Clinical Usefulness of Scintigraphy with ^{99m}Tc-Galactosyl-Human Serum Albumin for Prognosis of Cirrhosis of the Liver

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Scintigraphy with ^{99m}Tc-diethylenetriamine pentaacetic acid-galactosyl-human serum albumin (^{99m}Tc-GSA) is useful for evaluating hepatic functional reserve. We assessed the clinical usefulness of this technique, including its value in establishing a prognosis, in patients with cirrhosis of the liver. **Methods:** Scintigraphy with ^{99m}Tc-GSA was performed in 10 healthy subjects, 42 patients with chronic hepatitis and 158 patients with cirrhosis. Computer acquisition of gamma camera data were started just before the injection of ^{99m}Tc-GSA. Time-activity curves for the heart and liver were generated from regions of interest (ROIs) for the heart and the entire liver. A receptor index was calculated by dividing the radioactivity of the liver ROI by that of the liver-plus-heart ROI 15 min after the injection. An index of blood clearance was calculated by dividing the radioactivity of the heart ROI at 15 min by that of the heart ROI at 3 min. **Results:** The median receptor index was lower in patients with cirrhosis than in patients with chronic hepatitis or in healthy subjects, and the median index of blood clearance was higher. The receptor index was significantly lower when a complication (varices, ascites) was present. The index of blood clearance was significantly higher when a complication (varices and ascites) was present. Correlation of the two indices with classic indicators for functional reserve was significant. On the basis of the receptor index, the patients with cirrhosis were divided into two groups of roughly equal size: group A, receptor index over 0.85, and group B, receptor index 0.85 or less. On the basis of the index of blood clearance, the patients with cirrhosis were divided into two groups of roughly equal size: group A, index of blood clearance $<$ 0.70, and group B, index of blood clearance $\geq$ 0.70. The cumulative survival rates were lower in group B than in group A. **Conclusion:** Scintigraphy with ^{99m}Tc-GSA is clinically useful, especially in establishing the prognosis of patients with cirrhosis of the liver.

Key Words: ^{99m}Tc-DTPA-galactosyl-human serum albumin; prognosis; cirrhosis of the liver

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Two radionuclide examinations that have been conventionally used to evaluate liver disease are colloid scintigraphy (*1*), reflecting mainly Kupffer cell function, and hepatobiliary scintigraphy (*2*), reflecting mainly biliary excretion. A newer scintigraphic technique that uses ^{99m}Tc-diethylenetriamine pentaacetic acid with galactosyl human serum albumin (^{99m}Tc-GSA) permits relatively noninvasive assessment of liver function. This synthetic radioligand binds to asialoglycoprotein receptors on the plasma membrane of hepatocytes. It is then transferred to the hepatic lysosomes, where receptor-mediated endocytosis occurs (*3*). The results of earlier attempts at liver scintigraphy with a radiocolloid were affected by Kupffer cell function, and hepatic reticuloendothelial failure may be identified in alcoholic subjects on the basis of poor uptake of radiocolloid into the liver (*4,5*). However, hepatic imaging with ^{99m}Tc-GSA is affected only by hepatocyte function, not by Kupffer cell function. Hepatic receptor imaging with ^{99m}Tc-GSA also enables us to measure hepatic functional reserve quantitatively by the receptor index and the index of blood clearance, providing a more objective assessment than was possible previously (*6–8*).

In this study, we calculated these indices by scintigraphy with ^{99m}Tc-GSA and examined the results in relation to (a) the outcome of various liver function tests and (b) two clinical signs of cirrhosis (varices and ascites) to evaluate the clinical usefulness of our methods. We also investigated the relationship between the results of scintigraphy with ^{99m}Tc-GSA and the cumulative survival rate of patients with cirrhosis to evaluate the prognostic value of our indices.

MATERIALS AND METHODS

Subjects

We studied 10 healthy volunteers and 200 patients with liver diseases (42 with chronic hepatitis and 158 with cirrhosis) who were admitted to our hospital between August 1990 and August 1998. All patients had underlying infection by hepatitis B or C virus. Cirrhosis and chronic hepatitis (10 with chronic persistent hepatitis and 32 with chronic active hepatitis) were diagnosed by examination of specimens obtained by laparoscopy or by needle biopsy performed under sonographic guidance. Within 1 wk of admission, all patients with suspected or confirmed cirrhosis underwent barium esophagography or endoscopy to detect esophageal varices; in addition, all patients underwent abdominal sonography to detect ascites.

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Measurement of Receptor Index and Index of Blood Clearance

^{99m}Tc-GSA (185 MBq) was injected intravenously, and dynamic images were recorded with the patient supine under a large-field-of-view gamma camera with a low-energy, all-purpose, parallel-hole collimator. Computer acquisition of the gamma camera data was started just before the injection of the ^{99m}Tc-GSA and was stopped 20 min later. Digital images (128 × 128 pixels) were acquired in byte mode at the rate of 60 s per frame. Accumulation images in an anterior abdominal view were obtained for the first 20 min after the injection. Time-activity curves for the heart and liver were generated from regions of interest (ROIs) for the whole liver and precordium. The receptor index was calculated by dividing the radioactivity of the liver ROI by the radioactivity of the liver plus heart ROIs 15 min after the injection. The index of blood clearance was calculated by dividing the radioactivity of the heart ROI 15 min after the injection by the radioactivity of the heart ROI at 3 min (*8*).

Classic Indicators of Functional Reserve

The prothrombin test, the serum albumin level, the retention of indocyanine green in the plasma after 15 min and the Child-Turcotte classification (CTC) score were studied as validated classic indicators of functional reserve (*9–11*). The CTC score was calculated on the basis of the modification of Pugh et al. (*12*). In studies that used Cox's proportional hazards model, the prothrombin time (*9,10*) and the CTC score (*13,14*) have been found to accurately reflect prognosis in patients with cirrhosis.

Statistical Analysis and Evaluation of the Cumulative Survival Rate

Results are expressed as medians with 25th and 75th percentiles. The significance of differences between median values was evaluated by the Mann-Whitney U test (two-tailed). Differences with probability values of less than 0.05 were considered to be significant. We examined the cumulative survival rate in the 158 patients with cirrhosis who were monitored (mean time 32 mo) since their first evaluation by scintigraphy with ^{99m}Tc-GSA. To evaluate whether the receptor index and index of blood clearance added new predictive information about survival after the CTC score and prothrombin time were already available, regression analysis with Cox's proportional hazards model was performed. Survival rates were calculated by the Kaplan-Meier method, and the significance of differences in these rates was examined by the generalized Wilcoxon rank sum test; $P < 0.05$ was considered to show a significant difference (*15*).

RESULTS

The median (25th and 75th percentiles) of the receptor index was 0.95 (0.94 and 0.96) in healthy volunteers, 0.94 (0.92 and 0.96) in patients with chronic hepatitis and 0.86 (0.80 and 0.90) in patients with cirrhosis (Fig. 1). The difference in the receptor index between patients with cirrhosis and healthy volunteers or patients with chronic hepatitis was significant ($P = 0.0007$ and $P = 0.0075$, respectively). The median of the index of blood clearance was 0.51 (0.42 and 0.56) in healthy volunteers, 0.54 (0.48 and 0.61) in patients with chronic hepatitis and 0.69 (0.62 and 0.76) in patients with cirrhosis (Fig. 2). The difference in the index of blood clearance between patients with cirrhosis and healthy volunteers or patients with chronic hepatitis was significant ($P = 0.0007$ and $P < 0.0001$, respectively).

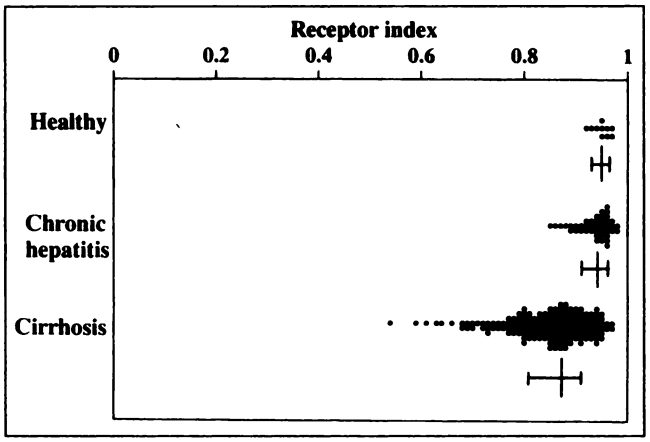

FIGURE 1. Receptor indices of healthy volunteers, patients with chronic hepatitis and patients with cirrhosis of liver. Vertical lines on bars show 25th percentile, median and 75th percentile, from left to right. Median index is significantly lower in patients with cirrhosis than in healthy volunteers or patients with chronic hepatitis ($P = 0.0007$ and $P = 0.0075$, respectively).

The median of the receptor index was 0.83 (0.78 and 0.87) in cirrhotic patients with varices and 0.88 (0.85 and 0.93) in cirrhotic patients without varices ($P = 0.0002$, Fig. 3). The median of the receptor index was 0.80 (0.69 and 0.84) in cirrhotic patients with ascites and 0.87 (0.80 and 0.92) in cirrhotic patients without ascites ($P < 0.0001$). The median of the index of blood clearance was 0.72 (0.66 and 0.78) in cirrhotic patients with varices and 0.64 (0.56 and 0.72) in cirrhotic patients without varices ($P = 0.0006$, Fig. 4). The median of the index of blood clearance was 0.77 (0.71 and 0.82) in cirrhotic patients with ascites and 0.67 (0.58 and 0.75) in cirrhotic patients without ascites ($P < 0.0001$).

The correlation of the receptor index with classic indicators of hepatic functional reserve is shown in Table 1.

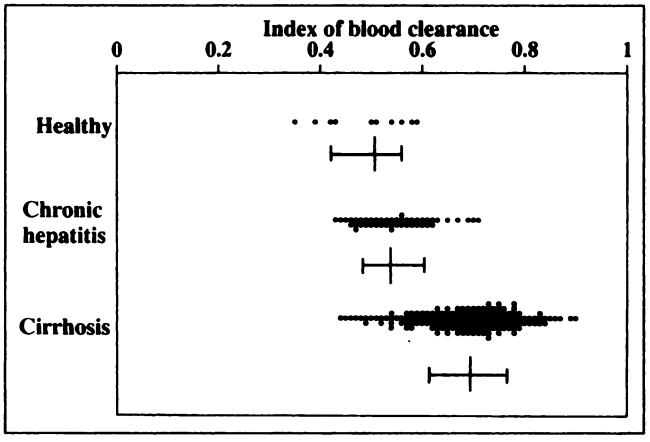

FIGURE 2. Indices of blood clearance in healthy volunteers, patients with chronic hepatitis and patients with cirrhosis of liver. Vertical lines on bars show 25th percentile, median and 75th percentile, from left to right. Median index is significantly higher in patients with cirrhosis than in healthy volunteers or patients with chronic hepatitis ($P = 0.0007$ and $P < 0.0001$, respectively).

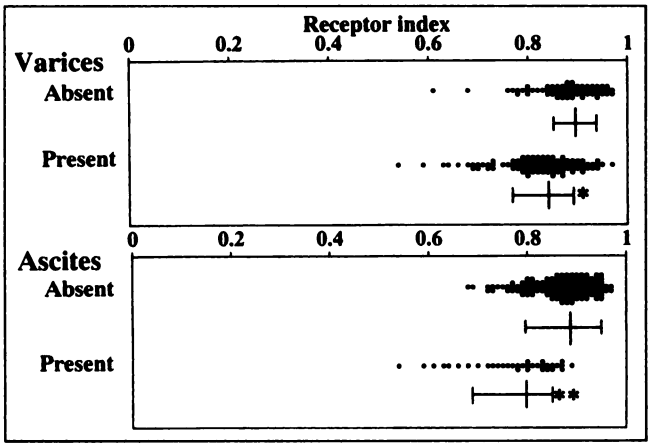

FIGURE 3. Relationship of receptor index to presence of esophageal varices or ascites in patients with cirrhosis of liver. Vertical lines on bars show 25th percentile, median and 75th percentile, from left to right. $^*P = 0.0002$; $^{**}P < 0.0001$.

Correlation was significant between the receptor index and the serum albumin level, results of the indocyanine green retention test, prothrombin time and CTC score. The correlation between the index of the blood clearance and classic indicators of hepatic functional reserve is shown in Table 2. Correlation was significant between the index of blood clearance and the serum albumin level, results of the indocyanine green retention test, prothrombin test and CTC score.

The cumulative 1-y survival rate was 95%, the 3-y survival rate was 88% and the 5-y survival rate was 70%. On the basis of the receptor index at presentation, the patients with cirrhosis were divided into two groups of roughly equal size: group A (n = 78), receptor index > 0.85, and group B (n = 80), receptor index ≤ 0.85. On the basis of the index of blood clearance, the patients with cirrhosis were divided into two groups of roughly equal size: group A (n = 77), index of blood clearance under 0.70, and group B (n = 81), index of

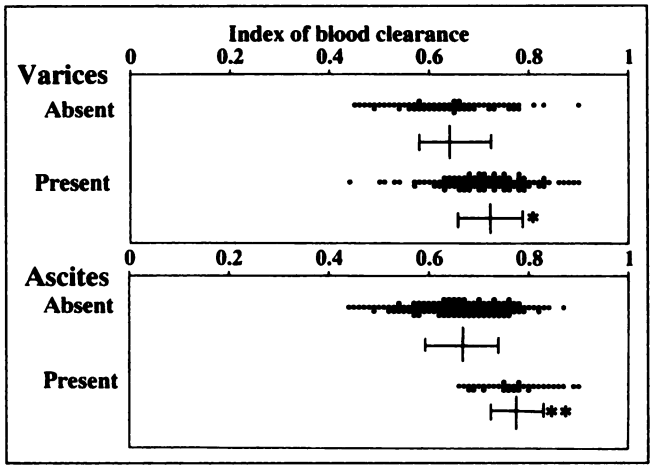

FIGURE 4. Relationship of index of blood clearance to presence of esophageal varices or ascites in patients with cirrhosis of liver. Vertical lines on bars show 25th percentile, median and 75th percentile, from left to right. $^*P = 0.0006$; $^{**}P < 0.0001$.

TABLE 1
Correlation of the Receptor Index with Classic Indicators of Hepatic Functional Reserve

Indicators of functional reserve	Albumin	Prothrombin time	ICGR-15	CTC score
No.	200	200	131	158
Correlation coefficient	0.577	0.639	−0.581	−0.584
P	<0.0001	<0.0001	<0.0001	<0.0001

ICGR-15 = retention of indocyanine green in plasma after 15 min; CTC = Child-Turcotte classification.

blood clearance 0.70 or more. The survival rates were lower in group B than in group A (Figs. 5 and 6). On regression analysis (Table 3), two indices, CTC score and index of blood clearance, were found to be significantly related to survival.

DISCUSSION

It is important to evaluate both hepatic functional reserve and the portal circulation in patients with chronic liver diseases, especially cirrhosis. The results of some tests currently used to evaluate hepatic functional reserve, such as the indocyanine green retention test, are affected by the portal circulation. Hepatic receptor imaging with ^{99m}Tc-GSA is a new method for the diagnosis of hepatic disease. It assesses the specific binding of hepatocytes to asialoglycoprotein receptors (*3*). Hepatic receptor imaging with ^{99m}Tc-GSA enables quantitative evaluation of hepatic functional reserve, and the results are not affected by the portal circulation. We have reported a significant relationship between an abnormal portal circulation as evaluated by per-rectal portal scintigraphy and the outcome of cirrhosis (*16,17*). In this study, we evaluated the relationship between the results of scintigraphy with ^{99m}Tc-GSA and outcome in patients with cirrhosis.

To identify factors most closely related to outcome in patients with cirrhosis of the liver, we reviewed various

TABLE 2
Correlation of the Index of Blood Clearance with Classic Indicators of Hepatic Functional Reserve

Indicators of functional reserve	Albumin	Prothrombin time	ICGR-15	CTC score
No.	200	200	131	158
Correlation coefficient	−0.487	−0.584	0.651	0.529
P	<0.0001	<0.0001	<0.0001	<0.0001

ICGR-15 = retention of indocyanine green in plasma after 15 min; CTC = Child-Turcotte classification.

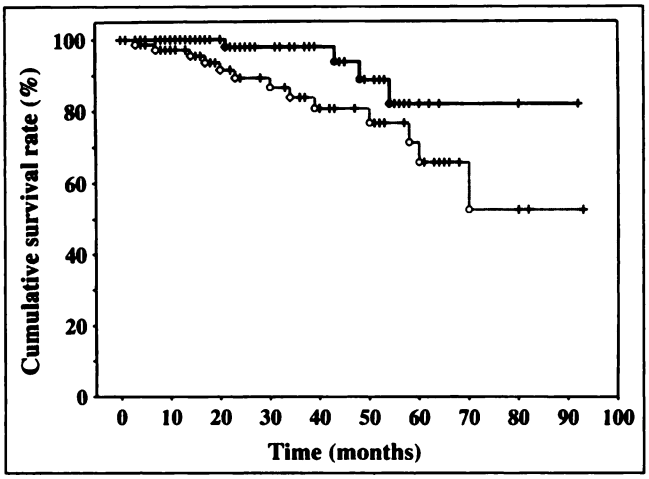

FIGURE 5. Cumulative survival rate in cirrhotic patients in group A (bold line), with receptor index > 0.85, and in group B (shaded line), with receptor index ≥ 0.85. Survival rate was lower in group B than group A ($P = 0.014$).

studies. Schlichting et al. (*9*) reported that several laboratory variables, including prothrombin time and cholinesterase activity, had prognostic value, as demonstrated by analyses by Cox's proportional hazards model of 162 variables in 488 patients with chronic liver disease. Orrego et al. (*10*) found in a study of 253 patients with alcoholic liver disease that albumin level, bilirubin level and prothrombin time were the most useful routine laboratory tests in establishing a prognosis. These statistically verified results agree with currently accepted clinical guidelines. The CTC score has long been used as a clinical index of prognosis for patients with liver disease. Its predictive value was statistically verified by Christensen et al. (*13*) in their study of 245 patients with cirrhosis, as well as by Infante-Rivard et al. (*14*) in their study of 177 patients with cirrhosis, using a multiple logistic regression model.

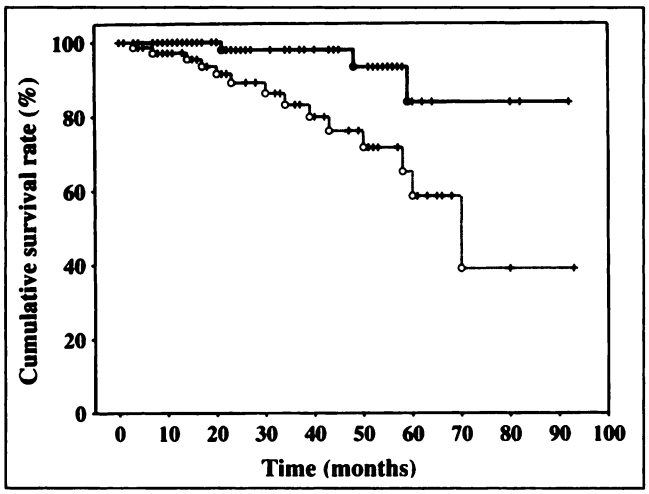

FIGURE 6. Cumulative survival rate in cirrhotic patients in group A (bold line), with index of blood clearance < 0.70, and in group B (shaded line), with index of blood clearance ≥ 0.70. Survival rate was lower in group B than group A ($P = 0.011$).

TABLE 3
Regression Results by Cox's Proportional Hazards Model

Variable	β	SE	t	F	*P*
Receptor index	−0.013	0.019	−0.672	0.452	0.501
Index of blood clearance	−0.030	0.014	−2.148	4.614	0.032
Prothrombin time	0.155	0.064	2.420	5.856	0.077
CTC score	0.103	0.006	1.766	3.120	0.016

CTC = Child-Turcotte classification.

On the basis of these reports, we selected prothrombin time and CTC score as clinical indicators of hepatic functional reserve and thus prognosis. We found that the index of blood clearance and the CTC score were significantly related to outcome in patients with cirrhosis. However, the CTC score is not always a meaningful index, because patients with cirrhosis may receive blood preparations. The efficacy of transjugular intrahepatic portosystemic shunt in the prevention of recurrent variceal bleeding has been reported (*18*). Because this therapy sometimes will worsen hepatic encephalopathy without changing the hepatic functional reserve, the CTC score after this treatment does not accurately reflect hepatic reserve. An advantage of scintigraphy with ^{99m}Tc-GSA is that the results are not affected by these factors. Kira et al. (*19*) reported that uptake of GSA by the liver in patients who underwent transjugular intrahepatic portosystemic shunt was influenced substantially by portosystemic shunt early (1–3 min) after injection, but the hepatic blood circulation reached equilibrium subsequently (5–10 min), and the uptake of GSA by the liver reflected the receptor concentration. The prognosis of patients with cirrhosis can be assessed more accurately on the basis of GSA data than by conventional methods. In this study, the relationship between GSA data and the outcome in patients with cirrhosis was slightly weaker than the relationship between CTC score and the outcome, probably because GSA examinations were performed in all patients before starting treatment for cirrhosis.

In this study, the survival rate was significantly lower in the group with the high index of blood clearance than in the group with the low index. It was also significantly lower in the low receptor index group than in the high receptor index group. Although regression analysis showed a significant correlation between the index of blood clearance and the outcome of cirrhosis, the receptor index did not significantly correlate with the outcome of cirrhosis. This was perhaps because the index of blood clearance showed a normal distribution, whereas the receptor index did not. The receptor index is useful for predicting the short-term outcome of severe hepatic disease, including fulminant hepatic failure, because of its broad distribution in patients with low hepatic function (*8*). On the other hand, the index of blood clearance seems to be more useful for predicting the long-term

outcome of cirrhosis, because of its broad distribution in patients with moderate hepatic function.

The decision to perform liver transplantation in patients with cirrhosis ultimately depends on expected benefits in terms of outcome. The results of scintigraphy with ^{99m}Tc-GSA may assist in the identification of patients with advanced cirrhosis who would benefit most from liver transplantation or other procedures.

CONCLUSION

Hepatic receptor imaging with ^{99m}Tc-GSA can be used to evaluate noninvasively the hepatic functional reserve of patients with various liver diseases. We conclude that this method is useful clinically in the diagnosis and prognosis of cirrhosis of the liver.

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