Technetium-99m HIDA Hepatic Lobar Distribution and Retention Ratios in Detection of Intrahepatic Lithiasis

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Technetium-99m HIDA hepatic lobar distribution and retention ratios were developed to evaluate patients with intrahepatic lithiasis. The data of 57 cases were analyzed. Results reveal a highly significant difference in these ratios between the patients and normal individuals. They are simple, objective, and easily obtainable. Thus, the determination of these ratios may replace [^{99m}Tc]HIDA sequential scintiphotography, which is qualitative and time consuming, for screening intrahepatic lithiasis.

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Liver (intrahepatic) stones lie in the right and/or left hepatic ducts or their branches, with or without stones in the common duct or gallbladder (*1*). They are not of cholecystic origin (*1–3*), have the highest incidence among the young and middle-age groups (*2*), and affect people in low-income brackets (*2,4,5*). Choledocholithiasis is an entirely different condition, for an intrahepatic stone consists chiefly of bilirubinates with low calcium content (*2*). Clinically, the attack is generally indicative of cholangitis. More often than not, all three features of Charcot's triad—fever, upper abdominal pain, and jaundice—are present. In severe cases, there are crisis-like attacks of such severity that shock-like reactions develop, and unless surgical decompression of the biliary tract is done immediately, the patient often dies (*2*).

This disease has been called Oriental cholangitis in the American literature. Ova and fragments of adult parasites, such as *Clonorchis sinensis* (*5*) and *Ascaris lumbricoides* (*6,7*) have been demonstrated in the center of calcium bilirubin stones, but the disease has also been reported in populations without heavy parasitic infestation (*2*). It may be reasonable to hypothesize that, in part, intrahepatic calculi are produced by organisms that hydrolyze conjugated bilirubin (bilirubin glucuronide) with their beta-glucuronidase (*8*).

The incidence of intrahepatic stones is quite low in the United States and Europe, whereas they occur with much greater frequency throughout the Far East, especially in China and Japan. As reported by Huang et al. (*9*), 30% of 110 patients with bile duct calculi also harbored intrahepatic stones (*9*). In Japan, the proportion of patients with pigment lithiasis approaches 70% in rural localities, and intrahepatic calculi occur in 70 to 80% of these cases (*10,11*). The true frequency of liver stones in western countries has not been established. The incidence has recently been reported as ranging from 1 to 2.4% of all biliary lithiasis (*12*), although the numbers of 5 to 8% were reported from much older series (*13–15*). Intraductal lithiasis in the absence of gallbladder stones is so rare that it presents difficult problems of diagnosis and management (*16,17*), and few American surgeons have more than a limited exerience in meeting the problems presented by this disease (*16*). In the Far East, the clinical diagnosis can be made readily because of the clinician's awareness of the condition of intrahepatic stone (*2*). For a screening study, plain abdominal radiographs are not helpful since all the stones are radiolucent (*2*). Oral and intravenous cholangiographic studies fail to yield useful information during the acute attack because of jaundice in almost all patients (*2*). Even during remission, 70% of conventional cholan-

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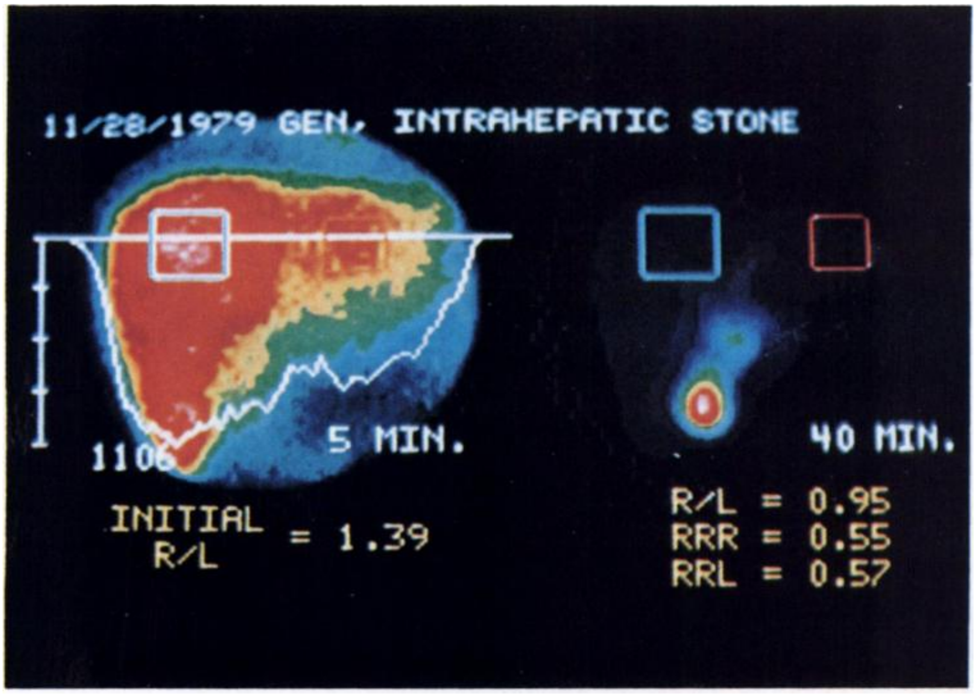

FIGURE 1
Final color TV display of [^{99m}Tc]HIDA hepatobiliary imaging and analysis at 5 min (left) and 40 min (right) after injection. For details of R/L, RRR, and RRL derivation see text

giographic studies fail to visualize the biliary tree (*2*). Although percutaneous transhepatic cholangiography has been tremendously helpful in the diagnosis and confirmation of intrahepatic stones (*2*), it is an invasive technique, carrying morbidity and even mortality (*18,19*). Even endoscopic retrograde cholangiography has significant complications in 3% and mortality in 0.2% (*20*). Furthermore, in only four of 36 patients was the diagnosis made preoperatively, in a series published in 1979, without benefit of technetium-99m (^{99m}Tc) hepatobiliary scanning (*12*). Accordingly, it is necessary to have a simple, safe, and reliable screening test for detecting intrahepatic stones.

Sequential scintiphotography with a hepatobiliary agent, technetium-99m pyridoxylideneglutamate ([^{99m}Tc]PG), has been used for detecting liver stones (*21*). However, it is qualitative and time consuming. This has led us to develop an alternative method, which is simple and quantitative, to obtain technetium-99m dimethylacetanilideiminodiacetate ([^{99m}Tc]HIDA) hepatic lobar distribution and retention ratios for detecting intrahepatic stones. A portion of this work has been published earlier in abstract form (*22*).

METHODS

In initial studies, a conventional gamma camera (Searle Pho/Gamma IV) was linked to a minicomputer (Informatek Simis 3), and the data stored on computer disks. In some of the patients studied lately, a digital gamma camera (Elscint Apex 410) was used together with another minicomputer (Informatek Simis 5). Data were acquired in the anterior hepatic region for 1 min at 5 and 40 min after i.v. injection of 5–7 mCi of [^{99m}Tc]HIDA with the patient in the same position. An anterior liver scintiphoto was recorded on Polaroid film during each data acquisition. A computer routine was used to calculate (a) the right and left lobar distribution ratio (R/L) with correction for the relative lobar thickness, and (b) individual lobar retention ratios (RRR for the right lobe, RRL for the left lobe) at 40 min.

To obtain these ratios, a series of operations was carried out as shown in Fig. 1. A horizontal cross-sectional distribution of radioactivity at 5 min was obtained from the right to left lobe, and two regions of interest (ROIs) corresponding to the right and left lobes were set in the area near the peak activity of each lobe. The count rates of these two ROIs were selected as the count rates of the right (C_R) and left (C_L) lobes at 5 min. C_R and C_L at 40 min were obtained by setting the ROIs in the same areas as those at 5 min. C_L in each case was normalized for the area of ROI in the right lobe. The hepatic lobar distribution ratio and retention ratio of individual lobes were then derived as follows:

$$R/L = \frac{C_R/C_L \text{ at 40 min}}{C_R/C_L \text{ at 5 min}} \quad (1)$$

where R/L has been corrected for the relative thickness

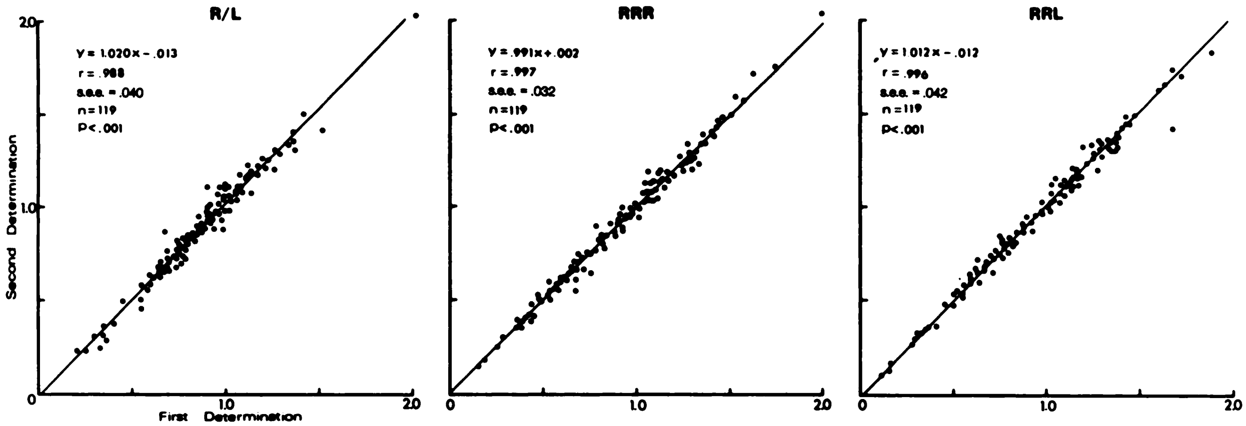

FIGURE 2
Plot of first compared with second determination of R/L, RRR, and RRL in 119 subjects. Note very high intraobserver agreement. R/L = lobar distribution ratio; RRR = right lobar retention ratio; RRL = left lobar retention ratio; s.e.e. = standard error of estimate; r = linear correlation coefficient

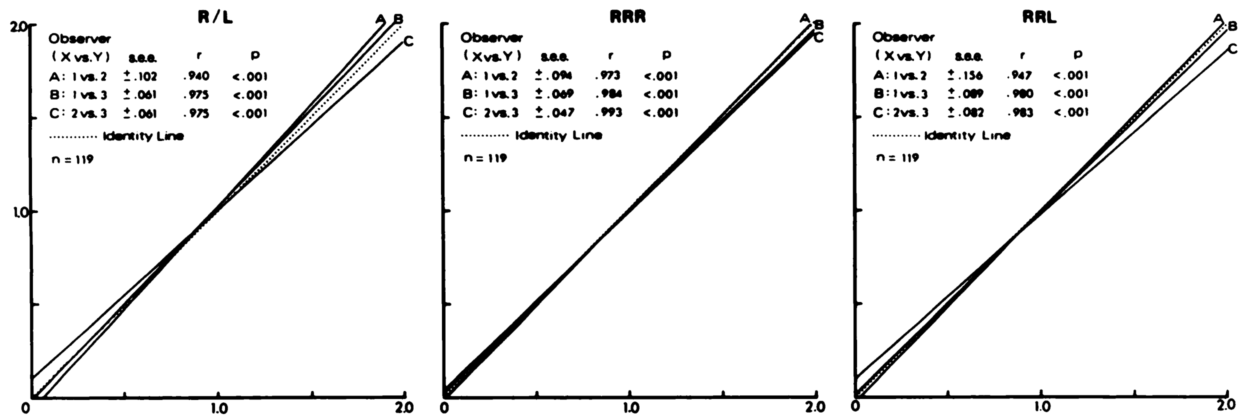

FIGURE 3
Regression equations obtained for R/L, RRR, and RRL from paired observers (1,2,3) in same 119 subjects. Note excellent correlations. Abbreviations as in Fig. 2

of the right and left lobes by dividing the ratio of the count rates of the right and left lobes at 40 min by that at 5 min, i.e., initial R/L;

$$\mathrm{RRR} = \frac{C_R \text{ at 40 min}}{C_R \text{ at 5 min}}, \quad (2)$$

$$\mathrm{RRL} = \frac{C_L \text{ at 40 min}}{C_L \text{ at 5 min}}. \quad (3)$$

The intraobserver variation for determining R/L, RRR, and RRL was assessed by having an operator repeat each analysis 1–5 days later without knowledge of the previously determined results. All ratio determinations were performed by experienced operators who were unaware of the clinical diagnosis. To determine the interobserver variation of the technique, these correspondent ratios obtained in Study 1 and Study 2, Study 1 and Study 3, and Study 2 and Study 3 were determined for each patient. Linear regression equations and correlation coefficients were obtained in a standard manner.

Regression plots for determining the intra- and interobserver errors for R/L, RRR, and RRL are illustrated in Figs. 2 and 3. The degree of intra- and interobserver agreement was very high, reflecting the ease with which the reproducible results can be obtained.

From November 1979 to November 1982, the present study was carried out in 93 patients with strong indications of intrahepatic stones. In 57 cases, proof of intrahepatic calculi was obtained by either endoscopic retrograde or percutaneous transhepatic cholangiography and T-tube cholangiography during laparotomy. These cases form the basis of this report. R/L, RRR, and RRL were also determined in a control group consisting of 36 individuals without evidence of hepatobiliary diseases. In all, serum bilirubin levels were within normal limits. The ratio determinations were done in ten additional proven patients with common duct calculi in 12 with

TABLE 1
$[^{99m}Tc]$HIDA Hepatic Lobar Retention Ratio in 57 Patients with Intrahepatic Lithiasis

Lobes	Number of patients	RRR* mean ± s.d.	RRL† mean ± s.d.	p‡
Unaffected				
Right	15	0.55 ± 0.17	—	N.S.§
Left	4	—	0.60 ± 0.26	N.S.
Affected				
Right	42	1.21 ± 0.31	—	<0.005
Left	53	—	1.33 ± 0.47	<0.005

* Mean ± 1 s.d. = 0.55 ± 0.17 in 36 normal control subjects.
† Mean ± 1 s.d. = 0.57 ± 0.18 in 36 normal control subjects.
‡ p value obtained from unpaired t-test comparing the ratios of the control individuals with those of the patients with intrahepatic lithiasis.
§ N.S. = not significant.

TABLE 2
$[^{99m}Tc]$HIDA Lobar Distribution Ratio in 57 Patients with Intrahepatic Lithiasis

Disease group	Number of patients	R/L* mean ± s.d.	P†
Unilobar			
Right	4	1.58 ± 0.26	<0.005
Left	15	0.47 ± 0.19	<0.005
Bilobate			
Equal involvement	24	0.93 ± 0.08	NS‡
Right predominance	8	1.28 ± 0.09	<0.005
Left predominance	6	0.65 ± 0.20	<0.005

* Mean ± 1 s.d. = 0.96 ± 0.14 in 36 normal control subjects.
† p value obtained from unpaired t-test comparing the ratios of the control individuals with those of the patients with intrahepatic lithiasis.
‡ N.S. = not significant.

acute viral hepatitis, and in four with Caroli's disease.

For comparison of the quantitative HIDA method with visual nonquantitative HIDA examination, receiver operating characteristic (ROC) analysis was performed for each method in the same individuals (36 normal subjects and 57 patients with intrahepatic lithiasis) on this study. In the quantitative method, the ROC curve was constructed by changing the criterion levels of retention ratios over a wide and continuous range. In qualitative method, the ROC curve was obtained by the results of the performance of one experienced observer, using the rating method on the basis of observing intrahepatic pooling of HIDA (*21*). The categories considered "positive" at four diagnostic-criterion levels were: (a) definitely abnormal; (b) definitely or probably abnormal; (c) definitely, probably, or possibly abnormal; and (d) definitely, probably, or possibly abnormal or probably normal. In addition, the Hanley and McNeil method (*23*) was used to calculate the area (A_z) under each ROC curve in this study and its standard error. When two methods are compared, the method with the better performance has the larger area under its ROC curve. The difference in this relationship between ROC curves in this study was analyzed by a new statistical technique for paired ROC data (*24*). For using this technique, the individual retention ratios were grouped according to the four diagnostic-criterion levels for "positive" cases and one diagnostic-criterion level for "negative" cases.

RESULTS

In 36 apparently normal persons acting as controls, the mean ratio ± 1 s.d. was 0.96 ± 0.14 for R/L, 0.55 ± 0.17 for RRR, and 0.57 ± 0.18 for RRL. In all 57 proven patients, 19 had unilobar and 38 had bilobate liver stones. The analysis of the hepatic lobar retention ratios in these patients is shown in Table 1. The retention ratio was 1.21 ± 0.31 (mean ± 1 s.d.) in 42 affected right lobes, and 1.33 ± 0.47 in 53 affected left lobes. The ratio was greatly increased in affected lobes when compared with that of the corresponding normal lobes ($p < 0.005$) (Fig. 4). In contrast, RRR and RRL of unaffected lobes

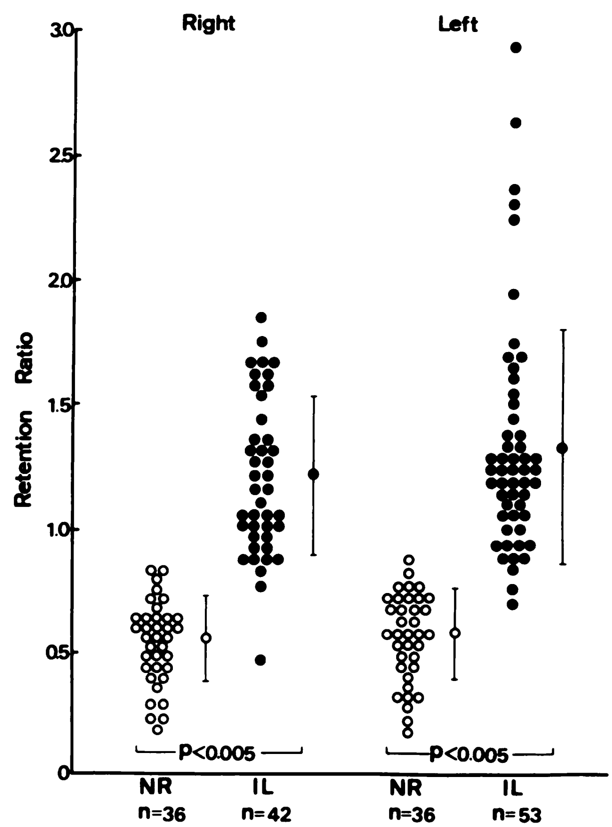

FIGURE 4
Lobes affected with intrahepatic lithiasis (IL) show great increase in retention ratio compared with corresponding lobes in normals (NR). Means ± s.d. are shown by bars

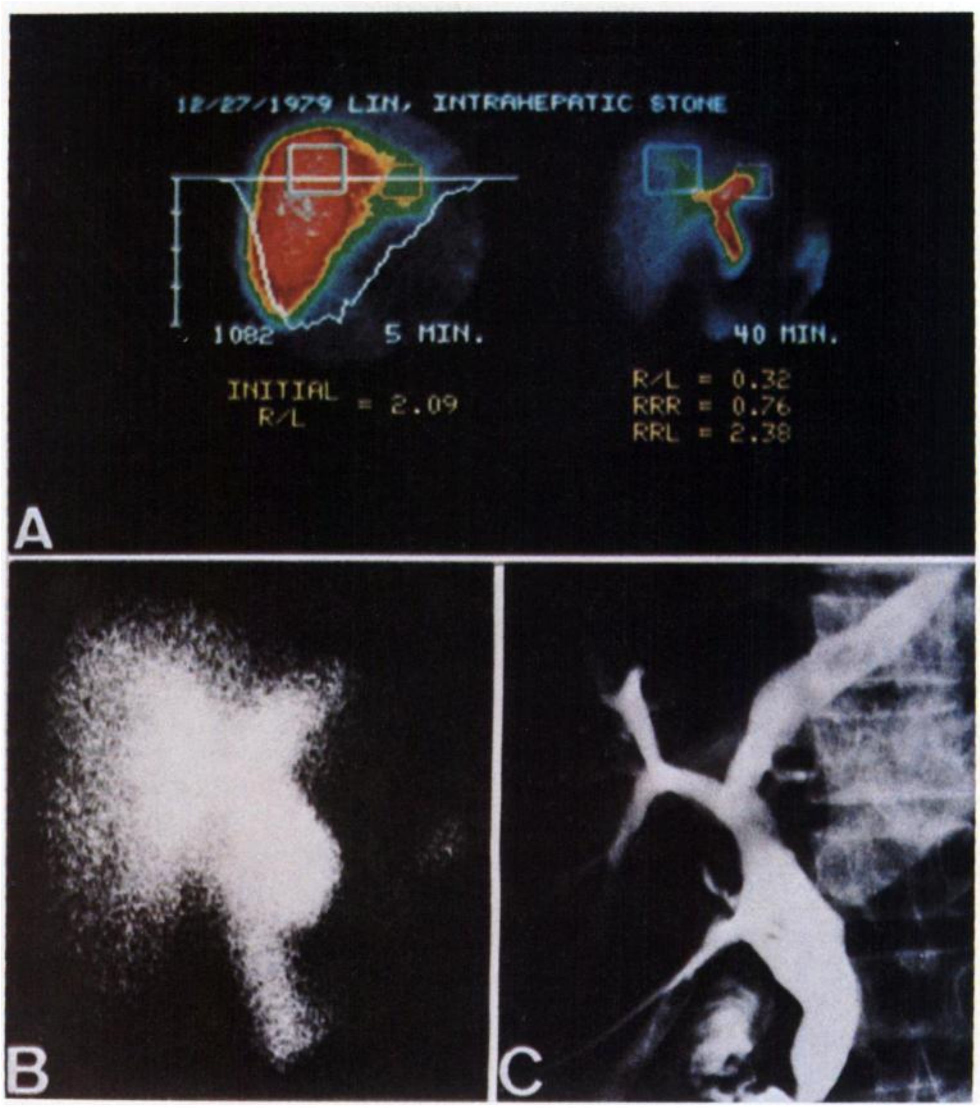

FIGURE 5
Unilobar intrahepatic lithiasis (left lobe). A: Final color TV display of [^{99m}Tc]HIDA hepatobiliary images and analysis; B: Correspondent hepatobiliary scintiphoto at 40 min; C: T-tube cholangiogram. Pooling in left lobe is clearly demonstrated on color TV display, whereas it is not well defined in scintiphoto. R/L, RRR, and RRL have their respective ratios of 0.32, 0.76, and 2.38, clearly indicating unilobar intrahepatic lithiasis. T-tube cholangiogram demonstrates tremendously dilated left hepatic duct with two or three large radiolucent calculi

(15 right; 4 left) did not differ significantly from those of the normal individuals, being 0.55 ± 0.17 and 0.60 ± 0.26, respectively.

It is clearly seen from Table 2 that R/L was outside the normal range in the unilobar patients. R/L was greatly decreased in 15 patients with intrahepatic lithiasis of the left lobe (0.47 ± 0.19) in contrast to a remarkable increase in four patients with the right lobe affected (1.58 ± 0.26), when compared with that of normal individuals (0.96 ± 0.14, $p < 0.005$). R/L's were within normal range in all 24 cases of the bilobate disease with approximately equal involvement of both lobes. Individual R/L's still reflected the predominant side of involvement in all 14 cases of unequal involvement compatible with corresponding retention ratios. R/L was 0.93 ± 0.08 in the patients with equal involvement and no significant difference was obtained between this group and normal individuals. All eight patients of right lobe predominance had R/L's above unity (1.28 ± 0.09), whereas all six patients of left lobe predominance had R/L's below unity (0.65 ± 0.20). Highly significant differences were noted in the results between either group of unequal involvement and controls (Table 2).

Figure 5 shows a final color TV display of [^{99m}Tc]HIDA hepatobiliary images and analysis, correspondent hepatobiliary scintiphoto at 40 min, and T-tube cholangiogram in a representative case of unilobar intrahepatic lithiasis.

The lobar distribution ratios in ten patients with common bile duct stones, 12 with acute hepatitis B, and four with Caroli's disease were 0.96 ± 0.28, 0.98 ± 0.21, and 0.95 ± 0.17, respectively. There was no difference in R/L in patients of bilobate lithiasis with equal involvement as compared with those with common bile duct stones, acute hepatitis B, or Caroli's disease. The lobar retention ratios of these patients are listed in the Table 3. RRR and RRL in all groups were significantly higher than in control subjects. The ratios in BIL with equal involvement were significantly increased in comparison with those in CDL and acute hepatitis B, but were significantly lower than in Caroli's disease. There was considerable overlap, however, between groups as shown in Fig. 6.

In the same 93 subjects ROC analysis showed that the determination of retention ratios had a higher true-positive fractions than the visual nonquantitative HIDA method over the entire range of false-positive fractions (Fig. 7), indicating the superior performance of the quantitative HIDA method. The A_z value for the quantitative method was significantly greater than that for the visual nonquantitative method ($p < 0.05$). In addition, the optimal decision threshold as determined by ROC analysis (Fig. 7) was the normal retention ratio + 1.25 s.d., i.e., 0.76 for RRR and 0.79 for RRL, with resultant sensitivity of 97% and specificity of 96% for normals.

DISCUSSION

A sequential scintiphotography with [^{99m}Tc]PG has been developed, carrying the advantage of often being successful in detecting intrahepatic stones when the plain film of the abdomen and conventional cholangiography fail to yield useful information (*21*). This technique has been regarded as another important use of ^{99m}Tc hepatobiliary scanning for a condition affecting millions of people, especially in the Orient (*25*). However, such an approach is qualitative and rather time-consuming. It necessitates serial imaging even up to 24 hr after injection to detect intrahepatic pooling and stasis (*21*).

On the other hand, the determination of [^{99m}Tc]HIDA hepatic lobar distribution and retention ratios is simple and takes only 1 min for each data acquisition at 5 and 40 min after i.v. injection of [^{99m}Tc]HIDA. This approach has permitted us to investigate intrahepatic lithiasis accurately and quantitatively, thereby obviating the difficulty in interpreting the analog sequential scintiphotos. Moreover, the result of visual and quantitative ROC curve analysis for comparing the quantitative and qualitative HIDA methods (Fig. 7) clearly indicates that the performance of the former is superior to that of the latter.

The results in the current study indicate that the [^{99m}Tc]HIDA hepatic lobar distribution and retention ratios are simple, objective, and useful parameters for detecting and localizing intrahepatic lithiasis. The retention ratios of the affected lobes were significantly higher than those of the corresponding normal lobes ($p < 0.005$). There was no significant difference in retention ratios between the unaffected lobes in unilobar cases and corresponding lobes in controls. R/L's were significantly outside the normal range (0.96 ± 0.14) in the unilobar cases ($p < 0.005$). Although there was no real difference in R/L's between bilobate cases with equal involvement

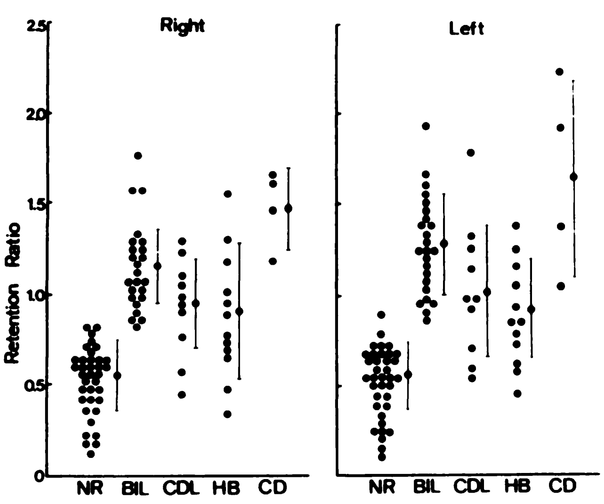

FIGURE 6
Retention ratios in intrahepatic lithiasis with equal involvement (BIL), common duct lithiasis (CDL), acute hepatitis B (HB), Caroli's disease (CD), and normals (NR). Means ± s.d. are shown by bars

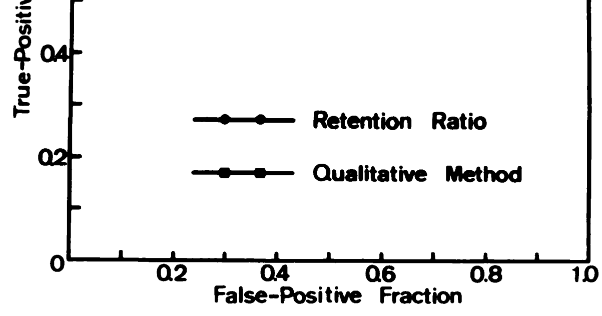

FIGURE 7
ROC curves for comparison of retention ratios and qualitative HIDA images in 93 subjects who had two examinations. Area under ROC curve for retention ratio is significantly larger than that for qualitative method. Open circle represents optimal decision threshold

TABLE 3
[^{99m}Tc]HIDA Hepatic Lobar Retention Ratio in Intrahepatic Lithiasis with Equal Involvement and Other Liver Diseases

Group	Retention ratio (mean ± s.d.)	p (compared with normals)	p (compared with BIL)
NR* (n = 36)			
Right	0.55 ± 0.17	—	<0.005
Left	0.57 ± 0.18	—	<0.005
BIL† (n = 24)			
Right	1.16 ± 0.23	<0.005	—
Left	1.25 ± 0.28	<0.005	—
CDL‡ (n = 10)			
Right	0.92 ± 0.27	<0.005	<0.01
Left	1.01 ± 0.36	<0.005	<0.025
HB§ (n = 12)			
Right	0.87 ± 0.36	<0.005	<0.005
Left	0.87 ± 0.29	<0.005	<0.005
CD¶ (n = 4)			
Right	1.49 ± 0.21	<0.005	<0.01
Left	1.65 ± 0.55	<0.005	<0.025

* NR = normals.
† BIL = intrahepatic lithiasis with equal involvement.
‡ CDL = common duct lithiasis.
§ HB = acute hepatitis B.
¶ CD = Caroli's disease.

and normal individuals, the presence of the disease was still reflected by increased both RRR and RRL. On the other hand, individual R/L's in bilobate cases with unequal involvement were different from those of controls, reflecting the predominant lobe of retention compatible with RRR and RRL.

In addition to being simple and timesaving, the determination of [^{99m}Tc]HIDA hepatic lobar distribution and retention ratios can sometimes provide information missed by sequential scintiphotography with [^{99m}Tc]-HIDA. For instance, bilobate intrahepatic lithiasis with predominant involvement of the right lobe was demonstrated by R/L, RRR, and RRL (Fig. 8A), whereas pooling was shown by the analog scintiphoto in the right lobe only (Fig. 8B). Exploration and T-tube cholangiography showed the presence of intrahepatic stones in both lobes. When the scintiphoto is recorded on Polaroid film by preset counts, the accumulation of the counts in a given region is proportional to its radioactivity and therefore this may account for no demonstration of pooling in the left lobe which was much less affected than the right lobe.

Apart from screening purposes before operation, the regular and sequential determination of the lobar retention ratio would be the best noninvasive and quantitative technique for postoperative surveillance of patients to follow the clinical response to treatment. Failure to observe a significant reduction in a previously raised lobar retention ratio strongly indicates the presence of residual stones. Usually, it is hard to have a complete removal of the liver stones. The ratio will be raised when the disease is progressing. It is well-known that there is an intractable recurrence rate of intrahepatic lithiasis after operation. Accordingly, measurement of the lobar retention ratio would provide us with an objective index useful, not only in the diagnosis of intrahepatic lithiasis, but in following its progress and evaluating its prognosis after surgery. Such a quantitative study is now in progress in our laboratory.

In this study, 24 of 57 patients (42%) had bilobate intrahepatic lithiasis with approximately equal involvement. No significant difference in R/L could be detected among bilobate lithiasis with equal involvement, common bile duct stones, acute hepatitis B, Caroli's disease, and controls. The mean RRR and RRL in bilobate lithiasis with equal involvement were significantly higher than those in common duct stones and hepatitis, but significantly lower than in Caroli's disease. The range of the ratios of all groups, however, overlapped to a large extent. Accordingly, it would be hard to differentiate bilobate intrahepatic lithiasis with equal involvement from common bile duct stones, acute hepatitis B or Caroli's disease because of such an overlapping. Nevertheless, RRR and RRL are still helpful in monitoring treatment, especially for lithiasis. Caroli's disease may lead to bile stasis (*26*), and therefore may present scintigraphic findings and retention ratios similar to those of intrahepatic stones (Fig. 6). However, this congenital condition is very rare (*26*).

We set the ROIs corresponding to the right and left lobes at the early hepatocyte phase, namely, 5 min after injection. Since there is very little of radioactivity accumulated in the hilar region and major biliary radicles at this phase, two peak activities of the right and left lobes plus a valley corresponding to the hilar region are noted in the horizontal cross-sectional distribution of radioactivity. The right and left hepatic ROIs are set near the peak activity of each lobe but kept as far away as possible from the valley radioactivity of the hilar region. Thus, setting ROIs over the hilum and major radicles can be avoided. In our experience, we are always able to obtain the correct ROIs, if the guidelines mentioned above are observed. On rare occasions, we did reset the ROIs in case of their turning out to be over the major biliary radicles.

In summary, our results indicate that [^{99m}Tc]HIDA hepatic lobar distribution and retention ratios are simple, objective, and useful parameters easily obtained for detecting intrahepatic lithiasis. Thus, this new technique

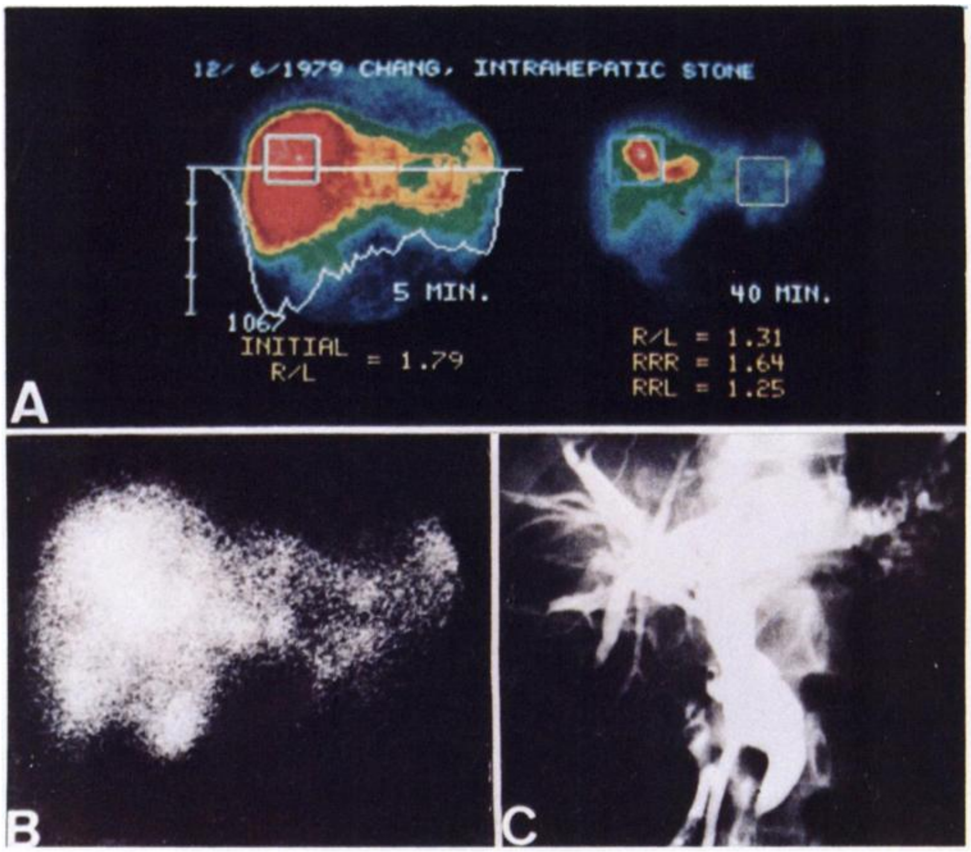

FIGURE 8
Bilobate intrahepatic lithiasis. A: Final color TV display of [^{99m}Tc]HIDA hepatobiliary images and analysis; B: Correspondent hepatobiliary scintiphoto at 40 min; C: T-tube cholangiogram. Color TV image and scintiphoto show pooling in right lobe only. However, R/L, RRR, and RRL have their respective ratios of 1.31, 1.64, and 1.25, indicative of bilobate involvement. T-tube cholangiogram confirms presence of multiple radiolucent calculi in dilated right and left hepatic ducts and their ramifications

may replace sequential scintiphotography, which is qualitative and rather time-consuming, for screening this disease.

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