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ORIGINAL ARTICLE

Using Artificial Neural Network to Predict Cirrhosis in Patients with Chronic Hepatitis B Infection with Seven Routine Laboratory Findings

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Background and Aims: **Chronic liver diseases could lead to cirrhosis and related complications. Histological diagnosis by liver biopsy has long been the gold standard for assessing the degree of fibrosis and diagnosis of cirrhosis, but it is an invasive procedure with inherent risk and sampling variability. The aim of this study was to assess the ability of the artificial neural network (ANN) to predict the presence or absence of cirrhosis in patients with chronic hepatitis B by using routine laboratory findings.**

Methods: **114 chronic hepatitis B patients who were admitted between 1996 and 2006 at Loghman Hakim hospital and the Tehran Hepatitis Center were evaluated. The disease was confirmed by hepatitis B virus (HBV) DNA, liver biopsies, and biochemistry values, which were obtained from all of patients. Back propagation ANN analyses were carried out by training the networks with the data. The patients were divided into two groups. The first group (92 patients) included two thirds of the cirrhotic patients (12 patients) and two thirds of the non-cirrhotic patients (80 patients) in a randomized rout.**

Results: **Ascitis, edema, pruritus, splenomegaly, and hepatomegaly were present in 26.3%, 31.6%, 21.1%, 63.2%, and 0% of cirrhotic patients, respectively, and 0%, 0%, 3.2%, 2.4%, and 0.8% of non-cirrhotic patients, respectively. The sensitivity, specificity, and positive and negative predictive ANN values in comparison with liver biopsy in the diagnosis of cirrhotic patients due to chronic HBV were 71.43%, 84.45%, 71.43%, and 95%, respectively.**

Conclusions: **In chronic hepatitis B patients, if the ANN value of certain laboratory manifestations is negative, there will be a 95% chance of having a negative liver biopsy.**

Keywords: **Hepatitis B Virus, Chronic Hepatitis, Cirrhosis, Artificial Neural Network**

Introduction

Chronic liver diseases could lead to cirrhosis and related complications. Cirrhosis is the most common non-neoplastic cause of death among hepatobiliary and digestive diseases [1-3]. Accurate diagnosis is crucial to the management of patients with chronic hepatitis B (CHB) or chronic hepatitis C (CHC) [4]. Histological diagnosis with liver biopsy has long been the gold standard for assessing the degree of fibrosis and diagnosis of cirrhosis, but it is an invasive procedure with inherent risk and sampling

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variability [5, 6]. In addition, the diagnostic accuracy depends on the size of the biopsy specimens [6, 7]. Serum-based tests of liver fibrosis have attracted more attention in recent years. Sim *et al.* [8] used a simple index of only aspartate transaminases and found that the platelet count was correlated with liver fibrosis. Li *et al.* [9] studied the effect of coagulation factors and their correlation with the severity of cirrhosis. Some researchers have measured the correlation of cirrhosis with serum transforming growth factor-beta1[10], serumal level of macrophage migration inhibitory factors, tumor necrosis factor alpha (TNF-α), interlukine-6 (IL-6) [11], and hepatitis B virus (HBV) DNA levels [12]. Haydon [13] showed that artificial neural network (ANN) analysis is likely to provide a non-invasive test for diagnosing cirrhosis in HCV-infected patients. ANN analysis is known to be particularly suitable for modeling complex multidimensional relationships [14-16].

In this study, we assessed the ability of ANN to predict the presence or absence of cirrhosis in patients with chronic hepatitis B by using routine laboratory findings.

Materials and Methods

114 chronic hepatitis B patients, who were admitted between 1996 and 2006 at Loghman Hakim Hospital and the Tehran Hepatitis Center, were evaluated.

The disease was confirmed by HBV DNA and liver biopsies, which were obtained from all patients. Liver biochemistry (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkalin phosphatase); prothrombine time (PT); international normalized ratio (INR); platelet count; total and direct bilirubin (Bil); albumin; globulin; cholesterol; glucose; AST/ALT ratio; and AST/platelet ratio were measured in all patients. According to the histopathological diagnosis, the liver disease was grouped as non-cirrhosis or established cirrhosis by the pathologist. Back propagation and ANN analysis were carried out by training the networks with data. Each neuron has a single output but can have multiple inputs. In the model, there were 8 neurons for input, 15 neurons for middle, and one neuron for output. The patients were divided into two groups. The first group (92 patients) included two thirds of the cirrhotic patients (12 patients) and two thirds of the non-cirrhotic patients (80 patients) in a randomized rout. The data from this group were used for training the network by using the significant variables obtained to predict the presence or absence of cirrhosis in this group. The second group (52 patients) included one third of the cirrhotic patients (7 patients) and one third of the non-cirrhotic patients (45 patients) in a randomized rout. The data from this group were used for testing the network. Then, the data were analyzed for sensitivity, specificity, and positive and negative predictive values for the diagnosis of cirrhotic patients.

Results

Of the 144 patients who were studied, 19 (13.2%) patients had histologically confirmed cirrhosis (3 females, 16 males), and 125 (86.8%) patients had no histological evidence of cirrhosis (23 females, 102 males). Ascitis, edema, pruritus, splenomegaly and hepatomegaly were present in 26.3%, 31.6%, 21.1%, 63.2%, and 0% of the cirrhotic patients, respectively. Ascitis, edema, pruritus, splenomegaly, and hepatomegaly were found in 0%, 0%, 3.2%, 2.4%, and0.8% of the non-cirrhotic patients, respectively. There was a significant correlation between confirmed cirrhosis and ascitis, edema, pruritus, and splenomegaly ($P<0.001$).The means of the laboratory findings for patients are shown in Table 1.

Artificial neural network analysis

In the first stage, the ANN analysis was performed by training the networks with Patient Group I and testing their performance on Patient Group II. To allow for a direct comparison, the multiple logistic regression model was also constructed from Group I, and its performance was assessed for Group II. The significant variables between cirrhotic and non-cirrhotic patients were selected as the input layer. Such variables included age (I1) and the mean values of PT (I2), INR (I3), platelet count (I4), direct bilirubin (I5), globulin (I6), AST/ALT (I7), and AST/platelet (I8). The presence of cirrhosis (U1) or non-cirrhosis (U0) was used as the output layer (Fig. 1).

The sensitivity, specificity, and positive and negative predictive values of ANN in comparison with liver biopsy in the diagnosis of cirrhotic patients due to chronic HBV are shown in Table 2.

Discussion

The latest American Association for the Study of Liver Diseases practice guidelines on CHB (2004) recommend that patients with HBV DNA concentrations of over 10^5 copies/mL and persistently or intermittently increased ALT should be evaluated

Table 1. The mean laboratory findings in cirrhotic and non-cirrhotic patients.

	P-value	Mean	Cirrhosis
Virus Load	0.608	63606787.53 ± 36160377.76	-
		9760816.38 ± 7911694.26	+
PT	0.000	13.31 ± 0.073	-
		14.89 ± 0.62	+
INR	0.000	1.07 ± 0.01	-
		1.45 ± 0.12	+
Platelet Count	0.000	206147.83 ± 7305.40	-
		117947.37 ± 12120.13	+
White blood cell (WBC)	0.094	6288.83 ± 149.08	-
		7676.84 ± 1878.96	+
Glucose	0.246	93.40 ± 2.31	-
		103.07 ± 15.07	+
Blood urea nitrogen (BUN)	0.052	17.42 ± 1.31	-
		29.22 ± 10.97	+
ALT	0.284	108.61 ± 11.42	-
		75.58 ± 23.33	+
AST	0.382	63.48 ± 4.66	-
		76.89 ± 24.84	+
Alkaline phosphatase	0.600	243.20 ± 16.74	-
		218.13 ± 24.88	+
Total Bil	0.503	1.15 ± 0.11	-
		1.35 ± 0.18	+
Direct Bil	0.000	0.27 ± 0.01	-
		0.45 ± 0.053	+
Albumin	0.274	60.72 ± 5.71	-
		45.11 ± 2.93	+
Triglyceride (TG)	0.719	120.92 ± 8.04	-
		113.43 ± 13.84	+
Cholesterol	0.236	174.08 ± 4.03	-
		161.33 ± 11.16	+
Globulin	0.000	20.53 ± 0.71	-
		28.70 ± 2.69	+
AST/ALT	0.000	0.73 ± 0.04	-
		1.41 ± 0.26	+
AST/Platelet Count	0.001	0.00033 ± 0.000028	-
		0.00068 ± 0.00018	+

further by liver biopsy [17]. Haydon's [13] study showed that ANN analysis could predict the presence or absence of cirrhosis in chronic hepatitis C patients based on a number of host and virus factors, without the need for a liver biopsy and laparoscopy, with a sensitivity of 92% and a specificity of 98.9%. As seen in our research, the sensitivity of ANN of some laboratory manifestations such as PT, INR, platelet count, direct bilirubin, globulin, AST/ALT, and AST/platelet in diagnosing cirrhosis due to chronic HBV was 71.43%, whereas the specificity of the ANN sensitivity value as compared to liver biopsy was 84.45%. Also, the positive predictive value of the ANN value of those laboratory manifestations in comparison with liver biopsy was 71.43%. In other words, if the ANN value of the abovementioned

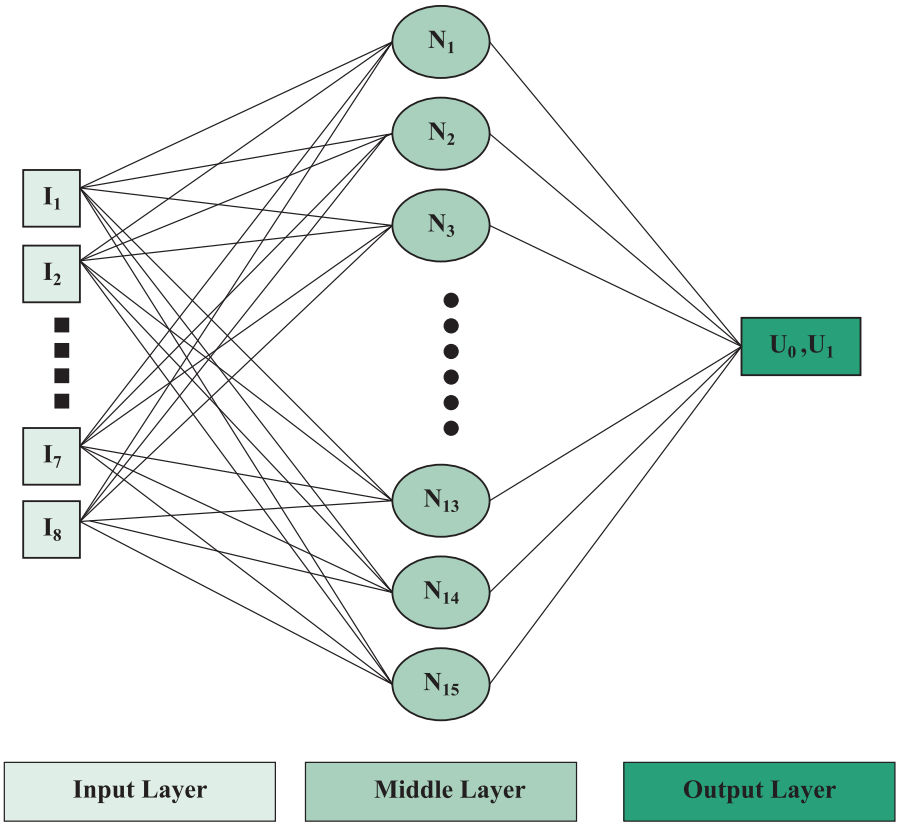

Figure 1. Artificial neural network with three layers: input, middle, and output (I1-I8: Input variables, N1-N15:15 neurons in middle layer, U0: no cirrhosis, U1: cirrhosis).

Table 2. Comparison of ANN with liver biopsy in the diagnosis of cirrhotic patients due to chronic HBV.

ANN result \ Liver biopsy	Cirrhosis	Non-cirrhosis	Total
Positive	5	7	12
Negative	2	38	40
Total	7	45	52

Sensitivity: 71.43%; specificity = 84.45%; positive predictive value = 71.43%; negative predictive value = 95%

laboratory manifestations is positive in a chronic hepatitis B patient, the patient's liver biopsy will likely be 71.43%. The negative predictive ANN value of the abovementioned laboratory manifestations was 95%. This means if the ANN value of some laboratory manifestations is negative for a chronic HBV patient, there will be a 95% chance of having a negative liver biopsy. Shiomi's [18] research determined artificial neural networks could be useful for the diagnosis of chronic liver diseases from liver scintiscans.

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