, specificity, accuracy, PPV and NPV of ANN and discriminant analysis model were evaluated. The specificity and PPV seemed to be equal between the two models while the others were obviously different. The AUC was used to compare ANN model and discriminant analysis in predicting accuracy of HCC. The AUC of ANN model was higher than discriminant analysis, there was statistical significance.

Based on the ANN, a classification model of HCC was established in this paper, whose effect was superior to traditional discriminant analysis. The reason is that discriminant analysis processed parameters by use of linear combination. The basic data must subject to the normal-distribution condition and have the same covariance matrix. However, in practical applications, many data are unable to meet those conditions. ANN is suitable to solve complex or non-linear problem and has a powerful of learning and memory, association and other functions, which adapt to the assisted diagnosis and data analysis better.
References


