

Assessment of risk of complications in cirrhosis using portal thallium scans

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risk factors for complications. We compared the cumulative incidence rates of complications during the follow-up period.

RESULTS: The thallium scan shunt index was significantly higher in the decompensated liver cirrhosis group than in the compensated liver cirrhosis group (0.91 ± 0.39 vs 0.39 ± 0.32 , $P < 0.001$). It was also higher in the varices group, the hepatic encephalopathy group, and the variceal bleeding group than in the control group ($P < 0.001$). Multivariate analysis showed that the index was an independent risk factor for predicting decompensated liver cirrhosis. When the cut-off value was 0.75, the shunt index had a sensitivity of 82.6%, a specificity of 84%, a positive predictive value of 61.5%, and a negative predictive value of 94.4% in diagnosing decompensated cirrhosis. When the shunt index was greater than 0.75, there was a significant increase in the number of decompensated events.

CONCLUSION: The thallium shunt index is a good predictor of cirrhosis-related complications.

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Key words: Liver cirrhosis; Portosystemic shunt; De-compensation

Abstract

AIM: To investigate the usefulness of a novel thallium scan shunt index for assessing portosystemic shunt-related cirrhotic complications.

METHODS: We enrolled 209 chronic hepatitis B-related cirrhosis patients. After rectal thallium instillation, radioactive isotope activity in the heart and liver was measured. The ratio of radiation uptake between the heart and the liver was calculated (the shunt index). This value indicates the degree of portosystemic circulation shunting. Blood tests, serum biochemistry tests, abdominal ultrasonography, gastroscopy and examination of clinical features such as the occurrence of varices, bleeding and hepatic encephalopathy were performed. Multivariate analysis was used to identify independent

Core tip: After rectal thallium instillation, radioactive isotope activity in the heart and liver was measured (the shunt index). It was higher in the varices group, the hepatic encephalopathy group, and the variceal bleeding group than in the control group ($P < 0.001$). Multivariate analysis showed that the index was an independent risk factor for predicting decompensated liver cirrhosis. When the shunt index was greater than 0.75, there was a significant increase in the number of decompensated events. The thallium shunt index is a good predictor of cirrhosis-related complications.

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INTRODUCTION

Increased intrahepatic vascular resistance and the occurrence of portosystemic shunts play central roles in the development of decompensation in cirrhotic patients. Collateral circulation and the formation of portosystemic shunts produce serious complications such as gastroesophageal varices, bleeding, ascites and hepatic encephalopathy, which are known to be some of the leading causes of death among liver cirrhosis patients^[1,2]. For this reason, measuring the amount of portosystemic shunting is important in predicting the incidence and prognosis of complications from liver cirrhosis. Measurement of the hepatic vein pressure gradient (HVPG) and cardiac output and systemic vascular resistance by cardiac catheterization are currently the best methods for assessing hyperdynamic states caused by liver cirrhosis. However, they are invasive and difficult to use in clinical practice^[3].

Various studies have investigated the prognostic factors of chronic liver disease, but most have focused on predicting intrahepatic fibrosis^[4-6]. Although measuring liver stiffness is very useful in diagnosing F4 hepatic fibrosis and liver cirrhosis, it has limited use in evaluating the severity of portosystemic shunting and hyperdynamic circulation. Furthermore, very few studies report on the effectiveness of elastographies in predicting complications such as variceal bleeding, ascites and hepatic encephalopathy. There are some studies of prediction of esophageal varices using the platelet count/spleen diameter ratio^[7-10], but their findings are restricted to esophageal varices and thus are difficult to apply to other complications. Structural changes in the liver, including hepatic fibrosis, do play an important part in the portosystemic shunt. However, the degree of hemodynamic changes or the amount of portosystemic shunting is not always correlated with the degree of intrahepatic fibrosis; changes in hemodynamic features and collateral systems in patients with advanced liver cirrhosis have other causes besides hepatic fibrosis^[5].

When thallium, an analogue of potassium, is administered to a healthy subject rectally, it is absorbed through the rectum and taken up mainly by the liver *via* the portal circulation. However, when a portosystemic shunt exists, thallium is taken up not only by the liver but by the heart, spleen and other organs *via* the portosystemic shunt or collateral circulation. When the heart's uptake capacity is normal, portal venous blood flow and liver cell viability affect thallium uptake by the liver; calculation of the thallium heart/liver ratio (the shunt index) can then be used to quantify the degree of portosystemic circulation shunting^[11-13]. Urbain *et al*^[13,14] demonstrated that liver

cirrhosis patients had a higher thallium scan shunt index than healthy people and chronic hepatitis patients. The thallium scan shunt index was shown not only to assist in diagnosing liver cirrhosis, but also to strongly correlate with the severity of liver disease^[15-17]. However, these were all case-control studies, and their subjects were patients with alcoholic liver disease and viral liver disease.

We wished to examine the correlation between the thallium scan shunt index and the incidence of decompensated liver cirrhosis in patients with hepatitis B-associated cirrhosis. We also aimed to test whether measuring changes in the thallium scan shunt index was useful for predicting esophageal varices, ascites, hepatic encephalopathy and variceal bleeding.

MATERIALS AND METHODS

Patients

We enrolled 209 patients with chronic liver disease caused by hepatitis B and hospitalized in our Department of Gastroenterology. The diagnosis of cirrhosis was confirmed by liver biopsy, by abdominal ultrasonography or abdominal computed tomography findings such as blunt liver edge or nodular liver surface, or by a history of overt complications of cirrhosis such as ascites, variceal bleeding or hepatic encephalopathy. All patients were aged 18 or older. We did not include patients with chronic hepatitis C, alcoholic liver disease, acute esophageal variceal bleeding, current systemic infection or acute kidney injury. Patients were followed up by thallium portal scans every 6-12 mo. Blood tests, serum biochemistry tests, abdominal ultrasonography, gastroscopy and examination of clinical features such as the occurrence of varices, bleeding and hepatic encephalopathy were carried out every 3-6 mo.

Thallium portal scan

Patients were told to fast from the evening before the test. To increase the accuracy of the results, an enema was administered on the morning of the test, using a YAL solution® (Bukwang, Seoul, South Korea) to expel all residual stools. Afterward, a Nelaton tube was inserted into the anus to a depth of 10-15 cm, and 20 cc of TI-201 20 MBq (0.5 mCi) was injected. Radiation in the liver and heart areas was measured for 20 min using a radioisotope camera (Siemens Orbiter 7500, Germany). When the radioisotope activity reached a plateau, the ratio of radiation uptake between the heart and the liver was calculated. This value, which indirectly indicates the degree of portosystemic circulation shunting, was adopted as the shunt index (normal: 0.24 ± 0.07)^[18,19].

Endoscopy

We used criteria from the Baveno Consensus Conference to assess the size of varices: thin, straight varices were categorized as small varices (F1), nodular varices as medium varices (F2), and thick, tumorous, coil-shaped varices as large varices (F3)^[20].

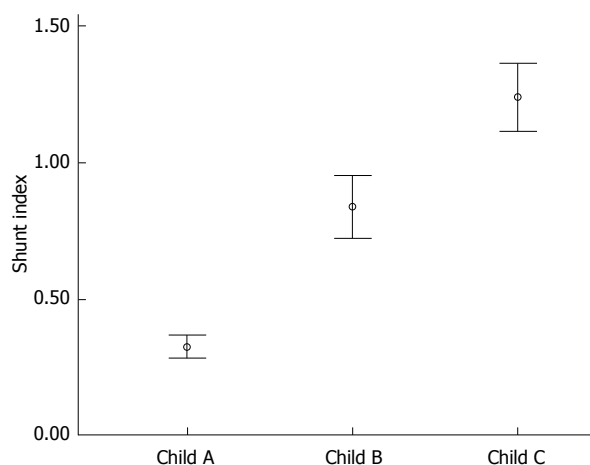


Figure 1 Correlation between Shunt index and Child-Pugh class. Among Child-Pugh class a patients, the median thallium scan shunt index was 0.31 ± 0.24 , among class B patients was 0.82 ± 0.39 , and among class C patients was 1.19 ± 0.30 . The thallium scan shunt index tended to increase as the Child-Pugh score became higher ($P < 0.01$). Shunt index: Transrectal thallium portal scan shunt index; Child: Child-Pugh class $P < 0.001$

Biochemical study

Liver biopsy was performed percutaneously guided by ultrasonography. The samples were fixed with formaldehyde, embedded in paraffin, and stained with hematoxylin-eosin and Masson's trichrome. The stages of hepatic fibrosis were defined as: no fibrosis (F0), portal fibrosis without septa (F1), portal fibrosis with a few septa (F2), numerous septa without cirrhosis (F3), and liver cirrhosis (F4), according to the technical guidelines for liver tissue provided by the Gastrointestinal Pathology Study Group of the Korean Society of Pathologists^[21].

We defined decompensated liver cirrhosis as follows: variceal bleeding, ascites due to portal hypertension (serum ascites albumin gradient > 1.1 g/dL), and hepatic encephalopathy^[22,23]. Compensated liver cirrhosis was diagnosed either by the existence of chronic liver disease with esophageal or gastric varices, or stage 4 fibrosis confirmed by liver biopsy.

Statistical analysis

The decompensated liver cirrhosis group and the compensated liver cirrhosis group were treated as dependent variables; the subject's age, platelets, aspartate aminotransferase, alanine aminotransferase (ALT), albumin, bilirubin, prothrombin time, and thallium scan shunt index were independent variables. Statistical significance was ascertained by *t* test. Logistic regression was used in multivariate analysis. For the predictive factors identified on the basis of logistic regression, receiver operating characteristic (ROC) curves were used to find the appropriate cut-off values for predicting exacerbation of decompensated liver cirrhosis. Pearson's correlation coefficient and logistic regression were also used to identify the correlations between the complications of liver cirrhosis (ascites, hepatic encephalopathy, varices, variceal bleeding), and also between blood test results and the shunt index. Again, appropriate cut-off values for each complication

Table 1 Thallium shunt index for each cirrhosis complication

	Thallium shunt index		
	Presence	Absence	^b <i>P</i> value
Varix	0.76 ± 0.41	0.41 ± 0.34	< 0.001
Ascites	0.91 ± 0.40	0.40 ± 0.32	< 0.001
Hepatic encephalopathy	1.11 ± 0.70	0.48 ± 0.36	< 0.001
Variceal bleeding	1.04 ± 0.09	0.47 ± 0.38	< 0.001
Decompensation	0.91 ± 0.39	0.39 ± 0.32	< 0.001

Mean \pm SD (%), ^b $P < 0.01$ by the *t* test.

were identified using ROC curves. The Kaplan-Meier method was used to compare the cumulative incidence rates of the various complications during the follow-up period, with $P < 0.05$ as the standard for determining statistical significance. For survival analysis, we included 89 patients without associated varices, ascites or hepatic encephalopathy among the 209 cirrhosis patients.

RESULTS

Patients

A total of 209 chronic hepatitis B-related cirrhosis patients were enrolled: 101 (48.3%) were diagnosed with liver cirrhosis by liver biopsy. The remaining 108 (51.7%) were diagnosed with liver cirrhosis based on image diagnosis, laboratory findings and clinical features; 61 (29.1%) were found to have varices, two of them with previous variceal bleeding; 46 (22%) had ascites; and 49 (23.4%) were diagnosed with decompensated liver cirrhosis. The mean follow-up time was 49.6 mo.

Correlation between thallium scan shunt index and liver cirrhosis complications

As the thallium scan shunt index increased, platelet count ($r = -0.67$, $P < 0.001$), albumin ($r = -0.67$, $P < 0.001$) and prothrombin time ($r = -0.69$, $P < 0.001$) decreased. Those in the decompensated liver cirrhosis group were older, and had lower platelet counts and albumin, but higher bilirubin, ALT, prothrombin times and thallium scan shunt indexes ($P < 0.05$). The median thallium scan shunt index was 0.31 ± 0.24 for the Child-Pugh A group, 0.82 ± 0.39 for the Child-Pugh B group, and 1.19 ± 0.30 for the Child-Pugh C group. The index increased as the Child-Pugh score increased ($P < 0.01$) (Figure 1). At the same time, the thallium scan shunt index was found to be high in the varices group (0.76 ± 0.41 *vs* 0.41 ± 0.4 , $P < 0.001$), as well as in the ascites group (0.91 ± 0.40 *vs* 0.40 ± 0.32 , $P < 0.001$), hepatic encephalopathy group (1.11 ± 0.7 *vs* 0.48 ± 0.36 , $P < 0.001$), and variceal bleeding group (1.04 ± 0.09 *vs* 0.47 ± 0.38 , $P < 0.001$) (Table 1). Logistic regression on factors that demonstrated significance in univariate analysis revealed that when the thallium scan shunt index increased by one unit, the risk of developing ascites increased by 9.5-fold [EXP (B) = 9.49, 95% confidence interval (CI): 1.90-47.34, $P = 0.006$], and of developing varices by 5.1-fold [EXP (B) = 5.10, 95%CI: 1.36-19.12, $P = 0.015$]. In multivariate analysis, only the

Table 2 Multivariate analysis of independent risk factors for liver decompensation

	Decompensation				Varices				Ascites		
	Exp(B)	95%CI	^a P value		Exp(B)	95%CI	^a P value		Exp(B)	95%CI	^a P value
Shunt index	8.55	2.24-54.97	0.003	5.10	1.36-19.12	0.015	9.49	1.90-47.34	0.006		
AST/ALT	1.14	0.66-1.93	0.64	0.93	0.59-1.45	0.75	1.19	0.69-2.06	0.51		
Bil (mg/dL)	0.96	0.84-1.09	0.54	1.02	0.91-1.16	0.64	0.96	0.83-1.10	0.55		
PLT ($\times 10^3$)	0.99	0.97-1.00	0.19	0.98	0.97-1.00	0.04	0.98	0.97-1.00	0.14		
Alb (g/dL)	0.37	0.13-1.07	0.06	0.31	0.12-0.75	0.01	0.48	0.17-1.35	0.16		
PT (%)	0.96	0.93-1.00	0.07	0.95	0.97-1.03	0.95	0.95	0.92-0.99	0.03		

Odds ratios with 95%CI from logistic regression analysis, ^aP < 0.05. AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; PLT: Platelet count; Alb: Albumin; PT: Prothrombin time.

thallium scan shunt index was an independent predictor of decompensation [EXP (B) = 8.55, 95%CI: 2.24-54.97, $P = 0.003$] (Table 2).

Predictive value of the thallium scan shunt index for liver cirrhosis complications

ROC curves were constructed to identify the diagnostic capacity of decompensation. The area under the ROC curve (AUROC) of the thallium scan shunt index was 0.911. When the cut-off value was set at 0.75, the sensitivity of diagnosis was 82.6%, the specificity was 84%, the positive predictive value was 61.5%, and the negative predictive value was 94.4%. In diagnosing esophageal varices, the AUROC of the thallium scan shunt index was 0.854. When the cut-off value was set at 0.854, the sensitivity of diagnosis was 80.4%, the specificity 79.7%, the positive predictive value 56.1%, and the negative predictive value 80.9%. With the cut-off value for ascites set at 0.75, the sensitivity of diagnosis was 80.4%, the specificity was 80%, the positive predictive value was 60%, and the negative predictive value was 95.1%. When the thallium scan shunt index was divided into quartiles, the rates of decompensated liver cirrhosis, varices and ascites increased with increased shunt index.

Cumulative incidence of liver cirrhosis complications

The 89 patients without associated varices, ascites or hepatic encephalopathy among the 208 cirrhosis patients were followed up by regular thallium scan. During follow-up, 7 patients developed variceal bleeding, 4 developed hepatic encephalopathy, 20 developed varices, and 13 developed ascites. Eight (3.8%) died as a result of their complications. The mean shunt index value was 0.56 for the patients who developed any cirrhotic decompensation, and 0.54 for those who developed esophageal varix. For those who developed ascites, it was 0.57. The cumulative rates of complications due to liver cirrhosis were compared using a thallium scan shunt index of 0.75 as the reference value. The rates of cirrhotic complications ($P < 0.001$), varices ($P < 0.001$), ascites ($P = 0.001$) and hepatic encephalopathy ($P < 0.001$) were higher in cases with shunt indexes of 0.75 or more (Figure 2).

DISCUSSION

This study showed that the thallium shunt index was an

independent risk factor for hepatic decompensation. As the shunt index increased by one point, the risk of ascites and varices increased by factors of 9.5 and 5.1, respectively. In multivariate analysis, the thallium shunt index was seen to be a useful predictor of decompensated liver cirrhosis. These results suggest that the transrectal thallium scan shunt index is useful for predicting complications in patients with cirrhosis.

HVPG is used as an indirect method for evaluating portal pressure. When HVPG is 10 mmHg or higher, varices and ascites occur due to clinically significant portal hypertension^[24,25]. When HVPG is 12 mmHg or more, the risk of variceal bleeding increases. Accordingly, HVPG has been adopted for monitoring patients undergoing pharmacological treatment to prevent variceal bleeding, and is also useful as a prognostic factor^[25-27]. Although HVPG is one of the best methods of assessing portal pressure and hemodynamic circulation, there are problems with using it in clinical practice. First, since it is an invasive procedure, repeat measurements may not be possible. Second, there has been inadequate cost-benefit analysis^[3,28]. Thirdly, the measuring procedure and protocol need to be standardized. Unlike HVPG, a transrectal thallium scan is non-invasive and is the chief method of evaluating a portosystemic shunt. The shunt index can be measured every 3 or 6 mo according to the patient's clinical setting. We used the thallium scan index to estimate the amount of portosystemic shunt. Our results showed that patients with portal hypertension have a significantly higher heart/liver ratio than compensated cirrhosis patients. The thallium scan heart/liver index was reproducible with low inter- and intra-observer variation. It involves a patient-friendly technique that can be performed in an outpatient setting, and takes under 30 min in the clinic or at the bedside, with immediate results and high acceptance by patients.

In recent years, numerous studies have investigated biochemical markers of hepatic fibrosis and radiologic diagnosis as non-invasive approaches to evaluate the progression of hepatic fibrosis^[29]. Direct hepatic fibrosis-specific markers that measure changes in the extracellular matrix (laminin, procollagen III, N-peptide, hyaluronic acid, tissue inhibitors of metalloproteinase, collagen type IV) are useful in diagnosing severe hepatic fibrosis and liver cirrhosis. However, there is no consensus as to the optimal combination of markers and cut-off values

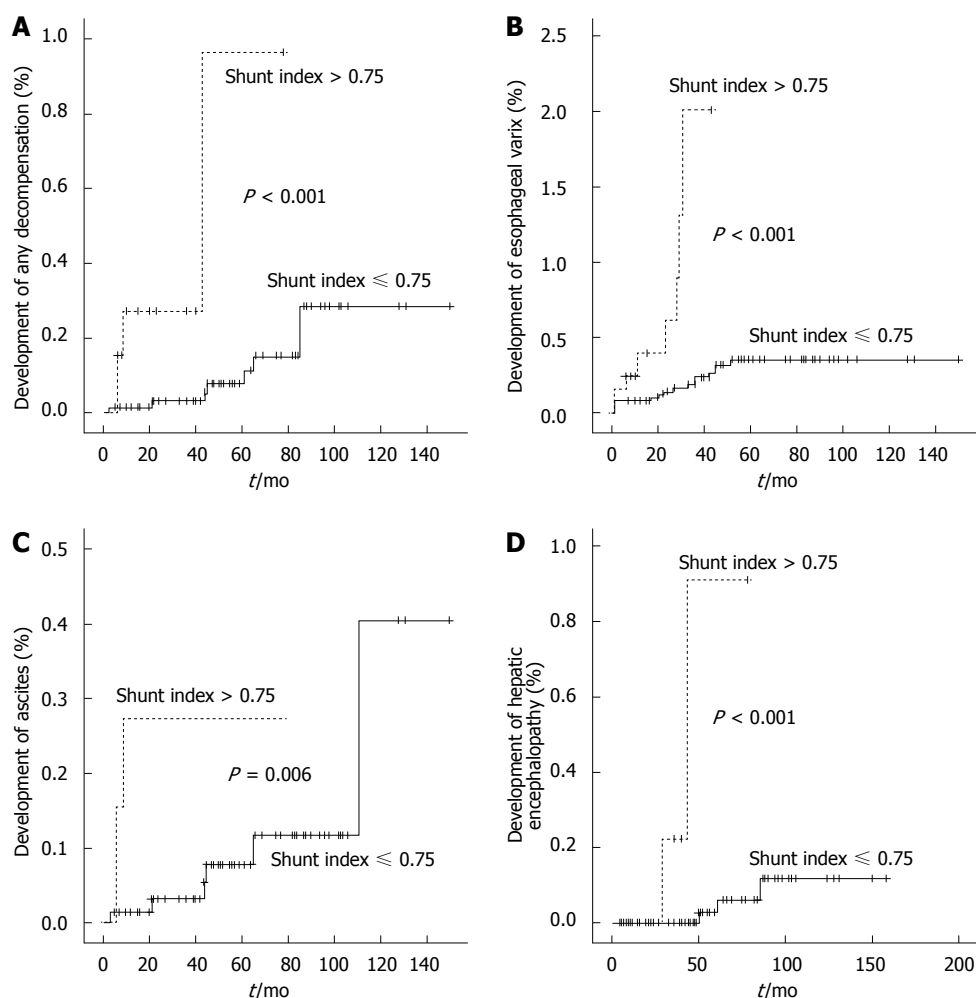


Figure 2 Cumulative incident rate for decompensation, esophageal varix, ascites, hepatic encephalopathy according to shunt index. Reference value of shunt index was 0.75. Shunt index: Transrectal thallium portal scan shunt index

for the various liver diseases, and their measurement is overly expensive for clinical use. Moreover, there are few studies using such tests to predict complications in liver cirrhosis patients^[29-32]. Transient elastography is a recently developed diagnostic method that measures liver stiffness in a quick, non-invasive way, enabling a simple assessment of the severity of hepatic fibrosis. However, it cannot be used on patients with ascites^[33], nor does it adequately reflect increases in portal pressure^[5]. Vizzutti *et al.*^[34] reported that liver stiffness measurements (LSM) using transient elastography were closely correlated with portal pressure in hepatitis C patients ($r = 0.81$, $P < 0.001$), but the correlation between LSM and HVPG was low in patients whose HVPG was 12 mmHg or higher^[35,36]. Cas-téra *et al.*^[4] reported that the cut off value for the presence of esophageal varices stage 2/3 was 27.5 kPa, for a past history of ascites it was 49.1 kPa, for hepatocellular carcinoma it was 53.7 kPa, and for esophageal bleeding it was 62.7 kPa. However, most of the tools were designed to determine the extent of fibrosis, and there have been few longitudinal studies of the prediction of decompensation

in cirrhotic patients.

There are some limitations to our study. Although none of the patients took antiviral medication, the dosages of, and compliance with, diuretics and beta-blockers were not considered. Secondly, 101 (48.3%) were diagnosed from a liver biopsy, but the remaining 108 (51.7%) were diagnosed by clinical judgment. The study included some advanced cirrhotic patients, and 47 (22%) had ascites or a history of cirrhotic complications. We investigated the usefulness of the shunt index in predicting the risk of new hepatic complications. We included only hepatitis B-associated cirrhotic patients, but the severity of liver disease was very variable. Thus, further validation of the shunt index cutoff for predicting decompensation is required.

In conclusion, the portosystemic shunt index is highly correlated with hepatic decompensation and complications caused by portal hypertension. The shunt index score is a non-invasive technique for estimate liver fibrosis, and a useful predictor of complications of portal hypertension in hepatitis B-associated cirrhosis.

COMMENTS

Background

Collateral circulation and the formation of portosystemic shunts produce serious complications such as gastro-esophageal varices, bleeding, ascites and hepatic encephalopathy, which are known to be some of the leading causes of death among liver cirrhosis patients. For this reason, measuring the amount of portosystemic shunting is important in predicting the incidence and prognosis of complications from liver cirrhosis.

Research frontiers

When thallium, an analogue of potassium, is administered rectally to a healthy subject, it is absorbed through the rectum and taken up mainly by the liver via the portal circulation. However, when a portosystemic shunt exists, thallium is taken up not only by the liver but by the heart, spleen and other organs via the portosystemic shunt or collateral circulation.

Innovations and breakthroughs

The thallium scan shunt index was shown not only to assist in diagnosing liver cirrhosis, but also to strongly correlate with the severity of liver disease. However, these were all case-control studies, and their subjects were patients with alcoholic liver disease and viral liver disease. The authors wished to examine the correlation between the thallium scan shunt index and the incidence of decompensated liver cirrhosis in patients with hepatitis B-associated cirrhosis. They also aimed to test whether measuring changes in the thallium scan shunt index was useful for predicting esophageal varices, ascites, hepatic encephalopathy and variceal bleeding.

Applications

The study results suggest that the portosystemic shunt index is highly correlated with hepatic decompensation and complications caused by portal hypertension. The shunt index score is a non-invasive technique for estimate liver fibrosis, and a useful predictor of complications of portal hypertension in HBV-associated cirrhosis.

Terminology

Thallium: an analogue of potassium; Shunt index: when the heart's uptake capacity is normal, portal venous blood flow and liver cell viability affect thallium uptake by the liver; calculation of the heart/liver ratio (the shunt index) can then be used to quantify the degree of portosystemic circulation shunting¹

Peer review

This study is a good prospective study in which the shunt index is correlated with hepatic decompensation and complication due to portal hypertension.

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