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^{99m}Tc-Phy portal perfusion index imaging helps predict the severity of hepatitis B virus cirrhosis: a preliminary study

Ning-Hu Liu[a,b], Meng-Jie Dong[a], Hao Liu[a], Xi-Li Lu[a], Dan Tian[a], Jun Zhang[a], Jun Yang[a], Jun-Hui Sun[c,d,e], Li-Hua Wu[a], Jian-Li Bi[a] and Bo Zhang[a]

Objective **The aim was to perform exploratory research on the application of technetium phytate (^{99m}Tc-Phy) portal perfusion index (PPI) imaging in predicting the complications of hepatitis B cirrhosis and their severity.**

Patients and methods **A total of 65 hepatitis B cirrhosis patients were stratified, respectively, into three groups from classes A to C according to Child–Pugh scores and five groups from stages 1 to 5 according to the five-stage prognostic system. PPIs were compared and analyzed, respectively, among the three and five groups. The correlations between PPIs and major biochemical indices of liver function were also analyzed. One-way analysis of variance was used to compare the PPIs among the various groups and a nonparametric Spearman test was used to analyze the correlations between PPIs and various biochemical indices.**

Results **PPIs of the five groups decreased gradually from stage 1 to stage 5 (73.03 ± 8.49, 52.96 ± 16.22, 46.24 ± 15.25, 29.99 ± 17.36, and 11.50 ± 6.37, respectively); with the exception of the difference between stages 2 and 3 ($P = 0.252$), the differences between the remaining groups were statistically significant ($P < 0.05$). The PPI showed positive correlations with serum total protein, serum albumin, and albumin/globulin results ($r = 0.292$, 0.559, 0.520, respectively; $P < 0.05$), and negative correlations with serum globulin ($r = -0.366$, $P < 0.05$).**

Conclusion **Technetium phytate PPI could be a promising noninvasive and effective method for predicting the complications of hepatitis B cirrhosis and their severity; a lower PPI value indicates a higher severity of complications for hepatitis B cirrhosis patients. PPI can provide very meaningful reference data for clinical practice.** ***Nucl Med Commun*** **39:818–824** **Copyright © 2018 The Author(s). Published by Wolters Kluwer Health, Inc.**

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[a]Department of Nuclear Medicine, [b]Institute of Nuclear Medicine, Zhejiang University, [c]Hepatobiliary and Pancreatic Interventional Treatment Center, Division of Hepatobiliary and Pancreatic Surgery, The First Affiliated Hospital, College of Medicine, Zhejiang University, [d]Key Laboratory of Precision Diagnosis and Treatment for Hepatobiliary and Pancreatic Tumor of Zhejiang Province and [e]Key Laboratory of Combined Multi-organ Transplantation, Ministry of Public Health, Hangzhou, Zhejiang, People's Republic of China

Correspondence to Jun-Hui Sun, MD, PhD, Hepatobiliary and Pancreatic Interventional Treatment Center, Division of Hepatobiliary and Pancreatic Surgery, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou 310003, People's Republic of China
Tel: + 86 571 8723 6815; fax: + 86 571 8707 2577; e-mail: 1307005@zju.edu.cn

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Introduction

China is a major country for chronic hepatitis B (hereafter referred to as hepatitis B). During the course of disease development, hepatitis B can progress to cirrhosis, with the proportion of cirrhosis that eventually progresses to liver cancer also being relatively high. Some studies have shown that in the development model for hepatitis B–cirrhosis–liver cancer, the probability of cirrhosis progressing to primary liver cancer is as high as 9.2–28.6% [1,2]. Cirrhosis patients often have many complications. In particular, patients with decompensated cirrhosis have a rather high mortality rate [3]. At present, the Child–Pugh (C-P) score, the model of end-stage liver disease score, and the five-stage prognostic system are the main risk-assessment methods for determining the disease severity and prognosis of cirrhosis patients. The first two methods cannot effectively predict the prognosis of cirrhosis patients because of the presence of considerable subjectivity, the fact that specific objective indices may be influenced by many factors, failure to assess the effects of the severe complications of portal hypertension on the prognosis, and other limitations [4,5]. The five-stage prognostic system includes clinically closely related portal hypertension and its complications on the basis for staging, which is consistent with the disease progression of cirrhosis and the development of portal hypertension and complications reported by a relevant study [6]. Although several of the aforementioned methods can reflect changes in the condition of the cirrhosis to a certain extent, they cannot provide assessments through specific numerical values. Therefore, it is particularly important to explore a method to quantitatively evaluate cirrhosis complications and their severity.

Technetium phytate (^{99m}Tc-Phy), chelated with the calcium ions in the blood to form ^{99m}Tc-calcium phytate

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colloids, is the imaging agent of portal perfusion index (PPI). Normally, ~90% of the chelated complex is taken up as foreign bodies by liver Kupffer cells in phagocytosis and the rest is taken up by the mononuclear phagocytes of the spleen, lymph nodes, and bone marrow. Other ^{99m}Tc radiolabeled agents, which are hardly taken up by liver Kupffer cells, cannot accurately present the change of liver blood [7]. The PPI provided by ^{99m}Tc-Phy portal perfusion index imaging (^{99m}Tc-Phy PPI) represents a quantitative index for the proportion of hepatic portal perfusion; changes in the ratio can intuitively reflect changes in the liver blood supply. Moreover, as the severity of the cirrhosis changes, the PPI value also changes gradually [8,9]. On the basis of this, we carried out this retrospective study on the clinical data of 65 cirrhosis patients, whereby the patients were classified and categorized according to C-P scores and the five-stage prognostic system to compare changes in PPI values in various stages and to investigate the correlations of PPI with the main biochemical indices of liver function.

Patients and methods

Patients

Eligible patients were selected from among those who had undergone ^{99m}Tc-Phy PPI imaging between April 2011 and August 2016. All of the examined patients provided their informed consent to the study. A total of 65 consecutive hepatitis B patients [50 males, 15 females; age 16–82 years (mean: 50±10 years)] were recruited retrospectively. Patients with hepatitis B cirrhosis had been diagnosed on the basis of the criteria set by the Clinical Practice Guidelines [10,11] and several laboratory parameters were measured within 2 weeks of the ^{99m}Tc-Phy PPI examination: blood routine, biochemical indices of liver function, renal function, and hepatitis B virus.

The diagnosis of hepatitis B cirrhosis and the values of the five-stage prognostic system on the basis of the criteria set by D'Amico and colleagues [6,7,12] are as follows: stage 1: compensated cirrhosis without varices; stage 2: compensated cirrhosis with varices; stage 3: bleeding without other disease complications; stage 4: first nonbleeding decompensating event; and stage 5: any second decompensating event. The characteristics of the included patients are shown in Table 1.

C-P score

Points were accumulated according to whether the patients had hepatic encephalopathy, the severity of ascites, the serum total bilirubin values, the serum albumin values, and the prothrombin time values, and the patients were divided into three classes – classes A, B, and C – according to the accumulated points.

The patients were then scored on the basis of the modified C-P scoring system and divided into classes A, B, or C on the basis of the score obtained (Table 2) [13].

Table 1 shows the basic information on the hepatitis B cirrhosis patients. On classifying according to the C-P score, there were 38 patients in class A, 15 patients in class B, and 12 patients in class C; on staging according to the five-stage prognostic system, there were 12 patients in stage 1, 10 patients in stage 2, 18 patients in stage 3, 20 patients in stage 4, and five patients in stage 5. Table 3 details the basic information of staging for the 65 cirrhosis patients according to the five-stage prognostic system.

Table 1 Baseline characteristics of 65 patients

	Mean±SD or frequency (%)	Median (range)
Sex (male/fimale)	50 (76.9)/15 (23.1)	
Age (years)	50±10	50 (16–82)
Laboratory tests		
TP (g/l)	66.89±6.97	66.3 (47.6–78.8)
Alb (g/l)	37.33±8.17	37.2 (20.1–50.7)
GloB (g/l)	29.55±6.91	28.3 (13.7–44.9)
A/G	1.37±0.53	1.4 (0.4–2.5)
ALT (U/l)	40.72±63.92	24 (4–482)
AST (U/l)	47.31±66.60	31 (6–515)
ALP (U/l)	89.91±37.15	83.5 (27–202)
TB (μmol/l)	37.19±60.71	20 (8–421.9)
DB (μmol/l)	20.14±40.03	7 (2–264)
IB (μmol/l)	17.05±21.17	12 (3–158)
PT (s)	14.36±2.80	13.4 (11.1–28.4)
Child–Pugh score	6.69±2.10	6 (5–12)
PPI	44.55±22.78	47.4 (1.8–84.2)

A/G, albumin/globulin; Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DB, direct bilirubin; GloB, globulin; IB, indirect bilirubin; PPI, portal perfusion index; PT, prothrombin time; TB, total bilirubin; TP, total protein.

Table 2 Child–Pugh classification of cirrhosis patients

	Points		
Clinical and laboratory criteria	1	2	3
Encephalopathy	None	Mild to moderate (grade 1 or 2)	Severe (grade 3 or 4)
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Total bilirubin (μmol/l)	<34	34–51	>51
Albumin (g/l)	>35	28–35	<28
Prothrombin time (S)	<4	4–6	>6

Class obtained by adding the score for each parameter (total points).
Class A, 5–6 points (least severe); class B, 7–9 points (moderate severe liver disease); class C, 10–15 points (most severe liver disease).

Hepatic portal perfusion method and portal perfusion index calculation

(a) Image acquisition: a single-photon emission computed tomography instrument (Infinia GP3; GE Medical Systems, Milwaukee, Wisconsin, USA) was used. The examinee lay supine on the examination table in a resting state. The acquisition range included the left ventricle, the liver, the kidneys, and other organs of the chest and abdomen. After a bolus injection of 185 MBq ^{99m}Tc-Phy (provided by Hangzhou Atomic Tech Pharmaceutical Co. Ltd., Hangzhou, Zhejiang Province, China), the instrument was started up immediately to acquire images with a 64×64 matrix, a 140 KeV energy peak, and a 10% energy window that collected one frame every second for

Table 3 Characteristics of 65 patients in different stages on the basis of the five-stage prognostic system

		Sex				Child–Pugh classes		
Stages	*N*	Male	Female	Age	PPI	A	B	C
Stage 1	12	9	3	43±12	73.03±8.49	11	1	0
Stage 2	10	5	5	52±6	52.96±16.22	10	0	0
Stage 3	18	14	4	56±8	46.24±15.25	7	7	4
Stage 4	20	18	2	49±10	29.99±17.36	10	5	5
Stage 5	5	4	1	51±13	11.50±6.37	0	2	3
Total	65	50	15	50±10	44.55±22.78	38	15	12

PPI, portal perfusion index.

a continuous collection of 60 frames [14,15]. (b) Image processing: the acquired images were stacked and the 'region of interest outline technology' was used to separately draw the outlines of the left ventricle, the left kidney, and the liver, and then a time – radioactivity curve was constructed through computer processing. The slope method was used to calculate the PPI; that is, the peak value of the left ventricle curve was T0, the peak value of the left kidney curve was T1, the T0–T1 segment of the liver curve was the hepatic arterial perfusion segment, and the $T1-(T1+7\,s)$ segment was the hepatic portal venous perfusion segment. The slopes for the curves of the two segments were calculated separately, and G0 and G1 were obtained using the following formula (Fig. 1) [16,17].

$$\mathrm{PPI}(\%)=\mathrm{G1}/(\mathrm{G0}+\mathrm{G1})\times 100\,\%\,.$$

Research methods

A prospective research method was used. The PPI and clinical data of 65 hepatitis B cirrhosis patients who underwent outpatient and hospitalized treatments between April 2011 and August 2016 at the First Affiliated Hospital of Zhejiang University School of Medicine were collected and analyzed. Demographic data (sex, age, contact telephone, address, and other demographics), clinical manifestations (symptoms and signs), laboratory tests (routine blood examination, liver function, electrolytes, coagulation function, and other tests), and ultrasound, computed tomography, and MRI examination results of all patients were registered in detail. The cirrhosis patients included in the study were staged and scored one by one in accordance with the five-stage prognostic system and C-P scoring (Table 1). The relevant factors that affected cirrhosis complications and their severity were analyzed, and the predictive value of the PPI with the five-stage prognostic system and the C-P scoring system in cirrhosis complications and their severity were compared.

Statistical methods

The SPSS 17.0 software package was used to carry out a statistical analysis (SPSS Inc., Chicago, Illinois, USA). One-way analysis of variance was used to compare the PPIs among various groups and a nonparametric Spearman's test was used to analyze the correlations between PPIs and various biochemical indices. A difference of P less than 0.05 was considered statistically significant.

Results

Correlations between portal perfusion index and the main biochemical indices

The PPI of the 65 cirrhosis patients showed positive correlations with serum total protein, serum albumin, and albumin/globulin results (respectively, $r=0.292$, $P<0.05$; $r=0.559$, 0.520, $P<0.01$) and negative correlations with serum globulin, aspartate aminotransferase, alkaline phosphatase, and direct bilirubin results (respectively, $r=-0.366$, $P<0.05$; $r=-0.197$, -0.165, and -0.025, $P>0.05$; Table 4).

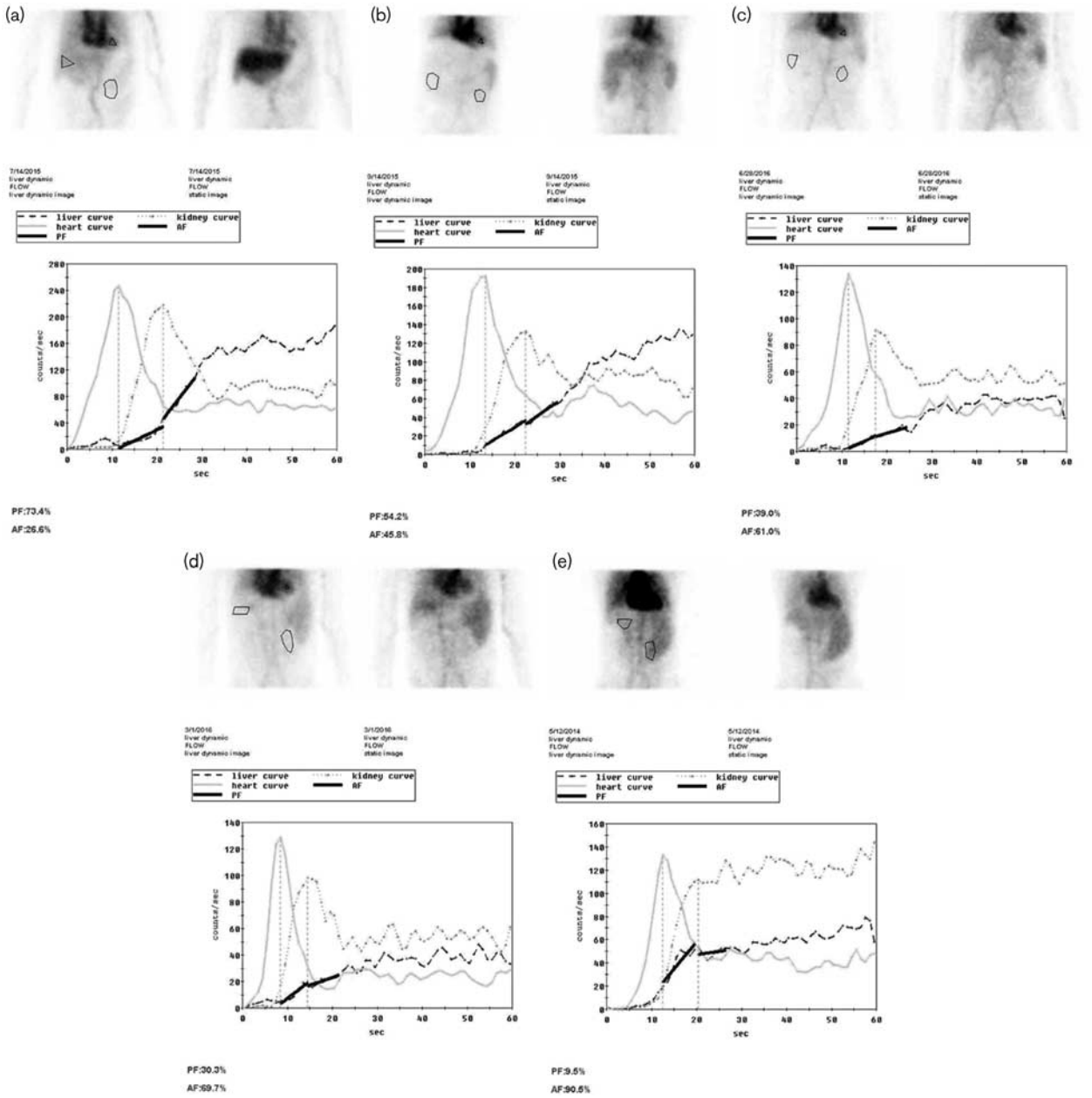
Comparison of portal perfusion indexes between all staged groups in the five-stage prognostic system

According to the five-stage prognostic system, the 65 cirrhosis patients could be divided into five groups. Their PPI mean values were, respectively, 73.03±8.49, 52.96±16.22, 46.24±15.25, 29.99±17.36, and 11.50±6.37; as the staging level increased, the PPI mean value decreased significantly. The PPIs between all groups were compared separately, and there were significant differences between stages 1 and 2, stages 1 and 3, stages 1 and 4, stages 1 and 5, stages 2 and 4, stages 2 and 5, stages 3 and 4, stages 3 and 5, and stages 4 and 5, with P less than 0.05; there was no statistically significant difference between stages 2 and 3 ($P=0.252$; Fig. 2).

Comparison of biochemical indices between all staged groups in the five-stage prognostic system

Serum total protein showed a significant difference between stages 2 and 3 (mean difference = 6.31, $P<0.05$). Serum albumin showed significant differences between stages 2 and 3 (mean difference = 8.11, $P<0.05$) and between stages 4 and 5 (mean difference = 8.08, $P<0.05$). Albumin/globulin showed significant differences between stages 1 and 2 (mean difference = 0.44, $P<0.05$) and between stages 4 and 5 (mean difference = 0.50, $P<0.05$). Alkaline phosphatase showed a significant difference between stages 4 and 5 (mean difference = −50.65, $P<0.05$). There were no significant

Fig. 1



Representative portal perfusion index images of patients in different stages on the basis of the five-stage prognostic system. Stages 1(a), 2(b), 3(c), 4(d), 5(e).

differences in the comparisons of all adjacent stages for all the remaining indices (Table 5).

Comparison of portal perfusion indexes between all groups classified by C-P scores

According to the C-P scoring criteria, the 65 cirrhosis patients could be divided as follows: 39 patients in class A, 15 patients in class B, and 11 patients in class C. Their PPI mean values were, respectively (%), 52.26 ± 20.48, 36.77 ± 20.88, and 27.80 ± 22.03. As the classification level increased, the PPI mean value decreased significantly. The PPIs between all groups were compared separately, and there were significant differences between classes A and B and between classes A and C, with P less than 0.05. There was no statistically significant difference between classes B and C ($P = 0.282$; Fig. 3).

Discussion

Hepatitis B cirrhosis is often complicated with hepatic fibrosis and hepatocellular damage. These pathological

changes generally affect hepatic hemodynamic changes [17,18], among which changes in portal venous and hepatic arterial hemodynamics are most able to reflect changes in liver function [19,20]; the hepatic PPI can intuitively reflect the proportion of liver blood supply. Therefore, in this paper, hepatitis B cirrhosis patients were categorized according to the C-P classification and the five-stage prognostic system staging to compare PPI changes between all classes and all stages, and to analyze the correlations between the patients' PPIs and their main biochemical indices.

The PPI value can be determined using the ^{99m}Tc-Phy PPI method. The quantitative determination of the two components of hepatic blood flow is based on the following assumption: the time in which a substance injected intravenously through a 'bolus' injection reaches the liver is not the same [7,12,13]. Before portal venous perfusion appears, the ^{99m}Tc-calcium phytate colloids that went through the hepatic artery have already arrived at the liver. Before hepatic artery recirculation appears, all ^{99m}Tc-calcium phytate colloids that went through the portal vein have already arrived at the liver [8]. Previous published work has used the method of mathematical modeling to verify the aforementioned hypothesis, and its results were close to the true hepatic blood flow shunt changes [17]. Other work reported on the use of PPI to study the relationship between hepatic perfusion and ascites in cirrhosis patients; as the hepatic portal vein perfusion decreased, the severity of ascites increased gradually [18]. However, in hepatic perfusion with multislice spiral computed tomography, PPI of patients with cirrhosis were significantly lower compared with the control group [21]. Similarly, noncontrast MRI techniques showed that the portal vein blood volume that flows into the intrahepatic volume in one and two cardiac cycles is significantly lower in portal hypertension patients than in healthy volunteers [22].

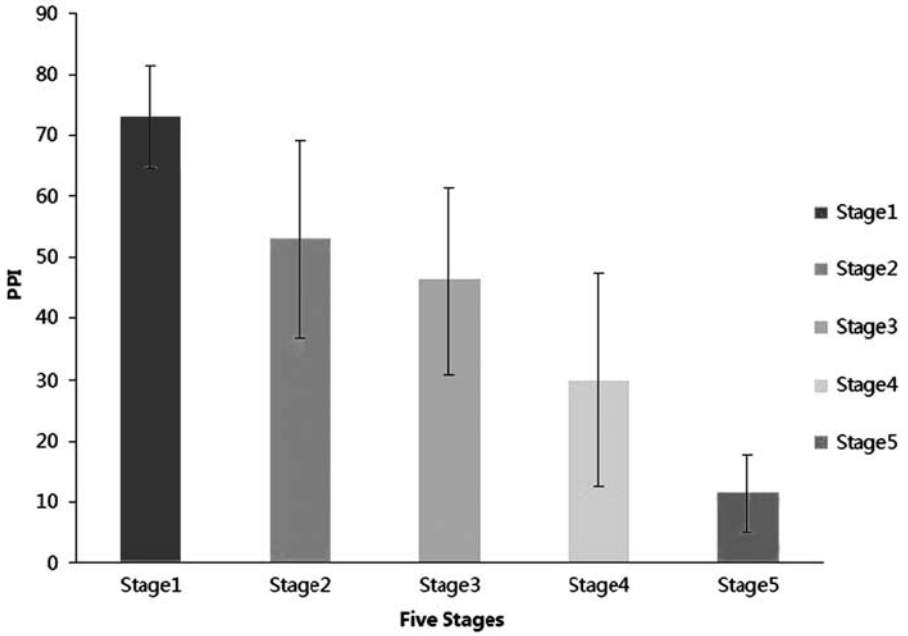
This study is the first to use PPI to detect changes in the proportion of liver blood supply in hepatitis B cirrhosis, which is an innovative use of a repeatable and quantitative nuclear medical imaging method and is useful for the intuitive assessment and prediction of hepatitis B cirrhosis complications and their severity.

Table 4 Correlations between portal perfusion index and the main biochemical indices (N = 65)

Biochemical indices	Result	Correlation (*r* value)	Significance (*P* value)
TP	66.89 ± 6.97	0.292*	0.018
Alb	37.34 ± 8.17	0.559**	< 0.001
GloB	29.55 ± 6.91	−0.366**	0.003
A/G	1.37 ± 0.53	0.520**	< 0.001
AST	47.31 ± 66.60	−0.197	0.115
ALP	89.91 ± 37.15	−0.165	0.189
DB	20.14 ± 40.13	−0.025	0.841

A/G, albumin/globulin; Alb, albumin; ALP, alkaline phosphatase; AST, aspartate aminotransferase; DB, direct bilirubin; GloB, globulin; TP, total protein.
*Shows significant correlation at the 0.05 level.
**Shows significant correlation at the 0.01 level.

Fig. 2



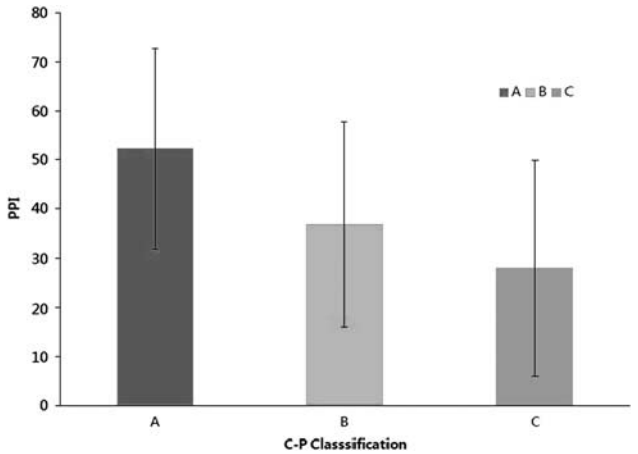
Portal perfusion index in different stages on the basis of the five-stage prognostic system; as the staging level increased, the portal perfusion index mean value decreased significantly. PPI, portal perfusion index.

Table 5 Characteristics of the main biochemical indices in different stages on the basis of the five-stage prognostic system

Biochemical indices	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
TP (g/l)	70.55±6.60	72.10±5.78	65.79±7.28	64.30±5.28	61.88±6.85
Alb (g/l)	46.18±3.68	42.72±5.30	34.61±6.74	34.52±6.70	26.44±5.72
GloB (g/l)	24.38±4.04	29.38±5.93	31.18±6.91	29.81±7.26	35.44±7.13
A/G	1.94±0.27	1.50±0.36	1.21±0.52	1.26±0.49	0.76±0.30
ALT (U/l)	76.67±131.02	27.90±23.23	35.33±42.04	32.90±30.17	30.80±16.57
AST (U/l)	45.08±41.62	29.00±21.17	43.78±37.83	58.30±108.92	58.00±31.87
ALP (U/l)	91.50±41.44	77.70±42.46	86.78±25.89	86.15±30.64	136.80±52.49
TB (μmol/l)	30.66±47.15	22.60±7.26	54.44±98.06	30.20±41.91	47.84±33.86
DB (μmol/l)	14.92±31.90	7.20±2.20	31.94±63.04	16.80±29.65	29.40±21.80
IB (μmol/l)	15.75±15.57	15.40±5.82	22.50±35.31	13.40±12.68	18.40±12.34

A/G, albumin/globulin; Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DB, direct bilirubin; GloB, globulin; IB, indirect bilirubin; PPI, portal perfusion index; PT, prothrombin time; TB, total bilirubin; TP, total protein.

Fig. 3



Portal perfusion index in different groups on the basis of the Child–Pugh classification; as the classification level increased, the portal perfusion index mean value decreased significantly. PPI, portal perfusion index.

Major biochemical indices of liver function, such as serum total protein, serum albumin, serum globulin, albumin/globulin, aspartate aminotransferase, alkaline phosphatase, and direct bilirubin, can all well reflect the states of liver protein synthesis, amino acid metabolism, bilirubin metabolism, and other functions [23]. In this experiment, the PPI showed positive correlations with serum total protein, serum albumin, and albumin/globulin and negative correlations with aspartate aminotransferase, alkaline phosphatase, and direct bilirubin, indicating that PPI is closely related to changes in liver function. As the PPI decreases gradually, liver function would also worsen, and vice versa. On comparing the PPI values of all stages with each other in the five-stage prognostic system, with the exception of no significant difference between stages 2 and 3, the PPIs between all other stages showed significant differences. The exception of no significant difference between stages 2 and 3 needs to be confirmed in a future study. This finding indicates that PPI also has a relatively good correlation with the five-stage prognostic system. As the staging level increased, the PPI showed a gradually decreasing trend. In addition, PPI is useful for separate assessments of changes in cirrhosis severity in the compensated period (stage 1 vs. stage 2) and the decompensated period (stages 3, 4, and 5). On comparing the main biochemical indices of all stages in the five-stage prognostic system, serum total protein and serum albumin showed significant differences between stages 2 and 3, which just so occur to be the boundary between the compensated period and the decompensated period for cirrhosis. The two indices of serum total protein and serum albumin may help distinguish compensated and decompensated cirrhosis. Whether the determination of these two indices is complementary with the PPI examination still requires thorough research with large amounts of sample data.

For the comparison of the PPIs between all groups in the C-P classification, significant differences were found between classes A and B and between classes A and C, suggesting that there is a relatively good correlation between PPI and C-P classification; as the classification level increased, the PPI showed a decreasing trend. This study found that there was no significant difference in the PPIs between classes B and C (P=0.282). This interesting phenomenon requires further thorough research with a large sample size. With increases in the C-P classification level and the five-stage prognostic system staging level, cirrhosis complications and the severity also increase gradually [24]. This study included only 65 hepatitis B cirrhosis patients; thus, the inadequate sample size can be considered a limitation. In addition, the literature has reported that serum hyaluronic acid, laminin, type III procollagen, and type IV collagen may have better applications in the assessment of hepatic fibrosis severity [9]. We will perform in-depth comparisons of those indices in our future study.

In summary, ^{99m}Tc-Phy PPI can function as a noninvasive nuclear medical examination method to noninvasively and effectively predict the complications of hepatitis B cirrhosis and their severity. A lower PPI indicates a higher severity of complications for hepatitis B cirrhosis patients.

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Conflicts of interest

There are no conflicts of interest.

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