Simple Computer Quantitation of Spleen-to-Liver Ratios in the Diagnosis of Hepatocellular Disease

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Increased splenic uptake of radiocolloids is a helpful sign in the scintigraphic diagnosis of various hepatocellular diseases, but little attempt has been made to quantify this physiologic phenomenon. We have devised a simple computer method that compares average splenic activity to average right-lobe liver activity. The method is reproducible ($r = 0.97$) and exhibits little interobserver variation ($r = 0.99$). One hundred clinically normal subjects were found to have a nearly symmetrical distribution of S/L ratios around a mean of 0.77, with a s.d. of 0.20. Fifteen subjects normal by biopsy were found to have a similar mean spleen-to-liver (S/L) ratio of 0.74. Based upon a normal range of 0.37 to 1.17 (0.77 ± 2 s.d.), elevated S/L ratios were found in fatty metamorphosis (85%), cirrhosis (67%), and chronic hepatitis (43%). Abnormal S/L ratios in the range from 1.17 to approximately 1.4 were not visually obvious. Overall sensitivity of the S/L ratio in these three diseases is 69%. When combined with the other scintigraphic indications of hepatocellular disease (nonhomogeneous colloid uptake, hepatomegaly, splenomegaly, and bone-marrow colloidal uptake), the liver scan was found to have a sensitivity of 93%.

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The extrahepatic distribution of radiocolloids is a well-recognized manifestation of certain hepatocellular diseases. Castell and Johnson (*1*) determined liver and spleen scores based upon visual estimation of Au-198 colloid in bone marrow and spleen, and demonstrated a nearly linear correlation between liver-scan score and maximum arterial ammonia concentration in 20 patients with chronic liver disease. Using a similar scoring method, Millette et al. (*2*) found a significant positive correlation between the portohepatic gradient (free portal-venous pressure minus free hepatic-venous pressure) and extrahepatic distribution of Au-198 colloid. Fernandez et al. (*3*) found that the presence of spleen or bone-marrow Au-198 colloid accurately differentiated all patients with wedge hepatic-venous pressures greater than 18 mm Hg, and suggested that extrahepatic Au-198 colloid may be a more sensitive indicator of portal hypertension than the presence or absence of varices on gastroscopy. Geslien et al. (*4*), using visual estimation of spleen-to-liver (S/L) ratios in combination with other scintigraphic criteria of hepatocellular disease, demonstrated an overall sensitivity of 83% in diffuse hepatocellular diseases, ranging from 100% in cirrhosis to 60% in portal fibrosis. Although they found that nonuniform colloidal uptake in the liver was the most sensitive indicator, it correlated significantly only if accompanied by spleen or bone-marrow colloidal uptake. Geslien also found that all grades of increased splenic or bone marrow uptake correlated significantly with hepatocellular disease.

All of the above studies have depended upon visual estimation of the S/L ratio. Few attempts have been made to quantitate this phenomenon. Eddleston et al. (*5*) compared peak activity over spleen to peak liver activity, expressed as a per-

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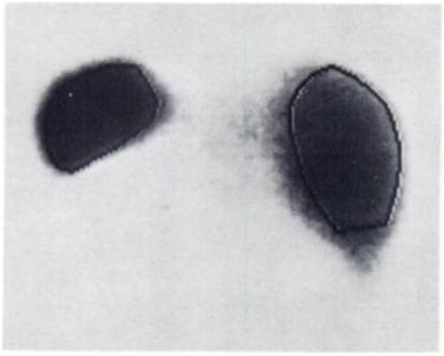

FIG. 1. Typical location of computer AOI over spleen and liver.

centage, and determined that normal subjects ranged from 0 to 35%. They found that 59% of cirrhotic patients had peak splenic activities that were 70% or more above the peak liver activity.

The purpose of this study was to evaluate a simple computer quantitation of S/L ratio, to determine normal ranges, and to determine S/L ratios for various hepatocellular diseases.

MATERIALS AND METHODS

Patient Selection. The study group consisted of 68 patients who had both liver scan and liver biopsy performed during the past 2 yr. No patient was selected for biopsy on the basis of the S/L ratio. An additional 100 subjects without liver biopsy were used to establish the normal range. These 100 subjects without liver biopsy had no clinical, biochemical, or scintigraphic evidence of liver disease, and most were referred for metastatic evaluations. A small additional group of patients with normal biopsies are discussed separately in the data.

Liver-spleen imaging. Scintigraphy was performed at 15 min following i.v. injection of 6 mCi of Tc-99m sulfur colloid. Scintillation-camera images were obtained in the anterior, anterior erect, right anterior oblique, right lateral, and posterior projections using high-resolution collimation.

Data processing. All posterior liver-spleen images were recorded on a minicomputer. If both liver and spleen could not be included in a single image, an equally-timed computer image of each organ was obtained. A large area of interest (AOI) was placed over each organ, as illustrated in Fig. 1. The lateral placement of the liver AOI was selected in order to minimize differences in counting geometry. The total counts in the AOI were divided by the number of pixels in the AOI, and the mean count rate per pixel calculated. The mean spleen counts were divided by the mean liver counts to determine the S/L ratio.

Liver biopsy. All liver biopsies were performed by the percutaneous route. One or two samples were obtained with the Menghini, Jamshidi, or Vim-Silverman needles; biopsy diameters ranged from 1.2 mm to 1.6 mm.

Liver scan interpretation. In addition to S/L ratio, liver scans were interpreted blindly with respect to four other characteristics of hepatocellular disease: a) hepatomegaly, b) splenomegaly, c) nonhomogeneous colloid distribution, and d) bone-marrow colloidal uptake. Liver size was determined on the anterior view by a single measurement at the midclavicular line.

RESULTS

This method of quantifying S/L ratio was first tested for interobserver variation. A physician and a technologist independently determined an AOI over both spleen and liver, and S/L ratios were then calculated as described above. The small interobserver variation is shown in Fig. 2. The correlation coefficient is 0.99

Reproducibility of the technique was tested on ten patients having liver scans on two different dates. Any patient receiving chemotherapy or developing apparent liver disease in the time between scans was excluded. Reproducibility was also acceptable, having a correlation coefficient of 0.97 (Fig. 3).

The distribution of S/L ratios in the clinically normal group of 100 subjects without liver biopsy is shown in Fig. 4. The mean S/L ratio in this group is 0.77, with a range from 0.33 to 1.23. The distribution approximates a normal distribution, and limits of two standard deviations yield a normal range of 0.37–1.17.

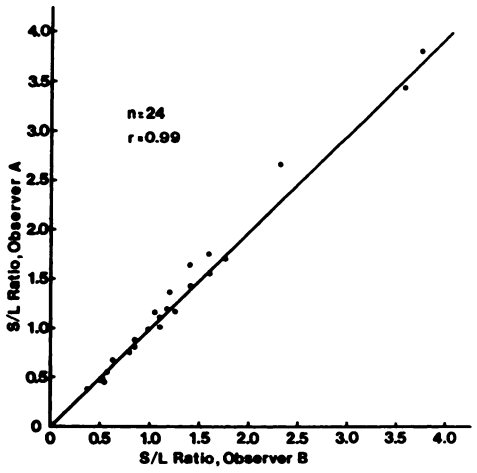

FIG. 2. S/L ratios as determined by two independent operators on 24 patients, demonstrating correlation coefficient of 0.99.

Twenty-five patients had "normal" liver biopsies, but ten of these had definite clinical and laboratory indications of liver disease, including one patient with established portal hypertension. These ten patients were therefore excluded from the normal group and presumably represent false-negative biopsies. The remaining 15 patients with normal liver biopsies had S/L ratios ranging from 0.19 to 1.31, with a mean of 0.74; the distribution of these S/L ratios is similar to that of the 100 clinically normal cases.

The distribution of S/L ratios in 29 patients with diffuse hepatocellular disease is shown in Fig. 5. The 13 patients with fatty metamorphosis had S/L ratios ranging from 0.72 to 4.6. Eleven of the 13 (85%) had S/L ratios greater than 1.17. Of the nine patients with cirrhosis, six (67%) had abnormally elevated S/L ratios, with a range from 0.91 to 5.0. Three of seven patients with chronic active hepatitis had elevated S/L ratios, with a generally lower range from 0.14 to 1.24. For all three of these groups with hepatocellular disease, the S/L ratio by itself had a sensitivity of 69%.

An additional 15 patients with various abnormalities on liver biopsy had S/L ratios as shown in Fig. 5. The diagnoses included cholangitis (4), portal fibrosis (3), capsular fibrosis (2), cholestatis (1), hemosiderosis (1), granulomatous hepatitis (1), lymphocytic infiltration (1), eosinophilic infiltration (1), and abscess (1).

When the liver-scan interpretation includes the other four characteristics (hepatomegaly, splenomegaly, nonhomogeneous colloid distribution, and bone-marrow colloidal uptake) in addition to the S/L ratio, the overall sensitivity of the study is improved (Table 1). All patients with cirrhosis and fatty metamorphosis had abnormal scans by these criteria, compared with 80% in chronic hepatitis. Thus, overall sensitivity of the liver scan for cirrhosis, fatty metamorphosis, and chronic hepatitis is 93%.

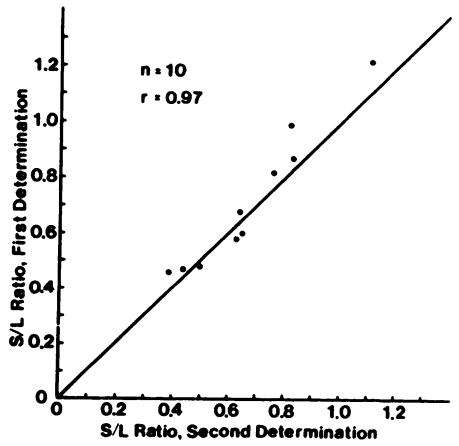

FIG. 3. S/L ratio as determined for ten patients on two separate occasions, demonstrating correlation coefficient of 0.97.

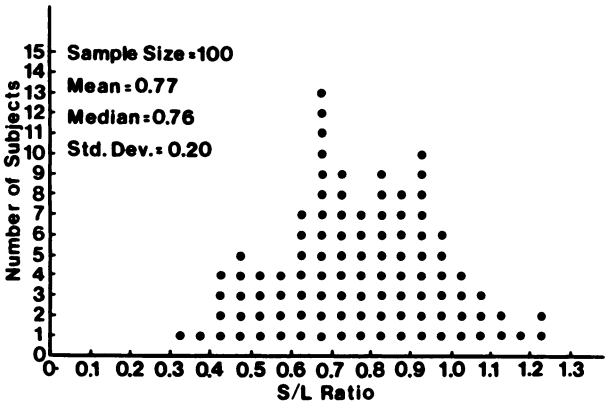

FIG. 4. Distribution of S/L ratios in clinically normal subjects.

DISCUSSION

Increased splenic uptake of Tc-99m colloid is a recognized finding in diffuse hepatocellular disease. The mechanism has usually been attributed to poor extraction of colloid by the reticuloendothelial cells in the liver secondary to intrahepatic arteriovenous shunts (*4,6,7,*). As a physiologic radionuclide finding, the S/L ratio is potentially quantifiable. The simple computer method described here is performed upon routine posterior images of liver and spleen, and requires less than 10 min of computer time.

Before employing the computer method, we evaluated S/L ratio quantification using a 1-cm^2 gamma-camera AOI. Because of sampling errors and variation in operator placement of the AOI, the resulting S/L ratios demonstrated unacceptable variability and lack of reproducibility. We therefore abandoned this technique in favor of the computer method, which permits averaging of activity over a large sample of the organ. This method is quite reproducible when the same patient is studied at different times, exhibiting a correlation coefficient of 0.97. As compared with a small 1-cm^2 AOI, placement of the AOI is less critical with the computer method, so long as the liver AOI is confined to the lateral right lobe, which is similar in counting geometry to the spleen. The interobserver variability in determining S/L ratio is also quite low, with a correlation coefficient of 0.99.

In attempting to establish a normal range, we have looked at two groups of patients. Since most patients having liver biopsies already have suspected liver disease, very few normal liver biopsies

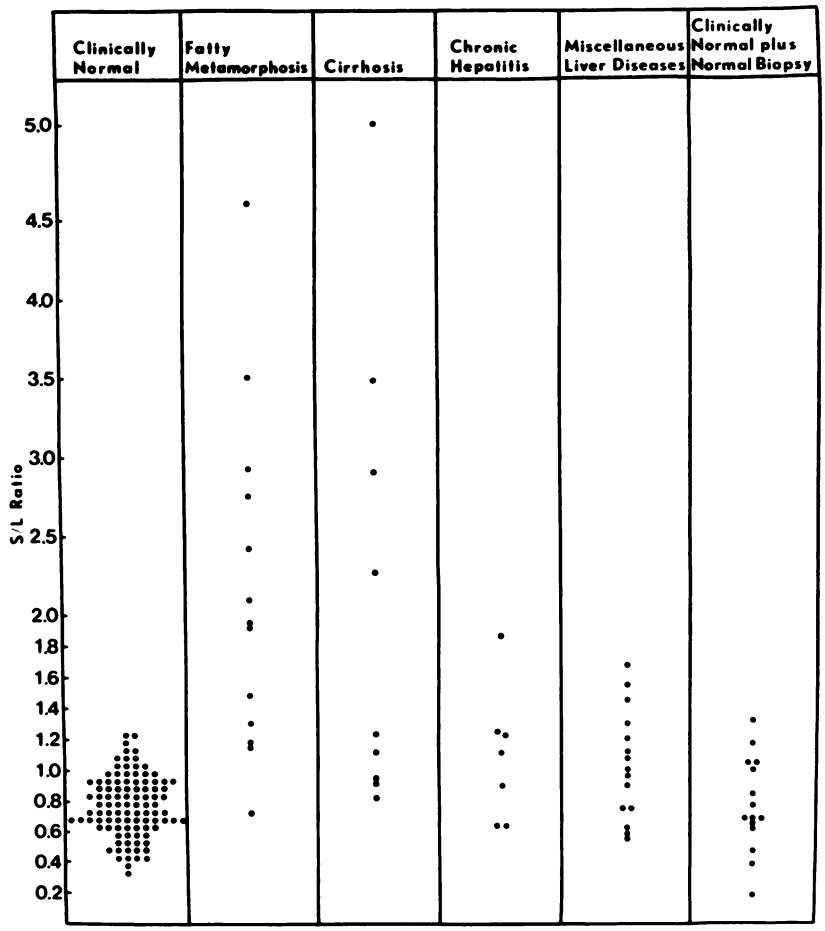

FIG. 5. Distribution of S/L ratios in normals and in various hepatic diseases.

are available. In addition, because of sampling errors with needle biopsy of the liver, falsely normal biopsies may be obtained. Sampling errors are most likely to occur in cirrhosis. Vido et al. (*8*) found that needle biopsy demonstrated cirrhosis in only 49% of cirrhotic patients. In a similar study, Soloway et al. (*9*) confirmed cirrhosis in only 33% of cases. Sampling error is smaller, however, in fatty liver, passive congestion, alcoholic hepatitis, and chronic active hepatitis (*9,10*). In our group of 25 "normal" liver biopsies, ten had definite clinical evidence of liver disease, including one patient with established portal hypertension. The remaining 15 patients had a range of S/L ratios from 0.19 to 1.31, with a mean of 0.74.

The second group of 100 patients consisted primarily of patients being screened for hepatic metastases. None had clinical or biochemical evidence of liver disease, and many had grossly normal livers at laparotomy. Although it is known that nonhepatic malignancies can cause elevation of the S/L ratio (*11–13*), the mean S/L ratio (0.77) in this group of 100 patients is similar to the mean ratio (0.74) in the smaller group with normal liver biopsies. Because of possible false-negative biopsies in the latter group, and the effect of nonhepatic malignancies in the former group, the predicted normal range of 0.37–1.17 probably overestimates the true normal range. It is also possible that the S/L ratio may vary with the preparation of sulfur colloid used; there-

TABLE 1. SENSITIVITY OF VARIOUS LIVER-SCAN CHARACTERISTICS IN HEPATOCELLULAR DISEASES

Biopsy diagnosis	Elevated S/L ratio	Hepatomegaly	Splenomegaly	Bone-marrow colloid	Nonhomogeneous distribution	Any positive characteristic
	(%)	(%)	(%)	(%)	(%)	(%)
Fatty metamorphosis	85	100	33	46	92	100
Cirrhosis	67	40	40	70	100	100
Chronic hepatitis	43	20	40	20	80	80
Combined	69	53	38	45	91	93

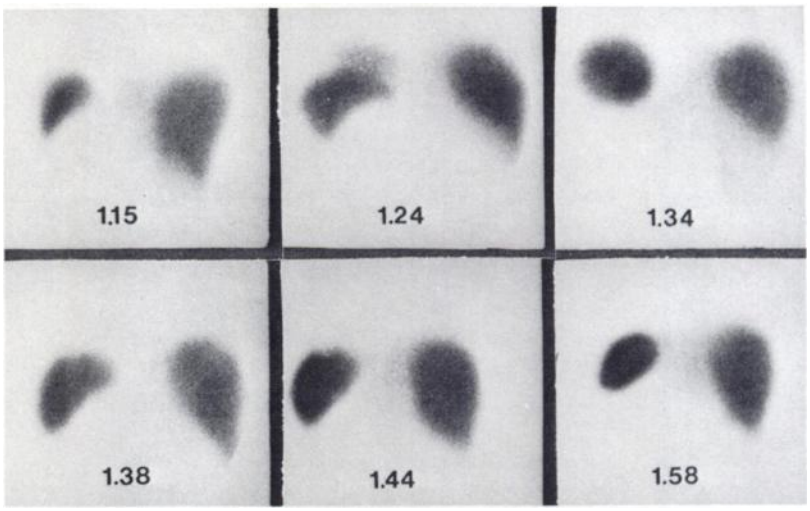

FIG. 6. Images corresponding to six abnormal S/L ratios, showing difficulty of visual interpretation in the range from 1.15 to 1.44.

fore, each individual laboratory would need to verify its own normal range.

Despite these problems in establishing the normal range, the S/L ratio was abnormally elevated in 85% of patients with fatty metamorphosis, 67% with cirrhosis, and 43% with chronic hepatitis. Of particular interest is the fact that the abnormal S/L ratios in the range from 1.17 to approximately 1.4 are not obvious from visual inspection of the scan alone, as shown in Fig. 6. Some of our patients with chronic hepatitis had prior liver scans that were interpreted as normal, but were correctly reclassified as abnormal when the computer S/L ratio was performed. Of the 20 patients with elevated S/L ratios, seven were in the range that were not visually apparent. Therefore, an additional 35% of elevated S/L ratios were detected by computer, as contrasted with visual inspection of the scan.

Geslien et al. (*4*) previously determined that the liver scan had a sensitivity of 83% for diffuse hepatocellular disease. Using identical diagnostic criteria, except for quantification of the S/L ratio, we have found an overall liver-scan sensitivity of 93%. The improvement in sensitivity is considered to be secondary to the improved S/L ratio determination.

Of the five criteria of diffuse hepatocellular disease (hepatomegaly, nonhomogeneous colloidal distribution, splenomegaly, bone-marrow uptake, and elevated S/L ratio), nonhomogeneous distribution had the highest sensitivity (91%) for the three hepatocellular diseases studied (Table 1). This, however, is a highly subjective finding that inherently lacks specificity. The second most sensitive criterion was the S/L ratio, with an overall sensitivity of 69%. This measurement has the advantage of being quantitative and reproducible and has a specificity of 97% [specificity = true negatives/(true negatives + false positives)]. Although none of the 27 patients with abnormal scans had elevation of S/L ratio as the sole abnormality, it was the determining factor in 11 of the 27 clinical interpretations. In our clinical practice, nonhomogeneous distribution and/or mild hepatomegaly are not considered sufficiently reliable to be diagnostic. When these abnormalities are also associated with an elevated S/L ratio, however, the combination is considered clinically reliable. In terms of actual clinical interpretation, the S/L ratio improved our sensitivity from 62% to 93%.

Notably, 100% of patients with fatty metamorphosis had hepatomegaly, as contrasted with 40% in cirrhosis and 20% in chronic hepatitis. Therefore the presence of hepatomegaly associated with an elevated S/L ratio may have some value in differentiating fatty metamorphosis from chronic hepatitis. The S/L ratios in fatty metamorphosis also had a significantly higher range than those in chronic hepatitis.

We conclude that simple computer quantification of the S/L ratio is a valid and useful adjunct to the interpretation of liver-spleen scans, and may increase the sensitivity and specificity of the procedure in the diagnosis of hepatocellular disease.

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