Int J Clin Exp Med 2017;10(6):9495-9501
www.ijcem.com /ISSN:1940-5901/IJCEM0053179

Original Article

Liver volume measured on magnetic resonance imaging in cirrhosis patients with hepatitis B: association with severity of esophageal varices

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Received March 17, 2017; Accepted April 28, 2017; Epub June 15, 2017; Published June 30, 2017

Abstract: *Objective:* To determine the associations of the change of liver volume parameters on magnetic resonance (MR) imaging with endoscopic grade of esophageal varices in cirrhotic patients with hepatitis B. *Material and methods:* Eighty-six enrolled consecutive patients with cirrhosis resulting from chronic hepatitis B, who received endoscopy for grading the esophageal varices, underwent liver contrast-enhanced MR imaging. The total liver volume (TLV), and segmental liver volumes including left lateral liver lobe volume (LLV), left medial liver lobe volume (LMV), right liver lobe volume (RV), and caudate lobe volume (CV) were assessed statistically to determine the associations of the changes of liver volume parameters with the presence and severity of esophageal varices. *Results:* TLV, LMV and RV tended to decrease while LLV and CV increased from Grades 0 to 3 esophageal varices and from Grades 0-1 to 2-3 (all $P < 0.05$, except for LLV). Furthermore, the differences in the TLV, LMV, RV and CV among patients with Grade 0, 1, 2 and 3 varices or between Grade 0-1 and 2-3 were significant (all $P < 0.05$), while there was no statistical difference in LLV among patients with Grade 0, 1, 2 and 3 varices or between Grade 0-1 and 2-3 (all $P > 0.05$). *Conclusion:* Total and segmental liver volumes except for LLV tend to be associated with endoscopic grades of the esophageal varices in liver cirrhosis patients with hepatitis B.

Keywords: Liver cirrhosis, esophageal varices, magnetic resonance imaging, liver volume

Introduction

Liver cirrhosis is the final stage of various chronic liver disorders with poor outcomes [1]. The common cause of cirrhosis is viral hepatitis, especially hepatitis B, which leads to an increasing morbidity and mortality [2]. Clinically, the change in the volume of the liver, liver dysfunction and esophageal varices are the most common signs and symptoms in patients with liver cirrhosis [1]. It has been demonstrated that the volume of the liver increases in earlier liver disease and decreases with progressive cirrhosis, which may be caused by congestive (possibly vascular) effects in early liver disease and fibrotic effects in later disease. The change in the liver volume is closely related to the prognosis and severity of liver cirrhosis [3-5]. Additionally, the presence of esophageal varices which have the greatest clinical impact and the most severe complications is a key event in the evolution of liver cirrhosis when portal hypertension develops [6]. According to the criteria proposed by the Japanese Research Society for Portal Hypertension, Grade 2 and 3 esophageal varices have a high risk of causing life-threatening upper gastrointestinal hemorrhage [7]. The presence and severity of esophageal varices depend on the severity of portal hypertension secondary to liver cirrhosis, which is association with the change in the volume of the liver. Hence, we could presume that the presence and severity of esophageal varices might be associated with the change in the volume of the liver in patients with cirrhosis. To our knowledge, there was no report about the asso-

Table 1. Grading system for esophageal varices proposed by the Japanese Research Society for Portal Hypertension

Grades	Endoscopic criteria*
0	No varices
1	Varices run straight
2	Varices show beaded appearance
3	Varices run in an oblique course and are tortuous with tumor-like appearance

Note: *On the basis of the size and morphology of the largest varix.

ciation of the volume of the liver with esophageal varices in cirrhosis patients.

To evaluate the volume of the liver, magnetic resonance (MR) imaging should be the optimal imaging technique due to its high signal-to-noise ratio, smaller and safer injection of contrast agent, and no radiation [3, 8, 9]. Furthermore, MR imaging is often used to monitor hepatocellular carcinoma in patients with liver cirrhosis which could be used as a "one-stop-shop" approach to evaluate the volume of the liver at the same time without the need for a second study [10]. Thus, the purpose of this study was to determine the associations of the presence and severity of esophageal varices in cirrhotic patients with hepatitis B with the change of the volume of the liver measured on MR imaging for better understanding and preventing the occurrence and development of esophageal varices.

Materials and methods

Ethics statement

The study was approved by the institutional review board and the ethics committee of our university hospital with the following reference number: 2012ER(AR)-006 and written informed consent was obtained from all participants prior to the study.

Patient population

From January 2013 to August 2015, consecutive patients were enrolled into this study according to the following inclusion criteria: (1) cirrhosis resulting from chronic hepatitis B was confirmed by clinical data, laboratory examinations and imaging study according to the American association for the study of liver diseases (AASLD) practice guidelines 2015-chronic hepatitis B [11]; (2) all the patients underwent contrast-enhanced MR imaging of the liver and upper gastrointestinal endoscopy, and the interval between each MR scan and endoscopy was less than 5 days; and (3) patients have not received any treatment to this disease before this study. Patients who had a history of upper gastrointestinal bleeding, hepatic carcinoma, or other diseases which might lead to the portal hypertension were excluded from this study.

Endoscopic technique and interpretation

Common upper gastrointestinal endoscopy was performed in each patient by two gastroenterologists (the forth and ninth authors who had more than 15 years of experience in gastroenterology and upper gastrointestinal endoscopy) in consensus. Digital images of all endoscopic studies were captured and reviewed in consensus in a picture archiving and communication system by the previous gastroenterologists who were blinded to the patients' clinical data and MR findings. Based on the presence and severity of the varices as shown on the endoscopic findings, patients with the esophageal varices were divided into 4 grades according to the criteria proposed by the Japanese Research Society for Portal Hypertension (**Table 1**). Among the 4 grades of the varices, Grades 2 and 3 varices were defined as high-risk varices for developing an esophageal variceal hemorrhage, while Grades 0 and 1 varices were defined as low risk ones [7].

MR technique

All scans in our study were performed on a 3.0 T whole body MR scanner (Discovery 750; GE Medical Systems, Milwaukee, WI) using a 32-channel phased-array torso coil. The MR sequences included spoiled gradient recalled (SPGR) T1-weighted imaging (T1WI), and fast

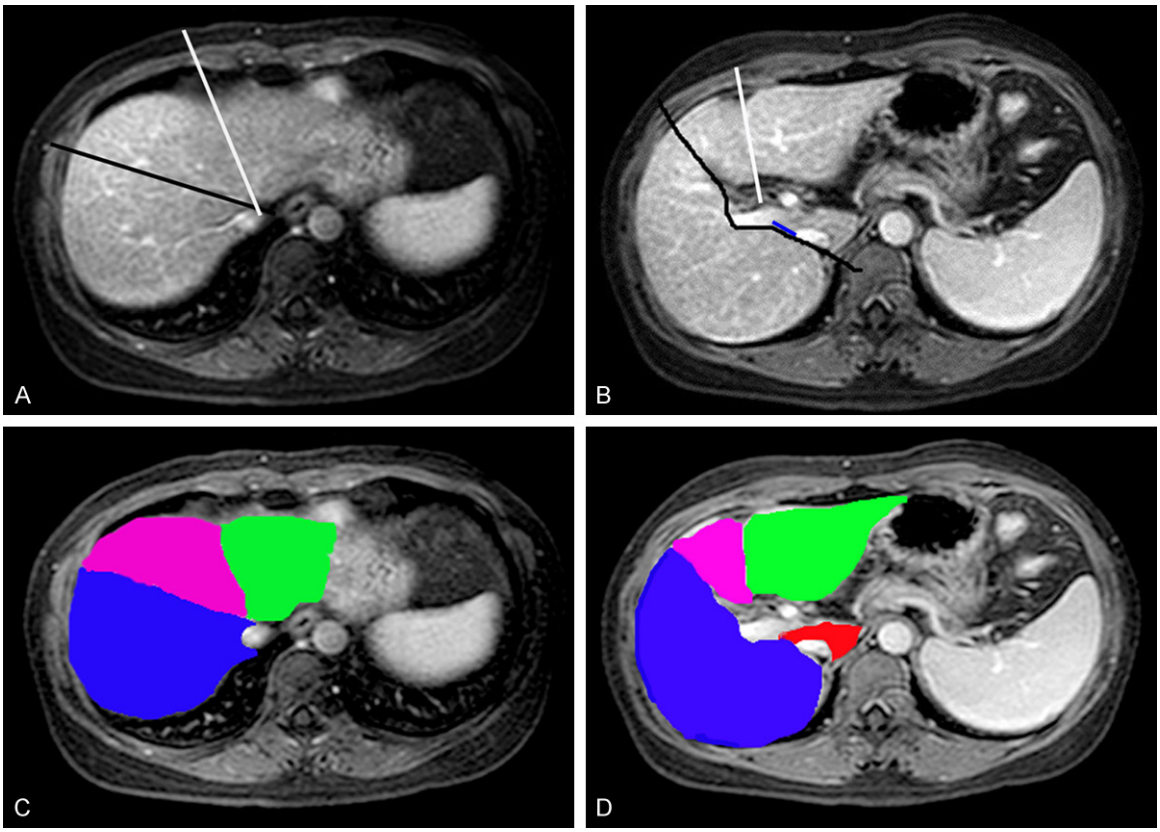

Figure 1. The division of liver lobes. On the level of the second liver portal (A, C), right liver lobe (C, filled with blue) is differentiated from left liver lobe by middle liver vein (A, black line), and left lateral liver lobe (C, filled with green) is differentiated from left medial liver lobe (C, filled with pink) by left liver vein (A, white line). On the level of the first liver portal (B, D), middle liver fissure (B, black line), and liver interlobar fissure (B, white line) are used as landmarks to differentiate right liver lobe (D, filled with blue) from left liver lobe, and left lateral liver lobe (D, filled with green) from left medial liver lobe (D, filled with pink), respectively; and the caudate lobe (D, filled with red) is differentiated from right liver lobe by the line (B, blue line) linking the inferior vena cava to the right branch of the portal vein.

recovery fast spin echo (FRFSE) T2-weighted imaging (T2WI), and contrast-enhanced three-dimensional liver acquisition with volume acceleration (3D-LAVA). The scanning parameters for T2WI axial FRFSE fat-suppressed sequence were repetition time (TR)/echo time (TE), 3000/97.3 ms; band width, 62.5 kHz; section thickness, 5.0 mm; overlap, 1.0 mm; field of view (FOV), 512 × 512 mm; and matrix, 256 × 192 mm. As for T1WI, TR/TE was 3.7/1.7 ms, and the other scanning parameters were same as those used for T2WI. The axial 3D-LAVA was performed with a bolus injection of gadolinium chelate (Magnevist; Berlex Laboratories, Wayne, NJ) via an automated pump injector (Spectris MR Injection System, MedradInc., USA) into an antecubital vein at a dose of 3 mL/s for a total of 0.2 mmol per kilogram of body weight followed by a 20-mL saline solution flush. The scanning parameters used for the contrast-enhanced MR imaging were as follows: TR/TE, 3.6/1.7 ms; FOV, 512 × 512 mm; slice thickness, 5.0 mm; and matrix of 256 × 192 mm. The scan coverage was from the level of the diaphragm to that of the inferior border of the liver. Each sequence was acquired within a breath-hold.

Image analysis

All original MR data were transferred to the workstation (GE, AW4.4, Sun Microsystems, Palo Alto, CA, United States). According to the Goldsmith and Woodburne system, the liver was divided into four lobes: left lateral and medial lobes, right lobe and caudate lobe (**Figure 1**). Compared to arterial or delayed phase images, the portal veins and hepatic veins for tracing the boundaries of each liver lobe could be better depicted on the portal

Table 2. The Child-Pugh classifications of the patients with different endoscopic grades of the esophageal varices

Endoscopic grades	Child-Pugh classifications		
	Child A	Child B	Child C
Grade 0 (n = 30)	25	5	0
Grade 1 (n = 23)	15	7	1
Grade 2 (n = 16)	0	9	7
Grade 3 (n = 17)	0	6	11

venous phase images. Thus, the portal venous phase images were used to measure the total and segmental liver volumes by two radiologists (the first author and the corresponding author with 10 and 18 years of experiences in abdominal radiology, respectively) independently who were blinded to the clinical data.

The total liver volume (TLV) profile was manually traced excluding the inferior vena cava and gallbladder on each transverse image, and the portal veins and hepatic veins were also excluded for measuring each liver lobe volume. The software automatically calculated the number of pixels enclosed by the traced liver lobe contour, and provided the cross-sectional area of the liver lobe on a slice-by-slice basis [12]. This previous process was repeated for each contiguous transverse level until the entire liver lobe had been covered. Left lateral liver lobe volume (LLV), left medial liver lobe volume (LMV), right liver lobe volume (RV), and caudate lobe volume (CV) were obtained by means of the sum of the corresponding areas multiplied by the section thickness [12].

Statistical analyses

Statistical analyses were carried out with the Statistical Package for Social Sciences version 17.0 (SPSS, Chicago IL, USA). A *P* value less than 0.05 was considered as significant difference. All the measurements were given as the mean ± standard deviation. Reliability of the liver volume measurements were evaluated by using the concordance correlation coefficient (r_c). A value of r_c more than 0.85 indicated very good concordance, while the values between 0.50 to 0.85 and less than 0.50 indicated moderate and poor concordance, respectively. Due to the skewed distribution of the liver volume parameters in this cohort, Spearman's rank correlation analyses were performed to assess the correlations between the liver volume parameters and the endoscopic grades of the esophageal varices. Meanwhile, Kruskal-Wallis tests were used to compare the volumes among patients with different endoscopic grades of the varices, together with Mann-Whitney tests for comparing the volumes between patients with Grades 0-1 and Grades 2-3 varices which have a high risk of causing life-threatening upper gastrointestinal hemorrhage.

Results

Patient samples

From January 2013 to August 2015, 86 consecutive patients with cirrhosis resulting from chronic hepatitis B (60 men and 26 women; mean age, 50.8 ± 11.8 years; age range, 19-80 years) who met the inclusion criteria and agreed to take part in the study, were included. As depicted on endoscopy, there were 30 patients with grade 0 esophageal varices, 23 patients with grade 1, 16 patients with grade 2, and 17 patients with grade 3. The Child-Pugh classifications of the patients with different grades of the varices are shown in **Table 2**. From Child A to C, the endoscopic grade of esophageal varices tended to increase (r = 0.760, $P < 0.001$).

Reliability of the liver volume measurements

In the 86 participants, no subject was excluded because of suboptimal imaging or coverage. The mean TLV, LLV, LMV, RV and CV measured by the first author were 1075.60 ± 370.89 cm^3 (range, 434.07-2252.83), 275.35 ± 117.46 cm^3 (range, 93.34-651.47), 141.79 ± 62.49 cm^3 (range, 44.40-342.13), 610.17 ± 245.02 cm^3 (range, 159.39-1434.30), and 26.40 ± 16.87 cm^3 (range, 8.33-109.53), respectively. For the repeated measurements by the corresponding author, the mean TLV, LLV, LMV, RV and CV were 1087.42 ± 301.57 cm^3 (range, 448.21-2270.64), 265.73 ± 108.19 cm^3 (range, 86.15-653.78), 138.65 ± 57.46 cm^3 (range, 40.80-335.63), 621.17 ± 248.12 cm^3 (range, 162.28-1447.60), and 25.45 ± 13.68 cm^3 (range, 8.98-107.64), respectively. The concordance between the two reviewers for the measurements on the portal venous phase images was good (all r_c values > 0.85, $P > 0.05$); and the measurements by the first author were used as the final volume values for further statistical analysis.

Table 3. Liver volume parameters corresponding to endoscopic grades of the esophageal varices

Endoscopic grades	Patients (n)	TLV (cm^3)	LLV (cm^3)	LMV (cm^3)	RV (cm^3)	CV (cm^3)
0	30	1177.06 ± 272.34	252.04 ± 88.98	171.11 ± 55.09	724.42 ± 202.52	21.42 ± 8.33
1	23	1114.34 ± 463.35	253.72 ± 127.21	134.30 ± 70.52	647.94 ± 272.49	24.53 ± 20.80
2	16	1007.75 ± 289.49	311.25 ± 87.78	128.63 ± 41.08	540.75 ± 201.71	29.27 ± 23.07
3	17	893.28 ± 402.14	316.48 ± 158.79	109.91 ± 61.73	406.77 ± 169.68	35.71 ± 12.41
0-1	53	1149.84 ± 364.94	252.77 ± 106.12	155.13 ± 64.31	691.23 ± 236.12	22.77 ± 14.97
2-3	33	948.67 ± 351.21	313.95 ± 127.32	118.97 ± 52.75	471.60 ± 194.97	32.60 ± 18.33

Notes: TLV, whole liver volume; LLV, left lateral liver lobe volume; LMV, left medial liver lobe volume; RV, right liver lobe volume; and CV, caudate lobe volume.

Liver volume parameters corresponding to endoscopic grades of the esophageal varices

The mean TLV, LLV, LMV, RV and CV corresponding to endoscopic grades of the esophageal varices are shown in **Table 3**. TLV, LMV and RV tended to decrease from Gade 0 to 3 ($r = -0.367$, -0.404 and -0.529, respectively; all $P < 0.05$). LLV ($r = 0.211$, $P > 0.05$) and CV ($r = 0.393$, $P < 0.001$) increased from Grade 0 to 3. From Grades 0-1 to 2-3, TLV, LMV and RV decreased ($r = -0.290$, -0.281 and -0.458, respectively; all $P < 0.05$), while LLV ($r = 0.286$, $P > 0.05$) and CV ($r = 0.419$, $P < 0.05$) increased.

Furthermore, the differences in the TLV, LMV, RV and CV among patients with Grades 0, 1, 2 and 3 varices or between Grades 0-1 and 2-3 were significant (all $P < 0.05$) according to Kruskal-Wallis tests or Mann-Whitney tests, while there was no statistical difference in LLV among patients with Grades 0, 1, 2 and 3 varices or between Grades 0-1 and 2-3 (both $P > 0.05$).

Discussion

As shown in the study, total and segmental liver volumes were measured on the portal venous phase images of contrast-enhanced MR imaging with a good reliability and repeatability. Most of liver volume parameters are associated with endoscopic grades of the esophageal varices. TLV, LMV and RV tended to decrease with the increasing endoscopic grade of the esophageal varices, while CV increased with the increasing grade. Furthermore, it is demonstrated that the differences in the liver volume parameters among different endoscopic grades of the esophageal varices were significant except for LLV.

The association of liver volume with endoscopic grade of the esophageal varices can be explained as following mechanisms. It is suspected that the decreasing of TLV, RV and LMV is closely related to the changes in pathology of liver and hemodynamics of the portal system in the progress of cirrhosis. In the typical cirrhosis, the increase of liver tissue fibrosis and the formation of pseudolobules results in the increase of the intrahepatic portal vein pressure and the irregular stenosis of the veins, which leads to a decrease of the liver vascular bed area and its blood flow, resulting in the obvious atrophy of total and segmental liver volumes including RV and LMV which are supplied by the portal veins dominantly [1, 3, 13]. In addition, the increase of the intrahepatic portal vein pressure resulted from the changes in the pathology of liver leads to portal hypertension [1, 14]. The development of portal hypertension can influence on the extrahepatic vascular beds in the splanchnic and systemic circulations, leading to the collateral vessel formation, especially esophageal varices [14, 15]. Based on the previous pathologic process, we can presume that the obvious atrophy of RV and LMV might be associated with esophageal varices. The higher endoscopic grade of the esophageal varices, the more obvious atrophy of previous segmental liver volumes which are supplied by portal veins dominantly, especially RV which achieved the largest absolute value of sample correlation coefficient (r) according to Spearman's rank correlation analyses. The change of RV is closely related to the blood perfusion of the right portal vein which is larger and directly into the right liver lobe parenchyma, leading to the RV susceptible to portal hypertension resulted from cirrhosis [13, 16].

In addition, our study indicated that LLV and CV tended to increase with the increasing grade of the varices, which might be attributed to the compensation of LMV and RV decreasing. But we did not achieve statistical significance in the association between LLV and the esophageal varices. In contrast, the differences in CV among patients with different grades of varices were significant. It is thought that the hypertrophy of the caudate lobe is linked to its blood supply. The caudate lobe is mainly supplied by the posterior branch of the right portal vein, which has a shorter intrahepatic course, and the hepatic venous drainage of this region is preserved [5, 17, 18].

As shown in our study, the increase of LLV and CV with the increasing endoscopic grade of the esophageal varices was less than the decrease of RV and LMV, hence, TLV tended to decrease with the increasing endoscopic grade of the esophageal varices, and it can be associated with endoscopic grade of the esophageal varices.

However, there were two limitations in this study. First, the enrolled patients in this study were only cirrhosis secondary to chronic hepatitis B, but our findings are specific to the particular cirrhotic participants with hepatitis B. In the future, we will perform a further study to enroll more patients with cirrhosis caused by different factors such as alcoholic cirrhosis, metabolic cirrhosis, cholestatic cirrhosis, and so on. Second, the diagnosis of cirrhosis in this study was confirmed by clinical data, laboratory examinations and imaging study according to AASLD practice guidelines 2015-chronic hepatitis B [11]. Patients enrolled had not undergone a liver biopsy because of its invasiveness [19], and the cirrhotic patients with prolongation of prothrombin time are not suitable for this biopsy because it might lead to bleeding. In conclusion, total and most of segmental liver volume parameters tend to be associated with endoscopic grades of the esophageal varices. There was a trend toward decrease of TLV, LMV and RV and increase of CV with the increasing grade of esophageal varices in patients with cirrhosis. The findings could be helpful for better understanding the occurrence and development of esophageal varices for preventing life-threatening upper gastrointestinal hemorrhage.

Acknowledgements

This study was supported by the National Natural Science Foundation of China (Grant No. 81050033), Key Projects in the Sichuan Province Science and Technology Pillar Program (Grant No. 2011SZ0237), and the Science Foundation for Distinguished Young Scholars of Sichuan Province, China (Grant No. 2010JQ-0039).

Disclosure of conflict of interest

None.

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