Diagnosis of Chronic Liver Disease from Liver Scintiscans by Fuzzy Reasoning

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We investigated the possibility that fuzzy reasoning might be used to standardize diagnosis of liver disease based on scintigraphic results and compared the results with those obtained when scintiscans were scored conventionally. **Methods:** Seventy-five patients with chronic liver disease (11 patients had chronic persistent hepatitis, 26 had chronic aggressive hepatitis and 38 had cirrhosis) and 25 controls were studied. Another 75 patients with hepatitis or cirrhosis were examined to test the effectiveness of the membership functions. Liver scintiscans were taken 20 min after the intravenous injection of 111 MBq of ^{99m}Tc-phytate. Fuzzy reasoning was used to evaluate the following five items: the ratio of the sizes of the left and right lobes, splenomegaly, radioactivity in the bone marrow, deformity of the liver and distribution of radioactivity in the liver. The degree of conformity to each of the three liver diseases being investigated was substituted into the membership function for the conclusion. The center of gravity for each patient's results was calculated. Conventional scoring was made with three levels for each of the five items examined by fuzzy reasoning. **Results:** Distinctions between chronic persistent hepatitis and chronic aggressive hepatitis were difficult to assess with fuzzy reasoning and conventional scoring. The diagnostic accuracy was 95% for patients with cirrhosis and 88% for patients with chronic hepatitis with fuzzy reasoning. With conventional scoring the accuracy was 86% for patients with cirrhosis and 75% for patients with chronic hepatitis. When fuzzy reasoning was used to examine the other 75 patients with chronic liver diseases, the accuracy was 93% for patients with cirrhosis and 86% for patients with chronic hepatitis. **Conclusion:** The method is simple and can be used routinely in clinical settings.

Key Words: fuzzy reasoning; technetium-99m-phytate; liver scintigraphy; hepatitis; cirrhosis

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After the first report of liver scintigraphy with a radioactive isotope in 1953 (*1*), various localized liver diseases (*2–5*) and diffuse hepatocellular diseases (*6–15*) have been diagnosed with this imaging technique. With advances in computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography and other diagnostic imaging methods, scintigraphy is being used less than before in the diagnosis of localized liver disease. In one diagnostic study of small hepatocellular carcinoma, the sensitivity of scintigraphy was 39%, ultrasonography was 50% and CT was 56% (*16*). The differential diagnosis of cystic lesions and solid tumors is possible by ultrasonography and by CT but not by scintigraphy. Liver scintigraphy with a colloid is based on phagocytosis of foreign matter by reticuloendothelial cells in the liver and provides information about liver morphology, splenomegaly, changes in bone marrow and intrahepatic radionuclide distribution. This method is still useful in the diagnosis of diffuse hepatocellular diseases. Accuracy was given in one comparison of three methods as 64% by CT, 51% by ultrasonography and 70% by scintigraphy (*17*).

A drawback to diagnoses based on liver scintigraphy is subjectivity in the evaluation of images. Zadeh (*18*) reported a method to make fuzzy information quantitative by using membership functions (fuzzy set theory). We examined the usefulness of reasoning based on the fuzzy set theory in the evaluation of liver scintiscans in the diagnosis of diffuse hepatocellular disease.

MATERIALS AND METHODS

Subjects

Liver scintigraphy was performed on 25 control subjects with healthy livers and 75 patients with hepatic viral infections. Scintigraphic diagnoses were compared with definitive analyses of hepatitis and cirrhosis through histological examination of liver specimens obtained by laparoscopy or needle biopsy done under ultrasonic guidance. Results of the histological examinations, performed in accordance with internationally established criteria (*19*), showed 11 patients had chronic persistent hepatitis (CPH), 26 had chronic aggressive hepatitis (CAH) and 38 had cirrhosis. Scintiscans of the patients were used to establish membership functions. Another 75 patients with chronic liver diseases were later evaluated to establish if the membership functions we created were suitable for clinical use. Nine of these patients had CPH, 24 patients had CAH and 42 patients had cirrhosis.

Liver Scintigraphy

Scintiscans were obtained starting 20 to 30 min after intravenous injection of 111 MBq of ^{99m}Tc-phytate. Images (400,000

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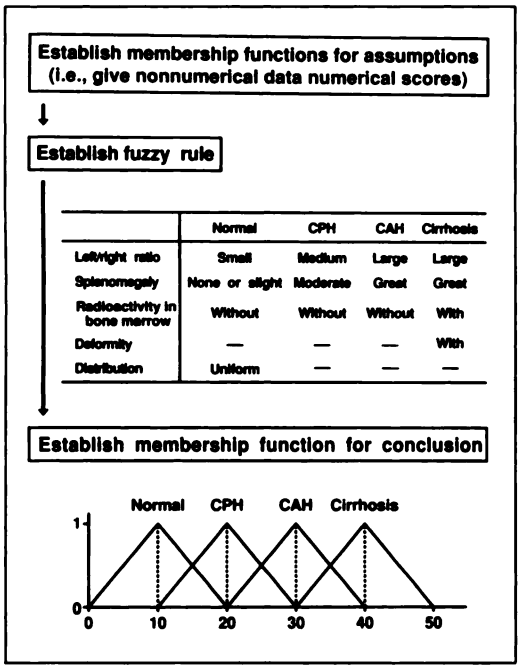

FIGURE 1. Steps in fuzzy reasoning. — = not used.

counts) were obtained in the anterior and posterior views with a scintillation camera.

Fuzzy Reasoning

Application of fuzzy reasoning involves three steps (Fig. 1). First, a method for scoring in which nonnumerical data are given numerical scores (membership functions) is established. Second, data from subjects already assigned to one of four groups by another method (Table 1) were analyzed, and the results were used to establish fuzzy rules. Fuzzy rules can be set out in a tabular format specifying what and how items are to be used in assignment of subjects in this particular application to a group. Some of the five items we selected (ratio of left and right lobe sizes, splenomegaly and radioactivity in bone marrow) were useful in assigning all four categories: normal, CPH, CAH and cirrhosis. Other items (deformity and distribution of radioactivity) were not useful in the assignment of all categories. Last, the membership function for the conclusion is established, which provides a method by which the various scores obtained from the different items are reduced to a single number. In our application, triangles (which are customarily used) were drawn with their peak at one on the y-axis whereas the numbers along the x-axis were chosen arbitrarily.

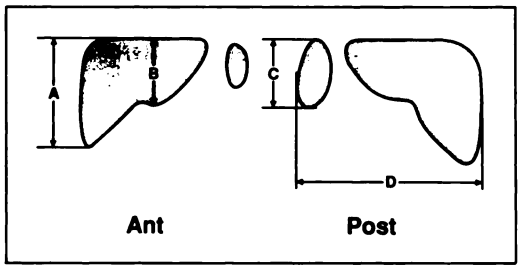

FIGURE 2. Calculation of the left-to-right ratio of the liver and splenomegaly from scintiscans.

A membership function is an ordered set of numbers associated with a probability for one of the items selected for examination. (Some researchers use the word probability, although the word is not completely satisfactory (*20*). Still, its use helps us to remember that each item is given a score from zero to one, in other words, a percent from 0% to 100%.) Probability expresses the degree of membership in a fuzzy set. To establish membership functions for the left-to-right ratio and splenomegaly, we measured image dimensions on the scintigrams of 100 subjects (Fig. 2).

The left-to-right ratio was calculated as B/A and splenomegaly was calculated as C/D. We found the mean left-to-right ratio for healthy controls to be 0.49 and defined a small left-to-right ratio to be equal to or below this mean. The mean C/D for the healthy controls was 0.29, and we defined none or slight splenomegaly to be equal to or less than this mean. Both a small left-to-right ratio and none or slight splenomegaly were scored as 1.0 on the y-axis (Fig. 3). The s.d.s of these means were 0.01 and 0.09, respectively. Values equal to or greater than the mean plus one s.d. (0.59 for a small left-to-right ratio and 0.38 for no or slight splenomegaly) were scored as zero on the y-axis. The score of an x-axis value in the intermediate regions was the y-value of the corresponding point on the straight line connecting y = 1 and y = 0. A medium left-to-right ratio and moderate splenomegaly were defined as values in the triangles shown in Figure 3, with the mean of the patients with a definitive diagnosis of chronic hepatitis based on histological findings scored as 1.0 and any value in the range of the mean ± s.d. scored as zero. A large left-to-right ratio and large splenomegaly were defined as being equal to or greater than the mean of patients with cirrhosis. Both were scored as 1.0. Values equal to or less than the mean minus one s.d. were scored as zero.

Without radioactivity of marrow and liver deformity, most clear-cut scintigrams were given x-axis values of zero, corresponding to a y-axis score of 1 (Fig. 4). A borderline finding, was

TABLE 1
Conventional Scoring of Scintigrams

Score	Left-to-Right ratio	Splenomegaly	Radioactivity in bone marrow	Deformity of the liver	Distribution of radioactivity in liver
1	B/A < 0.56	C/D < 0.26	None	None	Uniform
2	0.56 ≤ B/A < 0.70	0.26 ≤ C/D < 0.40	Moderate	Moderate	Intermediate
3	0.70 ≤ B/A	0.40 ≤ C/D	Marked	Marked	Not uniform

Intermediate = between uniform and nonuniform. See Figure 2 for areas A-D.

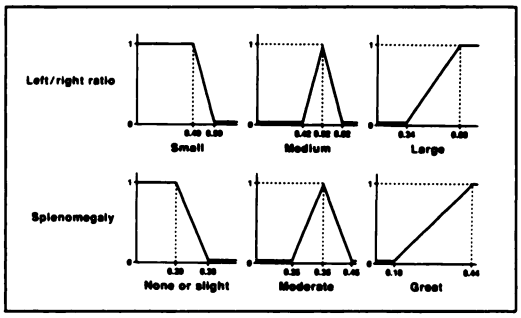

FIGURE 3. Membership functions for assumptions of the left-to-right ratio for liver and splenomegaly.

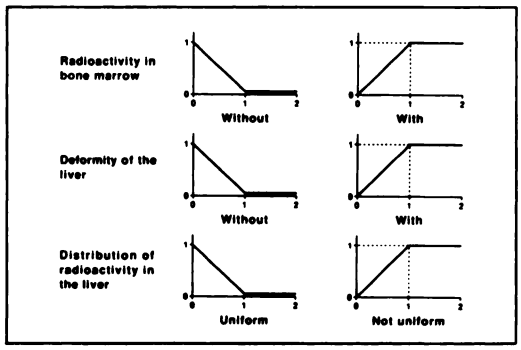

FIGURE 4. Membership functions for assumptions of radioactivity in bone marrow, liver deformity and radioactivity distribution in the liver.

given an x-axis value of 0.5, which corresponds to a y-axis score of 0.5. The x-axis value of one was used for mild but unmistakable radioactivity or deformity and was given the y-axis score of zero. For uniform distribution of radioactivity in the liver, the x-axis value of zero was used for unmistakably uniform results (y-axis score, 1), and the x-axis value of one was used for nonuniform results (y-axis score, 0), with higher values increasingly less uniform. For the category of not uniform distribution, the x-axis value of zero was used for uniform results (y-axis score, 1), and the x-axis value of one was used for nonuniform results (y-axis score, 0), with higher values increasingly less uniform.

Next, four fuzzy rules (Fig. 1) were prepared to distinguish between healthy subjects and patients with CPH, CAH or cirrhosis. A healthy subject was identified from the left-to-right ratio, splenomegaly, bone marrow and radioactivity distribution in the liver. A subject with CPH or CAH was identified from the left-to-right ratio, splenomegaly and bone marrow radioactivity. A subject with cirrhosis was identified from the left-to-right ratio, splenomegaly, bone marrow radioactivity and liver deformity.

Scoring using conventional methodology was done on a three-point scale for the same five items [Table 1, (*21*)]. The sum of the scores for each patient was used as the scintiscore. Fuzzy logic results were compared with this conventional method. Histological diagnosis was used to confirm the fuzzy logic findings.

Calculation by Fuzzy Reasoning

Examples of patients included among the first 100 subjects are given to illustrate the method used to establish membership functions and to illustrate practical use of the fuzzy rules we prepared.

Patient 1. CAH was diagnosed in a 34-yr-old male. From the scintiscan (Fig. 5), the left-to-right ratio (B/A) was 0.53, splenomegaly (C/D) was 0.42, bone marrow radioactivity was rated as without (x = 0), liver deformity was moderate (x = 1) and radioactivity distribution in the liver was uniform (x = 0). The conventional scintiscore of this patient was 3.0. The y-axis score of each item was calculated with membership functions. The score of a small left-to-right ratio was 0.60, medium ratio was 0.90 and the large ratio was 0.75. In other words, this patient's left-to-right ratio was 60% small, 90% medium and 75% large. The score of none or slight splenomegaly was 0, moderate splenomegaly was 0.15, severe splenomegaly was 0.90, without bone marrow radioactivity was one, with bone marrow radioactivity was 0, without liver deformity was 0, with deformity of the liver was 1, uniform radioactivity distribution in the liver was 1 and nonuniform radioactivity distribution in the liver was 0. From the fuzzy rule, the conformity to normal was zero, CPH was 0.15, CAH was 0.75 and cirrhosis was 0. The membership function for the conclusion shown in Figure 6 was used to reduce these four values to a single

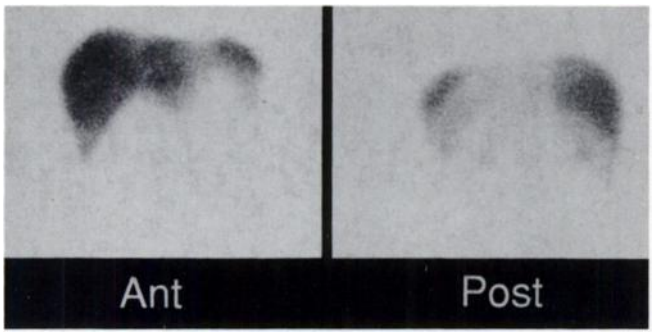

FIGURE 5. Scintiscan, Patient 1.

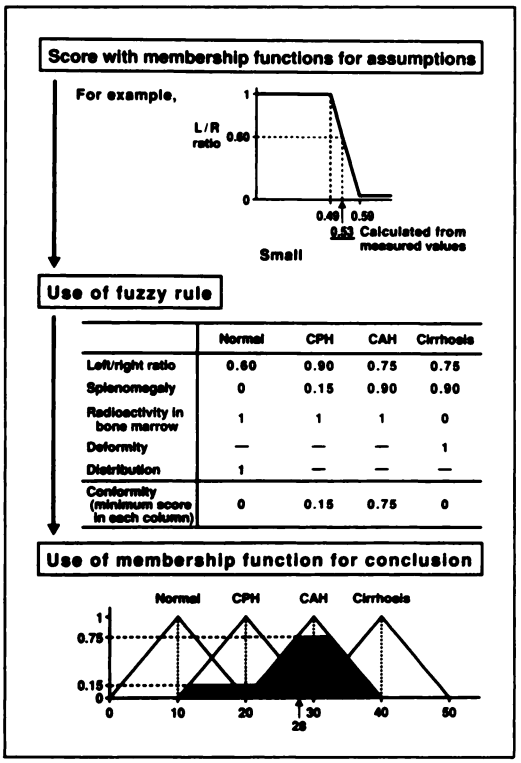

FIGURE 6. Results of fuzzy reasoning for Patient 1.

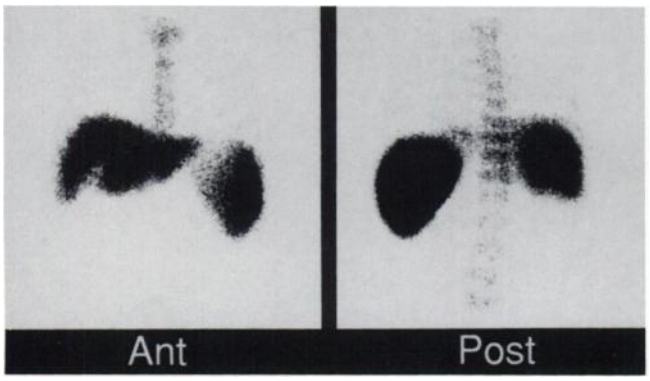

FIGURE 7. Scintiscan of Patient 2.

value. From the left, the conformity to CPH was 0.15, so the triangle for CPH was taken to be filled up to a y-axis value of 0.15. The same was done for conformity to CAH. The center of gravity was then calculated to give the single value. The center of gravity of the filled area in Figure 6 was 28. The meanings of the arbitrary numbers on the x-axis were as shown in the figure. Values of 10, 20, 30 and 40 meant that the subject was normal or had CPH, CAH or cirrhosis, respectively. Intermediate values such as 28 indicated that CAH was more likely than CPH. Fuzzy reasoning diagnosis was in agreement with the histological diagnosis.

Patient 2. Cirrhosis was diagnosed in a 64-yr-old male. From the scintiscan (Fig. 7), the left-to-right ratio was 0.74, splenomegaly was 0.52, bone marrow radioactivity was marked (x = 2.0), liver deformity was intermediate [between moderate and marked (x = 1.5)] and radioactivity distribution in the liver was intermediate [between uniform and nonuniform (x = 1.0)]. The conventional scintiscore of this patient was 8.5. From the fuzzy rule, the conformity to normal was zero, CPH was zero, CAH was zero and cirrhosis was 1.0. The center of gravity of the filled area in Figure 8 was 40.

RESULTS

The centers of gravity for the first 100 patients studied are shown in Figure 9. Dotted lines were drawn at the positions that gave the greatest accuracy based on histological diagnosis. The results of conventional scoring for the same subjects are given in Figure 10. The positions in

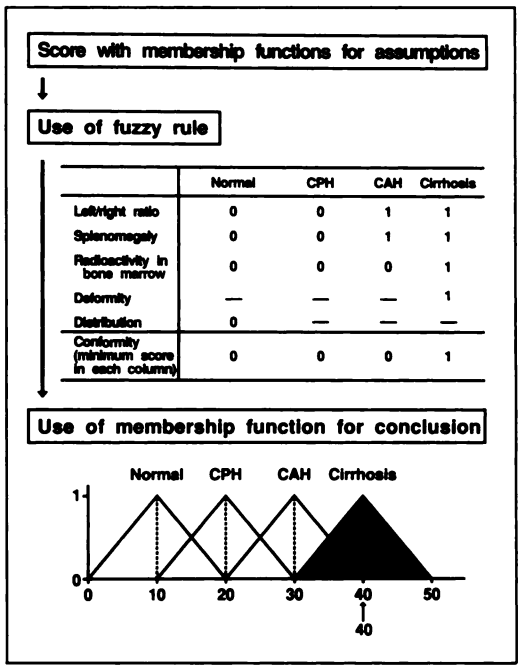

FIGURE 8. Results of fuzzy reasoning for Patient 2.

the dotted lines in Figure 9 were also used in Figure 10. With the boundaries established between categories, both methods discriminated among control subjects, patients with chronic hepatitis and patients with cirrhosis of the liver, but neither discriminated between CPH and CAH. Fuzzy reasoning was also used to evaluate the scintigrams of the other 75 patients with chronic liver diseases. The positions of the centers of gravity of the 75 patients and the same 25 control subjects are shown in Figure 11. Table 2 compares the results of fuzzy reasoning and conventional scoring.

DISCUSSION

About 20% of patients with viral hepatitis eventually develop cirrhosis, which often progresses to hepatocellular carcinoma (*22–25*). Therefore, accurate diagnosis of diffuse liver diseases is clinically important. Many different biochemical tests are now available, but their diagnostic

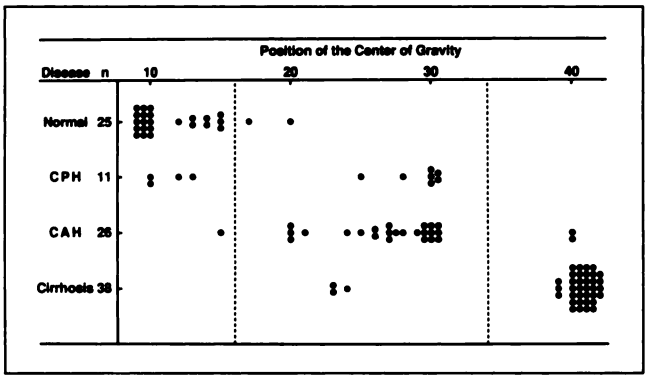

FIGURE 9. Centers of gravity for the first 100 subjects (25 healthy subjects and 75 patients with chronic liver diseases).

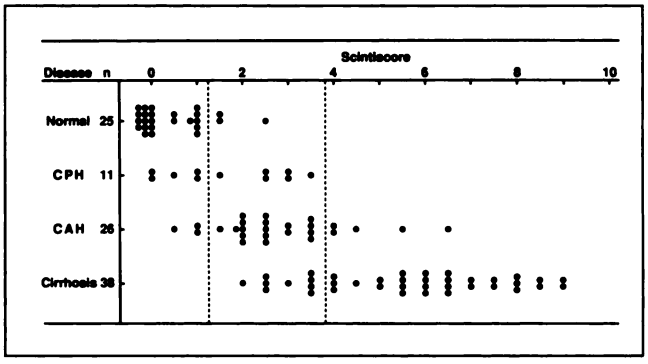

FIGURE 10. Conventional scintiscores for the first 100 subjects (25 healthy subjects and 75 patients with chronic liver diseases).

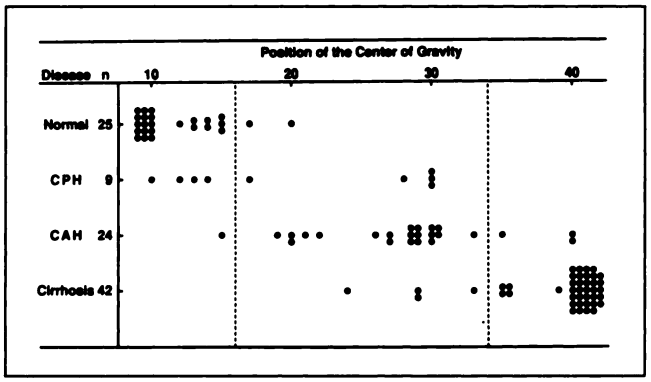

FIGURE 11. Centers of gravity for the second 100 subjects (the same 25 healthy subjects and another 75 patients with chronic liver diseases).

usefulness is unsatisfactory. For example, there are many cases of latent cirrhosis undetected by biochemical liver function tests (*26–28*). Diagnostic imaging examinations such as abdominal ultrasonography (*17,29–32*) and CT (*17,32*) are not accurate enough for the diagnosis of diffuse liver diseases. Scintigraphic diagnosis of liver diseases depends greatly on the interpreter's medical knowledge. Medical information is often not clear-cut and the use of fuzzy reasoning in the diagnostic process has been tried before (*33–38*), including interpretation of abdominal ultrasonography (*39*). We applied this process to the scintigraphic diagnosis of hepatic disorders.

Diagnosis is often based on reasoning such as: there is portal hypertension if splenomegaly is great or without splenomegaly, there is no portal hypertension. If the same patient is seen by two physicians, however, differing opinions may be formed about the presence of splenomegaly, or about its magnitude, if present. Fuzzy reasoning allows the use of such unclear data in syllogistic reasoning. Conclusions made on the basis of an evaluation of a hepatic scintiscan vary with the evaluation (*16*).

Important considerations in fuzzy reasoning include how to establish membership functions and fuzzy rules. We tried various combinations of categories in establishing fuzzy rules. Of those tested, the combinations shown in Figures 1–11 seemed most appropriate for analysis of our first 100 subjects. Other combinations are possible.

This methodology enabled differentiation between healthy subjects versus subjects with liver disease, as well as cirrhotic patients versus subjects without cirrhosis. Patients with CPH or CAH, however, could not be distinguished. Diagnosis of CPH and CAH requires histological analysis. There is little difference in liver morphology and function. Compared with results from the 100 patients whose data were used to establish the membership functions, the diagnostic success in the next 100 patients was only slightly lower. The score calculated by fuzzy reasoning gave more accurate diagnostic results than conventional scoring (*21*).

One merit of this method is that liver scintigrams obtained by ordinary methods can be used without further computer processing. If SPECT is available, the method can be used with minor modifications. Yet, there is some disagreement about the relative advantages of such CT and planar scintigraphy (*32,40*). Some researchers have applied fuzzy reasoning to the ultrasonographic diagnosis of thyroid diseases and reported that the method lessens diagnostic errors made by inexperienced physicians (*39*). Diagnosis based on fuzzy reasoning should be clinically useful.

TABLE 2A
Sensitivity, Specificity and Accuracy for Chronic Hepatitis

	Sensitivity	Specificity	Accuracy
Fuzzy reasoning	30/37	58/63	88/100
(initial 100 subjects)	(81%)	(92%)	(88%)
Conventional scoring	24/37	51/63	75/100
(initial 100 subjects)	(64%)	(81%)	(75%)
Fuzzy reasoning	25/33	61/67	86/100
(another 75 patients)	(76%)	(91%)	(86%)

TABLE 2B
Sensitivity, Specificity and Accuracy for Cirrhosis of the Liver

	Sensitivity	Specificity	Accuracy
Fuzzy reasoning	35/38	60/62	95/100
(initial 100 subjects)	(92%)	(97%)	(95%)
Conventional scoring	29/38	57/62	86/100
(initial 100 subjects)	(76%)	(92%)	(86%)
Fuzzy reasoning	38/42	55/58	93/100
(another 75 patients)	(91%)	(95%)	(93%)

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