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Original Article

Liver cirrhosis: evaluation by using proper hepatic artery to splenic artery diameter ratio and Gd-EOB-DTPA-enhanced MR

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Abstract: Objective: To assess the severity of liver cirrhosis by using proper hepatic artery diameter to splenic artery diameter ratio (HSR) and Gd-EOB-DTPA-enhanced MR. Materials and methods: A total of 276 patients were enrolled in this retrospective study. All patients underwent both Gd-EOB-DTPA-enhanced MR and DSA examination. HSR and relative enhancement (RE) of liver parenchyma were used to measure the severity of liver cirrhosis. Based on MELD score, the optimal cutoff of RE or HSR for differentiating each group were determined using ROC curve analysis. Results: According to ROC analysis, the optimal cutoff of HSR for distinguishing patients with non-cirrhotic livers from patients with MELD score ≤10 group, MELD score 11-18 group and MELD score >18 group were 0.923, 0.736, and 0.599, while for RE were 1.074, 0.512, and 0.290, respectively. The AUC values in distinguishing non-cirrhotic group to MELD score ≤10 group were 0.774 (HSR) and 0.716 (RE), MELD score ≤10 group to MELD score 11-18 group were 0.758 (HSR) and 0.705 (RE), MELD score 11-18 group to MELD score >18 group were 0.645 (HSR) and 0.553 (RE). Conclusion: HSR may be used to measure the severity of liver cirrhosis, which is better than the Gd-EOB-DTPA-enhanced MR.

Keywords: Gd-EOB-DTPA, cirrhosis, splenic artery, proper hepatic artery, MELD score

Introduction

It is well known that hemodynamic alteration including hyperdynamic circulation and portal hypertension is common in patients with liver cirrhosis [1]. Hyperdynamic circulation is characterized as increased of cardiac output and heart rate along with decreased of systemic vascular resistance and arterial pressure. Portal hypertension is manifested as hemodynamic changes in intrahepatic, systemic and portosystemic collateral circulation as well as changes in vascular structure, namely termed vascular remolding [2]. On celiac trunk angiography, dilatation of splenic artery accompanying with constriction of hepatic artery is always observed in patients with liver cirrhosis [3, 4]. In this study, the proper hepatic artery diameter to splenic artery diameter ratio (HSR) was used to measure the severity of liver cirrhosis which expressed as model for end-stage liver disease (MELD) score.

Materials and methods

Patients

Written, informed consent was obtained from all patients. The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of our hospital. A total of 342 patients underwent gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance (MR) of the liver from September 2011 to May 2014 were enrolled in the study.

Of the 342 cases, 213 cases were suspicion of unclear hepatic lesions and 129 cases were surveillance of hepatocellular carcinoma (HCC) in known liver cirrhosis. Totally, 276 cases had undergone DSA examinations due to the transarterial chemoembolization (n=192) or splenic artery embolization (n=84). Sixty-six cases were excluded based on the following criteria: hepat-

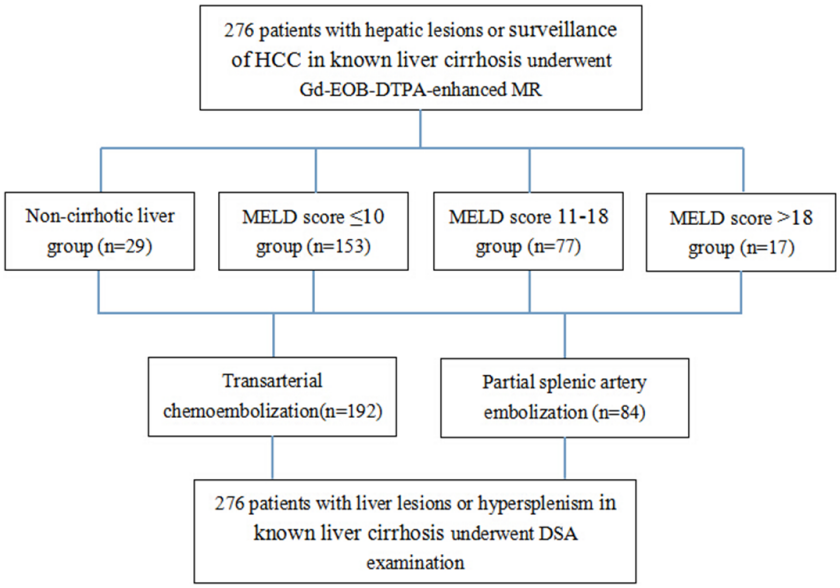

Figure 1. Flowchart of two hundred and seventy six consecutive patients who underwent celiac trunk angiography and Gd-EOB-DTPA-enhanced MR were enrolled in this study.

Table 1. Clinical detailed information of all patients

Variables	All (n=276)	Cirrhotic Group (n=247)	Healthy Group (n=29)
Age (range)	51.9±11.8 (24-83)	51.57±11.72	55.14±12.13
Gender			
Male	168	150	18
Female	108	97	11
Etiology			
Hepatitis B	-	206	-
Hepatitis C	-	21	-
Alcohol abuse	-	15	-
Autoimmune hepatitis	-	3	-
Primary biliary cirrhosis	-	2	-

ic artery variations (n=29); without digital subtraction angiography (DSA) examination (n=24); incomplete MR examination (n=8); with postsplenectomy (n=2); poor image quality (n=2); with hepatic arteriovenous fistula (n=1). Thus, the final study population was 276 cases including 168 males and 108 females with a mean age 51.9±11.8 years. Twenty-nine cases were in non-cirrhotic liver group and 247 cases were in cirrhotic liver group. Detailed information was shown in **Figure 1**.

The underlying causes of liver cirrhosis were hepatitis B (n=206), hepatitis C (n=21), alcohol abuse (n=15), autoimmune hepatitis (n=3), primary biliary cirrhosis (n=2). Patients diagnosed with liver cirrhosis were confirmed by histological evaluation in 82 cases (liver transplantation, n=11; partial hepatectomy due to hepatic lesions, n=42; liver biopsy, n=39) or based on combination of physical findings, biochemical tests, and radiological imaging features in 165 cases. Based on model for end-stage liver disease (MELD) score, the patient with liver cirrhosis could be divided into three groups. MELD score ≤10 group including 153 cases, MELD score 11-18 group including 77 cases, and MELD score >18 group including 17 cases. Detailed information was listed in **Table 1**.

Imaging technique

MR was performed within one week before DSA examination using a 3 T superconducting MR system (Achieva TX; Philips, Netherlands) with a phased array body coil (SENSE-XL-TORSO). MR protocols in Gd-EOB-DTPA-enhanced MR were as follows: 7 mm section thickness, 3 mm intersection gap; three dimension T1-weighted turbo field echo (3D-T1 TFE) sequence with SPIR fat suppression (repetition time: 3.0 ms, echo time: 1.35 ms, 350 mm×320 mm field of view, 124×100 matrix, 10° flip angle); respiratory-triggered T2-weighted fast spin echo (T2 FSE) sequence with STIR fat suppression (repetition time: 1113 ms, echo time: 70 ms, 350 mm×320 mm field of view, 268×200 matrix, 90° flip angle). Contrast-enhanced MR was performed before and after administration of

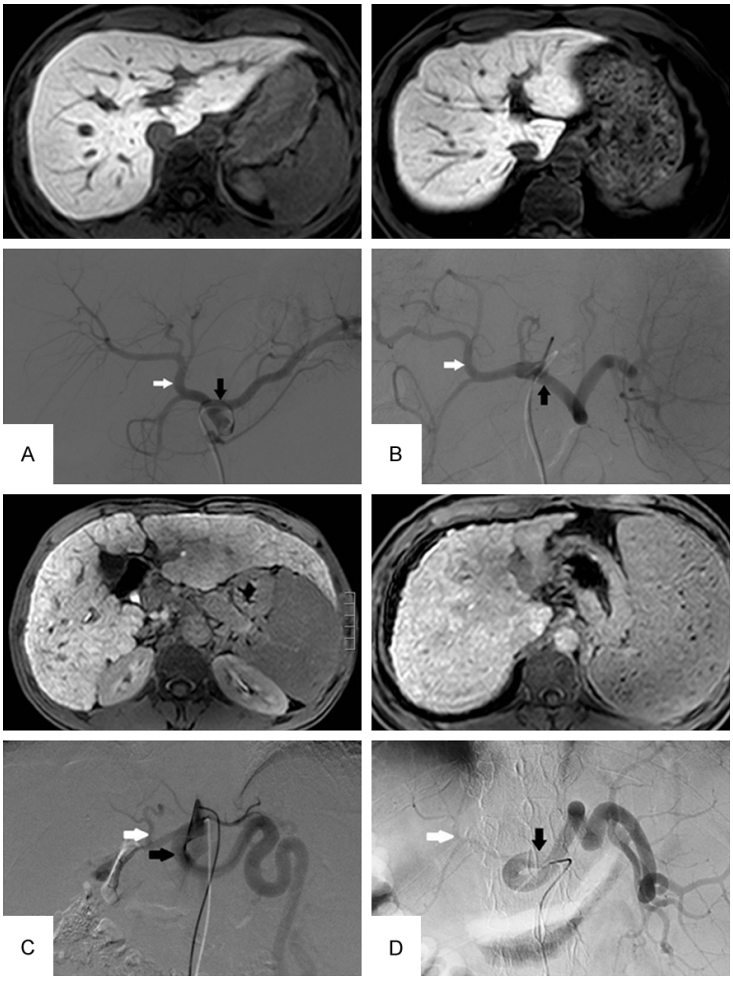

Figure 2. Images from four patients belongs to each group. The MR images in the figure were obtained 20 min after Gd-EOB-DTPA administration, and the DSA images were acquired from the same patient (A-D). With the elevated of MELD score, decreased of RE on MR images as well as dilatation of splenic artery (black arrow) and constriction of hepatic artery (white arrow) on DSA images could be observed.

Gd-EOB-DTPA at 15 s, 90 s, 3 min and 20 min. The contrast agent was used at a dose of 0.025 mmol/kg body weight and at an injection rate of 2 ml/s by 20 ml saline flush using a cubital intravenous line.

Hepatic artery and splenic artery angiography was performed under the GELCE bidirectional DSA. The Seldinger method was followed and catheter sheathe was inserted using a guide wire in the femoral artery. A Yashiro or RH catheter (Terumo, Tokyo, Japan) was sent to the celiac trunk. And then 24 ml of iohexol (General Pharmaceutical, Shanghai, China) at a rate of 8 ml/s was injected through the catheter.

Imaging analysis

Two radiologists with 21 and 8 years of abdominal radiology experience reviewed the MR images respectively. They were all blinded to the clinical data and imaging data. In evaluation of signal intensity (SI), three regions of interest (ROI) were placed in each lobe of the liver by the same operator. The ROIs were located in the same segment in each sequence, excluding big vessels, bile duct, hepatic lesions and imaging artifact. Each ROI was oval or circular, chosen as large as possible (size of ROI ranged from 1.5 cm^2 to 3.5 cm^2). The relative enhancement (RE) of liver parenchyma was calculated from SI measurements before (SI_{pre}) and after (SI_{post}) intravenous administration of Gd-EOB-DTPA that using the following formula: $(SI_{post}-SI_{pre})/SI_{pre}$. The RE was used to assess and compare the different enhancement effects in each liver function group according to the MELD score.

The splenic artery internal diameter and the proper hepatic artery internal diameter were measured on DSA images. Two radiologists mentioned above measured the diameter. The splenic artery diameter and the proper hepatic artery were measured at the point where they were 1 cm from its origin.

Statistical analysis

The data was presented as mean ± SD and analyzed using SPSS 19.0 software (SPSS Inc., Chicago, Illinois, USA). Receiver operating characteristic (ROC) curve analysis was used to identify the optimal cutoff values and area under the curve (AUC) values which aimed to differentiate from patients with non-cirrhotic liver group, MELD score ≤10 group, MELD score 11-18 group, and MELD score >18 group. The intraclass correlation coefficient (ICC) was used to evaluate the inter-observer agreement between two reviewers.

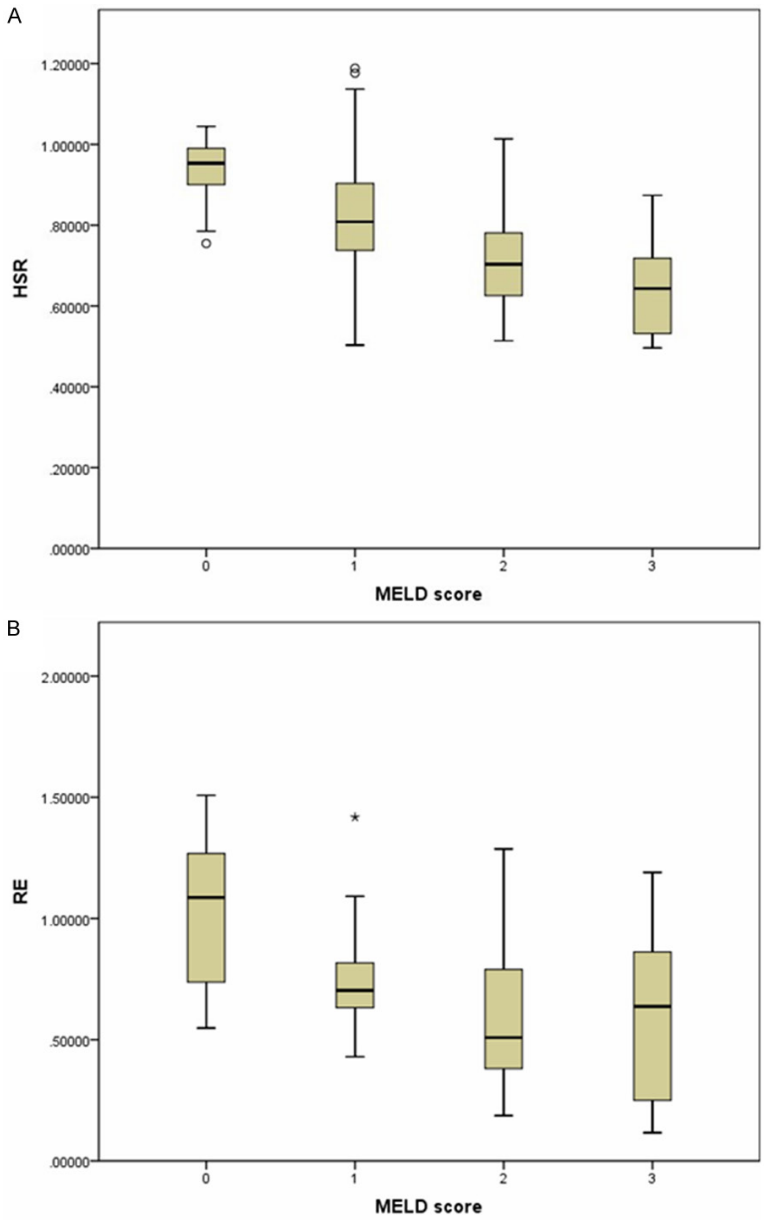

Figure 3. Relationships between HSR, RE and MELD score in the entire patient. The lower edge of each box represents the 25th percentile, and the upper edge represents the 75th percentile. The horizontal line represents the median located in the middle of the box. Lines extending from either end of the box represent the data beyond the 25th and 75th percentiles but within 1.5 times the interquartile range. Open circles or asterisks represent outliers (A, B)

Results

HSR and RE according to the MELD score

According to the MELD score, the reduction of HSR and RE could be observed in each group (**Figure 2A-D**).

The mean HSR in the entire population was 0.792±0.144, ranged from 0.496-1.188. Patients with non-cirrhotic liver group showed the highest HSR: 0.949±0.117. However, with the increasing severity of liver cirrhosis, a continuous reduction of HSR could be observed: MELD score ≤10 group, 0.821±0.127; MELD score 11-18 group, 0.706±0.107; MELD score >18 group, 0.644±0.114 (**Figure 3A**).

The mean RE in the entire population was 0.745±0.294, ranged from 0.116-1.507. Patients with non-cirrhotic liver group presented the highest RE: 1.016±0.311. Nevertheless, RE showed a tendency toward decreased Gd-EOB-DTPA uptake with the severity of liver cirrhosis: MELD score ≤10 group, 0.779±0.227; MELD score 11-18 group, 0.615±0.303; MELD score >18 group, 0.552±0.344 (**Figure 3B**).

ROC curve analysis

Using ROC curve analysis, the optimal HSR and RE cutoff values were determined to differentiate patients with non-cirrhotic liver group, MELD score ≤10, MELD score 11-18, and MELD score >18 (**Figure 4A-C**). The cutoff values of HSR for distinguishing patients with non-cirrhotic liver group from patients with MELD score ≤10, MELD score 11-18 and MELD score >18 were 0.923, 0.736, and 0.599 while the cutoff values of RE for differentiating each group were 1.074, 0.512, and 0.290. **Table 2** revealed the cutoff values of HSR and RE between each group as well as the corresponding AUC values, sensitivities, and specificities.

Inter-observer agreement between two reviewers

Based on the ICC analysis, there was satisfactory correlation between two reviewers for SI

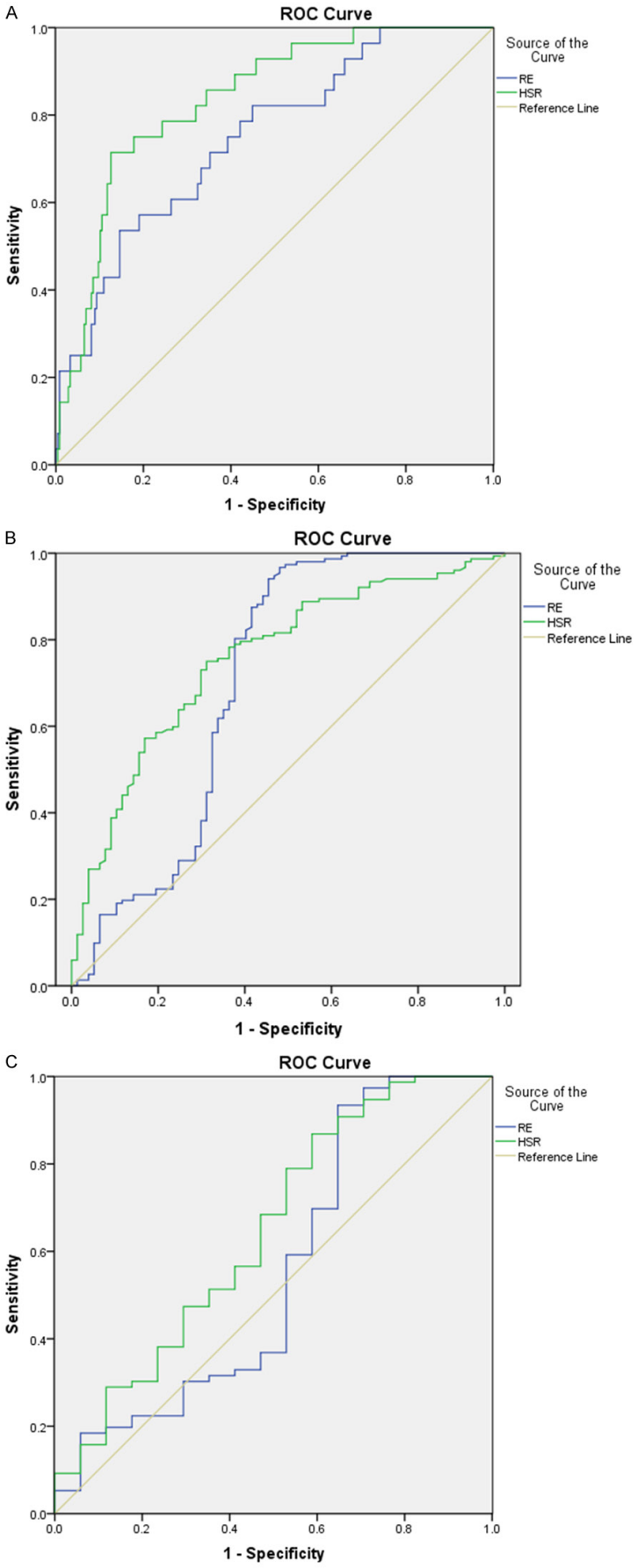

Figure 4. ROC curve analysis for identifying the optimal cutoff values. The AUC values in distinguishing healthy group from MELD score ≤10 group were 0.774 (HSR) and 0.716 (RE) (A). In distinguishing MELD score ≤10 group and MELD score 11-18 group were 0.758 (HSR) and 0.705 (RE) (B). And in distinguishing MELD score 11-18 group and MELD score >18 group were 0.645 (HSR) and 0.553 (RE) (C). The AUC values of HSR were higher in each group than RE, which revealed that HSR had better diagnostic efficiency comparing to RE in differentiating liver cirrhosis.

calculation and diameter measurement. Both of the ICC were greater than 0.75, which indicated acceptable inter-observer agreement. Detailed information was listed in **Table 3**.

Discussion

Liver cirrhosis, the final result of hepatic fibrosis, is characterized as a diffuse liver parenchyma disease manifested by portal hypertension and nodule regeneration of liver parenchyma [5]. Liver cirrhosis often leads to hemodynamic alterations which can have extensive impact to multiple systems, especially to the liver and the spleen [6]. On celiac trunk angiography, dilatation of splenic artery accompanying with constriction of hepatic artery is always observed in patients with liver cirrhosis [3, 4]. As the liver has a characteristic double blood supply, increased of splenic artery blood flow often leads to the decreased of hepatic artery blood flow [7]. The result is that the hepatocytes are in a chronic hypoxia status due to the hypoperfusion of hepatic artery [8]. If the sustained hypoperfusion of hepatic artery unable to correct, it will aggravate the liver function damage [9]. In this study, we are trying to determine whether HSR is of great clinical significance in patients with liver cirrhosis and to compare HSR with Gd-EOB-DTPA-

Table 2. ROC analysis for differentiating each group based on MELD score

MELD score	HSR				RE			
	Sensitivity	Specificity	Cutoffs	AUC	Sensitivity	Specificity	Cutoffs	AUC
Healthy group to MELD ≤10	69%	81%	0.923	0.774	55.2%	82.4%	1.074	0.716
MELD ≤10 to MELD 11-18	75%	68.8%	0.736	0.758	96.7%	51.9%	0.512	0.705
MELD 11-18 to MELD >18	86.8%	41.2%	0.599	0.645	93.4%	35.3%	0.290	0.553

MELD: model for end-stage liver disease; HSR: proper hepatic artery internal diameter to splenic artery internal diameter ratio; RE: relative enhancement.

Table 3. Inter-observer agreement between two reviewers

	SI calculation	Diameter measurement
ICC	0.87	0.94

ICC: Intraclass correlation coefficient; SI: Signal intensity.

enhanced MR enhancement effect to assess its efficacy in evaluating the severity of liver cirrhosis

Gd-EOB-DTPA is a liver specific contrast agent that can be uptake by functional hepatocytes through the active membrane transporter system such as organic anion-transporting polypeptide (OATP) [10, 11]. In liver cirrhosis, reduced of hepatocytes function may cause the decreased of Gd-EOB-DTPA uptake [12]. In addition, expression level of OATP is considered to be related to the degree of cirrhosis by Geier A, et al. [13]. Several studies have proved that Gd-EOB-DTPA-enhanced MR could be used to assess the severity of liver cirrhosis in different ways [14-16]. In the present study, Gd-EOB-DTPA-enhanced MR enhancement effect was used as a known method to compare with HSR.

Based on the MELD score, the optimal cutoff values for differentiating healthy group from MELD score ≤10 group were 0.923 (HSR) and 1.074 (RE). In differentiating MELD score ≤10 group and MELD score 11-18 group, the cutoff values were 0.736 (HSR) and 0.512 (RE). In differentiating MELD score 11-18 group and MELD score >18 group, the cutoff values were 0.599 (HSR) and 0.290 (RE). A retrospective study conducted by Zeng DB et al. revealed that the best cutoff value of splenic artery to proper hepatic artery ratio to predict cirrhosis and portal hypertension was 1.40, which was different to our study (0.923) [17]. The possible explanation for this difference was the different method for imaging calculation. In the present study, the splenic artery diameter and the proper hepatic artery diameter were measured by DSA while their calculation was carried on computed tomography (CT). As DSA was the golden standard for measurement of vascular diameter, the data was more accurate than the values reported by Zeng DB, et al. The AUC values in distinguishing healthy group from MELD score ≤10 group were 0.774 (HSR) and 0.716 (RE). In distinguishing MELD score ≤10 group and MELD score 11-18 group were 0.758 (HSR) and 0.705 (RE). And in distinguishing MELD score 11-18 group and MELD score >18 group were 0.645 (HSR) and 0.553 (RE). Quantitative results showed that with increased grades of MELD score, the AUC values were decreased which indicated decline of diagnostic efficiency. In addition, the AUC values of HSR were higher in each group than RE, which revealed that HSR had better diagnostic efficiency comparing to RE in differentiating liver cirrhosis. In this study, hepato-biliary phase images were obtained 20 min after contrast agent administration, which was the best time for enhancement effect as previous study described. However, it had been indicated that the hepatocytes uptake of Gd-EOB-DTPA was delayed in case of advanced cirrhosis [18]. This property might be associated with the relative poor diagnostic performance of RE.

This study had some limitations. First, the number of patients enrolled was relatively small. The median RE of MELD score 11-18 group was 0.508 while the median RE of MELD score >18 group was 0.637. The reason for this error was that there were only 17 cases enrolled in MELD score >18 group which leads to the relative poor reliability in statistical analysis. Second, we did not use hemodynamic parameter such as vascular resistance index to assess the severity of splenic artery steal. A cohort study conducted by Mogl MT, et al. revealed that in chronic liver cirrhosis patients, the vascular resistance index of hepatic artery was signifi-

cant elevated [19]. Third, case selection bias might have been existence due to the retrospective study design. Fourth, there were few patients who underwent the indocyanine green clearance (ICG) tests since most of our patients were not surgical candidates. ICG test, a comprehensive evaluation of hepatic function, is commonly used to preoperatively evaluate liver function [20]. Motosugi U, et al. had shown that ICG test could predict liver enhancement on Gd-EOB-DTPA MR [21]. Finally, the prognosis and the survival time were not included in the study. Further studies are required to use HSR to predict the prognosis and survival time of patients with different MELD score.

In conclusion, the prevalence of a low HSR value indicates the severity of liver cirrhosis especially in those patients with high MELD score. How to increase hepatic arterial blood flow to improve the liver function may be a new therapeutic target for patients with liver cirrhosis in future studies.

Disclosure of conflict of interest

None.

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References

[1] Moller S, Hobolth L, Winkler C, Bendtsen F and Christensen E. Determinants of the hyperdynamic circulation and central hypovolaemia in cirrhosis. Gut 2011; 60: 1254-1259.

[2] Alhassan N and Liu HQ. Hyperdynamic mesenteric circulation in cirrhosis: humoral or neural mechanism? Liver Int 2012; 32: 1191-1193.

[3] Dokmak S, Aussilhou B and Belghiti J. Liver transplantation and splenic artery steal syndrome: the diagnosis should be established preoperatively. Liver Transplant 2013; 19: 667-668.

[4] Manner M, Otto G, Senninger N, Kraus T, Goerich J and Herfarth C. Arterial steal: an unusual cause for hepatic hypoperfusion after liver transplantation. Transpl Int 1991; 4: 122-124.

[5] Ferrell L. Liver pathology: Cirrhosis, hepatitis, and primary liver tumors. Update and diagnostic problems. Mod Pathol 2000; 3: 679-704.

[6] La Villa G and Gentilini P. Hemodynamic alterations in liver cirrhosis. Mol Aspects Med 2008; 29: 112-118.

[7] Malnick S, Melzer E, Sokolowski N and Basevitz A. The involvement of the liver in systemic diseases. J Clin Gastroenterol 2008; 42: 69-80.

[8] Cannito S, Paternostro C, Busletta C, Bocca C, Colombatto S, Miglietta A, Novo E and Parola M. Hypoxia, hypoxia-inducible factors and fibrogenesis in chronic liver diseases. Histol Histopathol 2014; 29: 33-44.

[9] Hernandez-Guerra M, de Ganzo ZA, Gonzalez-Mendez Y, Salido E, Abreu P, Moreno M, Felipe V, Abrante B and Quintero E. Chronic intermittent hypoxia aggravates intrahepatic endothelial dysfunction in cirrhotic rats. Hepatology 2013; 57: 1564-1574.

[10] Van Beers BE, Pastor CM and Hussain HK. Primovist, eovist: What to expect? J Hepatol 2012; 57: 421-429.

[11] Huppertz A, Breuer J, Fels LM, Schultze-Mosgau M, Sutter G, Klein S, Frericks B, Hamm B and Wagner M. Evaluation of possible drug-drug interaction between gadoxetic acid and erythromycin as an inhibitor of organic anion transporting peptides (OATP). J Magn Reson Imaging 2011; 33: 409-416.

[12] Bickelhaupt S, Studer P, Kim-Fuchs C, Candinas D, Froehlich JM and Patak MA. Gadoxetate uptake as a possible marker of hepatocyte damage after liver resection-preliminary data. Clin Radiol 2013; 68: 1121-1127.

[13] Geier A, Dietrich CG, Voigt S, Kim SK, Gerloff T, Kullak-Ublick GA, Lorenzen J, Matern S, Gartung C. Effects of proinflammatory cytokines on rat organic anion transporters during toxic liver injury and cholestasis. Hepatology 2003; 38: 345-354.

[14] Verloh N, Haimerl M, Rennert J, Muller-Wille R, Niessen C, Kirchner G, Scherer MN, Schreyer AG, Stroszczynski C and Fellner C. Impact of liver cirrhosis on liver enhancement at Gd-EOB-DTPA enhanced MRI at 3 Tesla. Eur J Radiol 2013; 82: 1710-1715.

[15] Tamada T, Ito K, Higaki A, Yoshida K, Kanki A, Sato T, Higashi H and Sone T. Gd-EOB-DTPA-enhanced MR imaging: evaluation of hepatic enhancement effects in normal and cirrhotic livers. Eur J Radiol 2011; 80: E311-E316.

[16] Kuhn JP, Spoerl M, Nassif A, Mester M, Weitschies W, Siegmund W, Hosten N and Mensel B. Feasibility of gadoxetate disodium-enhanced MR cholangiography in chronic cholestatic biliary disease. Clin Radiol 2014; 69: 1027-1033.

[17] Zeng DB, Dai CZ, Lu SC, He N, Wang W and Li HJ. Abnormal splenic artery diameter/hepatic artery diameter ratio in cirrhosis-induced portal hypertension. World J Gastroentero 2013; 19: 1292-1298.

[18] Tamada T, Ito K, Sone T, Kanki A, Sato T and Higashi H. Gd-EOB-DTPA enhanced MR imaging: Evaluation of biliary and renal excretion in

normal and cirrhotic livers. Eur J Radiol 2011; 80: E207-E211.

[19] Mogl MT, Nussler NC, Presser SJ, Podrabsky P, Denecke T, Grieser C, Neuhaus P and Guckelberger O. Evolving experience with prevention and treatment of splenic artery syndrome after orthotopic liver transplantation. Transpl Int 2010; 23: 831-841.

[20] Park KH, Hwang JM, Kim JH, Yu HG, Yu YS and Chung H. Intraoperative extraocular Indocyanine Green (IE-ICG) dye test: a new method of detecting a peeled internal limiting membrane. Brit J Ophthalmol 2008; 92: 369-372.

[21] Motosugi U, Ichikawa T, Sou H, Sano K, Tominaga L, Kitamura T and Araki T. Liver parenchymal enhancement of hepatocyte-phase images in Gd-EOB-DTPA-enhanced MR imaging: which biological markers of the liver function affect the enhancement? J Magn Reson Imaging 2009; 30: 1042-1046.