Original Article | Gastrointestinal Imaging

eISSN 2005-8330
https://doi.org/10.3348/kjr.2021.0348
Korean J Radiol 2021;22(12):1985-1995

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Korean Journal of Radiology
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Liver-to-Spleen Volume Ratio Automatically Measured on CT Predicts Decompensation in Patients with B Viral Compensated Cirrhosis

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Objective: Although the liver-to-spleen volume ratio (LSVR) based on CT reflects portal hypertension, its prognostic role in cirrhotic patients has not been proven. We evaluated the utility of LSVR, automatically measured from CT images using a deep learning algorithm, as a predictor of hepatic decompensation and transplantation-free survival in patients with hepatitis B viral (HBV)-compensated cirrhosis.

Materials and Methods: A deep learning algorithm was used to measure the LSVR in a cohort of 1027 consecutive patients (mean age, 50.5 years; 675 male and 352 female) with HBV-compensated cirrhosis who underwent liver CT (2007–2010). Associations of LSVR with hepatic decompensation and transplantation-free survival were evaluated using multivariable Cox proportional hazards and competing risk analyses, accounting for either the Child-Pugh score (CPS) or Model for End Stage Liver Disease (MELD) score and other variables. The risk of the liver-related events was estimated using Kaplan-Meier analysis and the Aalen-Johansen estimator.

Results: After adjustment for either CPS or MELD and other variables, LSVR was identified as a significant independent predictor of hepatic decompensation (hazard ratio for LSVR increase by 1, 0.71 and 0.68 for CPS and MELD models, respectively; $p < 0.001$) and transplantation-free survival (hazard ratio for LSVR increase by 1, 0.8 and 0.77, respectively; $p < 0.001$). Patients with an LSVR of < 2.9 (n = 381) had significantly higher 3-year risks of hepatic decompensation (16.7% vs. 2.5%, $p < 0.001$) and liver-related death or transplantation (10.0% vs. 1.1%, $p < 0.001$) than those with an LSVR ≥ 2.9 (n = 646). When patients were stratified according to CPS (Child-Pugh A vs. B–C) and MELD (< 10 vs. ≥ 10), an LSVR of < 2.9 was still associated with a higher risk of liver-related events than an LSVR of ≥ 2.9 for all Child-Pugh ($p \leq 0.045$) and MELD ($p \leq 0.009$) stratifications.

Conclusion: The LSVR measured on CT can predict hepatic decompensation and transplantation-free survival in patients with HBV-compensated cirrhosis.

Keywords: *Deep learning; Cirrhosis; Liver; Spleen; Outcomes research; Hepatitis B*

Received: April 23, 2021 **Revised:** June 3, 2021 **Accepted:** June 30, 2021

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (2020R1F1A1048826) and the Bio and Medical Technology Development Program of the NRF, which is funded by the Ministry of Science and ICT (NRF-2016M3A9A7918706).

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INTRODUCTION

Cirrhosis is the end stage of chronic liver disease and is typically classified into compensated and decompensated cirrhosis [1]. Compared with asymptomatic compensated cirrhosis, decompensated cirrhosis is characterized by the development of complications from portal hypertension and liver dysfunction, with the highest mortality in patients with cirrhosis occurring in those in a decompensated state [1-3]. Therefore, the prediction of decompensation risk is important in the management of patients with compensated cirrhosis, as compensated patients at risk of decompensation may benefit from enhanced surveillance and prophylactic interventions [4].

The Child-Pugh score (CPS) and Model for End Stage Liver Disease (MELD) score have traditionally been used as prognostic markers for patients with cirrhosis [5]. More recently, liver and spleen stiffness measurements obtained using ultrasound or MR elastography have been increasingly implemented for the risk stratification of patients with cirrhosis or chronic liver disease in clinical practice [4,6,7]. However, previous studies have also suggested the utility of liver and spleen volume measurements on CT for the prognostication of patients with cirrhosis. Specifically, the liver-to-spleen volume ratio (LSVR) is reported to be useful for the detection of clinically significant portal hypertension and decompensated cirrhosis [8-10].

Despite the potential value of the LSVR, the time-consuming segmentation process that is required to measure liver and spleen volumes has hindered its use in clinical practice and research. Thus, as previous studies evaluating LSVR have been performed using small study populations, there is limited information about the role of LSVR as a predictor of hepatic decompensation and survival in patients with compensated cirrhosis [8-11]. However, deep learning algorithms have recently enabled the fully automated accurate measurement of liver and spleen volumes on CT [12-14]. If the LSVR can predict prognosis in patients with compensated cirrhosis, a deep learning algorithm for the automated measurement of LSVR on CT could generate valuable add-on information without requiring further time and effort. Given the widespread use of CT for assessing patients with cirrhosis, automatically measured LSVRs could be widely applied in clinical practice.

Chronic hepatitis B viral (HBV) infection is a leading cause of liver cirrhosis [15]. The progression of HBV cirrhosis is dependent on active viral replication, the use of antiviral therapy, and the degree of pre-existing liver damage and remnant liver function [16-18]. We hypothesized that LSVR, which potentially reflects portal hypertension, is a prognostic predictor in patients with HBV-compensated cirrhosis. Therefore, the purpose of our study was to automatically measure LSVR using a deep learning algorithm applied to CT and evaluate its use as a predictor of hepatic decompensation and transplantation-free survival in patients with HBV-compensated cirrhosis.

MATERIALS AND METHODS

This retrospective study involved standard care performed at a single tertiary institution and was approved by the Institutional Review Board of Asan Medical Center (IRB No. S2019-0013-0005). The requirement for written informed consent was waived.

Study Population

This retrospective study included consecutive adult patients with HBV-compensated liver cirrhosis who underwent liver CT at our institution between January 2007 and December 2010. Cirrhosis was diagnosed based on the results of histological examination of liver tissue or a combination of unequivocal radiological findings (liver surface nodularity, splenomegaly, or portosystemic collateral vein) and any of the following clinical parameters: endoscopically detected varices, platelet count of < 150 x 10^9/L, serum albumin of < 3.5 g/dL, prothrombin time (PT) international normalized ratio (INR) of > 1.1, or aspartate aminotransferase (AST)-to-platelet ratio of > 2 [7,19,20]. The exclusion criteria were as follows: 1) coexisting with other chronic liver diseases, 2) previous hepatic decompensation or decompensation developing within 3 months of enrolment, 3) pre-existing malignancy or malignancy developing within 6 months of enrolment, 4) previous liver resection or transplantation, 5) unavailable laboratory data, 6) loss to follow-up within 6 months of enrolment, and 7) previous splenectomy or numerous hepatic cysts precluding the volume measurements (Fig. 1). In our study, decompensation events were defined as ascites, hepatic encephalopathy, or variceal bleeding. The final study population consisted of 1027 patients (mean age, 50.5 ± 8.5 years; range, 26–74 years; 675 male and 352 female).

CT Examination

The CT scans were acquired using 4-channel (LightSpeed

https://doi.org/10.3348/kjr.2021.0348

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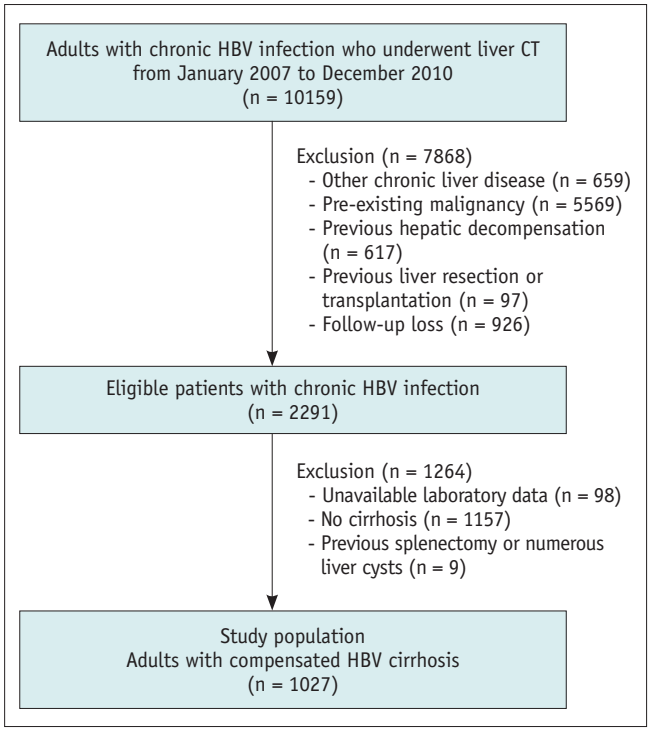

Fig. 1. Flow diagram showing the characteristics of the study population. HBV = hepatitis B viral

Plus; GE Healthcare; n = 341), 16-channel (Sensation 16; Siemens Healthineers; n = 314 or LightSpeed 16, GE Healthcare, n = 162), 64-channel (LightSpeed VCT, GE Healthcare, n = 199), or 128-channel (Somatom Definition AS+, Siemens Healthineers, n = 11) scanners. Portal venous phase imaging was performed 76 seconds after intravenous administration of a contrast agent, with a tube voltage of 120 kVp, a tube current of 200 mAs (LightSpeed plus) or 200–440 mA, and automatic exposure control. Axial CT images were reconstructed at a slice thickness of 5 mm (n = 1026) or 2.5 mm (n = 1) with no gaps.

Measurement of LSVR Using a Deep Learning Algorithm

Portal venous phase CT images were processed using a deep learning algorithm for automated liver and spleen segmentation [13] implemented in the web-based DICOM viewer software (GoCDSS; SmartCareworks Inc.). Details of the algorithm are as described in a previous study [13]. Briefly, the deep convolutional neural network was trained using labeled CT data from 813 patients, and liver and spleen volume measurements were performed with a measurement error of < 5% of the manually measured volume indices [13]. When CT data are uploaded, the software automatically performs liver and spleen segmentation and calculates the liver and spleen volumes (cm^3) by summing up consecutive areas of the liver and spleen and multiplying them by the slice thickness. The LSVR was calculated as liver volume divided by spleen volume. The processing time was 470 ms per image slice, resulting in a duration of 33 seconds for a typical CT examination containing 70 slices. After completion of the automated image analysis, one of the three radiologists reviewed the deep learning-generated segmentation results, corrected any segmentation errors, and recalculated the LSVR. A review of CT examination typically took < 1 minutes, and the time required to correct segmentation errors was recorded.

Data Collection and Outcome Measures

The date of CT acquisition was taken as the date of inclusion and was defined as the baseline. The baseline demographic characteristics and laboratory parameters that could potentially be associated with the prognosis of HBV cirrhosis [16-18], including AST, alanine aminotransferase (ALT), bilirubin, albumin, PT INR, platelets, creatinine, HBV e antigen (HBeAg), and serum HBV deoxyribonucleic acid (DNA), were recorded. The serum HBV DNA level was quantified using a polymerase chain reaction-based test (Abbott real-time HBV kit, Abbott) and categorized as ≤ 2000 IU/mL, 2000–200000 IU/mL, or > 200000 IU/mL [16]. Antiviral treatments such as adefovir, entecavir, lamivudine, telbivudine, tenofovir, and clevudine were recorded before and after the baseline. Liver function was evaluated at baseline using CPS and MELD and was dichotomized according to the following criteria: Child-Pugh A (CPS < 7) vs. Child-Pugh B–C (CPS ≥ 7) and MELD score < 10 vs. MELD score ≥ 10 [21-23]. The results of upper endoscopy within 6 months centered on CT acquisition were also recorded, if available. Esophagogastric varices were graded using the criteria proposed by the Japanese Research Society for Portal Hypertension [24]. Patients were followed up until death, their last clinical visit, or the end of the follow-up period (February 2019), and the primary and secondary outcomes were recorded. The primary outcome was hepatic decompensation, defined as the first occurrence of ascites, hepatic encephalopathy, or variceal bleeding [1]. The secondary outcome was transplantation-free survival.

Statistical Analysis

The associations of LSVR with hepatic decompensation and transplantation-free survival were evaluated using multivariable Cox proportional hazard analysis and Fine

 https://doi.org/10.3348/kjr.2021.0348

and Gray regression analysis [25], respectively, using backward elimination methods. The LSVR, sex, age, AST, ALT, platelets, creatinine, HBeAg, serum HBV DNA, CPS, MELD, and antiviral treatment before and after enrollment were entered into the multivariable analyses. Due to multicollinearity, the analyses were performed using two multivariable models, including either CPS or MELD; the variables incorporated into CPS or MELD (i.e., bilirubin, PT INR, creatinine, and albumin) were excluded. The missing data were handled with multiple imputations by employing the Markov chain Monte Carlo method [26].

To analyze transplantation-free survival, a competing risk analysis was performed with liver-related death (i.e., any mortality associated with liver neoplasm or complications of cirrhosis) and liver transplantation as the events and non-liver-related death as the competing risk. The performances of LSVR, CPS, and MELD for predicting the primary and secondary outcomes were evaluated using time-dependent receiver operating characteristic curves and Harrell's C-index [27] and were compared using the z-score test [28]. The 3- and 5-year risks of hepatic decompensation were estimated according to the LSVR using a univariable Cox proportional hazard model. The optimal cut-off point for LSVR was determined as the maximal sum of sensitivity and specificity for predicting hepatic decompensation within 5 years [29]. The cumulative probability of hepatic decompensation was assessed using Kaplan-Meier survival analysis, and differences between the patient groups were compared using the log-rank test. For transplantation-free survival, the cumulative incidence of liver-related death or transplantation was evaluated using the Aalen-Johansen estimator [30], with differences being tested using Gray's tests [31]. The agreement between the LSVRs automatically measured by the deep learning algorithm and those measured after the radiologists' corrections were evaluated using the 95% Bland-Altman limit of agreement and concordance correlation coefficient. Statistical significance was set at $p < 0.05$. The statistical analyses were performed using SAS software (version 9.4; SAS Institute Inc.) and R (version 3.6.0; R Foundation for Statistical Computing, http://www.R-project.org).

RESULTS

Characteristics of the Study Population

The baseline characteristics and follow-up results of 1027 patients in the study cohort are shown in Table 1. At

Table 1. Characteristics of the Study Population

Parameters	Value
Age*, year	50.5 ± 8.5 (26–74)
Sex	
Male	675 (65.7)
Female	352 (34.3)
CT volumetric index	
Liver volume*, cm^3	1111.3 ± 263.6 (450.2–2508.5)
Spleen volume*, cm^3	380.9 ± 244.1 (85.2–2611.0)
Liver-to-spleen volume ratio*	3.9 ± 2.1 (0.4–14.2)
Liver function	
Child-Pugh score†	5 (5–11)
A	933 (90.8)
B–C	94 (9.2)
MELD score†	8.5 (5.5–23.8)
< 10	828 (80.6)
≥ 10	199 (19.4)
Laboratory findings	
AST*, IU/L	52.6 ± 72.4 (14.0–1423.0)
ALT*, IU/L	51.2 ± 73.7 (2.0–1379.0)
Bilirubin*, mg/dL	1.4 ± 1.0 (0.3–23.6)
Albumin*, g/dL	3.8 ± 0.5 (1.3–4.8)
PT*, INR	1.1 ± 0.1 (0.9–2.1)
Platelets*, x 10^9/L	112.9 ± 46.6 (21.0–347.0)
Creatinine*, mg/dL	0.9 ± 0.4 (0.4–8.4)
Positive HBeAg	331 (33.6)
Serum HBV DNA level‡, IU/mL	
< 2000	410 (43.5)
2000–200000	196 (20.8)
> 200000	336 (35.7)
Antiviral treatment before enrollment	361 (38.3)
Antiviral treatment after enrollment	787 (83.5)
Upper endoscopy	
Available	332 (32.3)
Varix present	155 (15.1)
Follow-up duration†, months	116 (5–145)
Follow-up events	
Decompensation	164 (17.4)
Ascites	87 (53.0)
Variceal bleeding	64 (39.0)
Hepatic encephalopathy	18 (11.0)
Liver-related death	109 (10.6)
Liver transplantation	70 (6.8)

Unless otherwise indicated, data are numbers of patients with percentages in parentheses. *Data are mean ± standard deviation, with range in parentheses, †Data are median, with range in parentheses, ‡Values were missing for 85 (8.3%) patients. ALT = alanine aminotransferase, AST = aspartate aminotransferase, DNA = deoxyribonucleic acid, HBeAg = hepatitis B viral e antigen, HBV = hepatitis B viral, INR = international normalized ratio, IU = international unit, MELD = Model for End Stage Liver Disease, PT = prothrombin time

https://doi.org/10.3348/kjr.2021.0348

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baseline, most patients had well-preserved liver function with Child-Pugh class A (n = 933, 90.8%) or MELD score < 10 (n = 828, 80.6%). During the median follow-up of 116 months (range, 5–145 months), hepatic decompensation occurred in 164 (17.4%) patients, with an annual incidence of 1.96% per year. The most common initial decompensating event was ascites (n = 87, 53.0%), followed by variceal bleeding (n = 64, 39.0%) and hepatic encephalopathy (n = 18, 11.0%). Liver-related deaths occurred in 109 (10.6%) patients, and 70 (6.8%) patients underwent liver transplantation. The annual incidence of liver-related deaths or transplantations is 2.01% per year. Twenty-one (2.0%) patients died of non-liver-related causes.

LSVR

The LSVR ranged from 0.4 to 14.2 (mean ± standard deviation, 3.9 ± 2.1). LSVR showed significant negative correlations with the liver function measures of CPS (Spearman coefficient, -0.320; $p < 0.001$) and MELD score (Pearson coefficient, -0.376; $p < 0.001$) (Supplementary Fig. 1). In the 332 patients with available endoscopic data, the LSVR was significantly lower in patients with gastroesophageal varices (n = 155) than in those with no varix (2.7 ± 1.5 vs. 4.5 ± 2.1, $p < 0.001$).

Primary Outcome: Hepatic Decompensation

For both multivariable Cox models (Table 2), LSVR was a significant independent predictor of hepatic decompensation (hazard ratio [HR], 0.71; 95% confidence interval [CI], 0.63–0.79; $p < 0.001$ for the CPS model; HR, 0.68; 95% CI, 0.61–0.77; $p < 0.001$ for the MELD model), along with sex, age, HBeAg, CPS, MELD, and antiviral treatment after enrollment. The performance of LSVR (C-index, 0.72; 95% CI, 0.68–0.76) for predicting hepatic decompensation was better than that of CPS (C-index, 0.67; 95% CI, 0.63–0.71, $p = 0.066$) and MELD (C-index, 0.66; 95% CI, 0.62–0.71, $p = 0.017$), but the difference was statistically significant only for MELD. The estimated 3- and 5-year probabilities

Table 2. Univariable and Multivariable Cox Proportional Hazard Analysis for Factors associated with Hepatic Decompensation

Variables	Univariable		Multivariable Model 1*		Multivariable Model 2*	
	Unadjusted HR	*P*	Adjusted HR	*P*	Adjusted HR	*P*
Liver-to-spleen volume ratio (for increase by 1)	0.62 (0.55–0.69)	< 0.001	0.71 (0.63–0.79)	< 0.001	0.68 (0.61–0.77)	< 0.001
Sex (female compared with male)	0.83 (0.59–1.15)	0.262	0.70 (0.50–0.99)	0.043	0.68 (0.48–0.96)	0.029
Age (for 1 year)	1.03 (1.01–1.05)	< 0.001	1.04 (1.02–1.06)	< 0.001	1.05 (1.03–1.07)	< 0.001
AST (for 1 IU/L)	1.00 (1.00–1.00)	0.928				
ALT (for 1 IU/L)	1.00 (0.99–1.00)	0.182				
Bilirubin (for 1 mg/dL)	1.11 (1.02–1.21)	0.012				
PT (for 1 INR)	17.37 (8.10–37.23)	< 0.001				
Platelets (for 1 x 10^9/L)	0.98 (0.98–0.99)	< 0.001				
Creatinine (for 1 mg/dL)	1.16 (0.83–1.63)	0.375				
HBeAg (positive compared with negative)	1.43 (1.04–1.96)	0.028	1.82 (1.29–2.56)	0.001	2.00 (1.43–2.81)	< 0.001
Serum HBV DNA level, IU/mL						
< 2000	Reference					
2000–200000	0.97 (0.61–1.54)	0.884				
> 200000	1.30 (0.90–1.88)	0.156				
Child-Pugh score (for increase by 1)	1.77 (1.56–2.00)	< 0.001	1.45 (1.24–1.69)	< 0.001	Not included	
MELD score (for increase by 1)	1.18 (1.12–1.23)	< 0.001	Not included		1.10 (1.03–1.18)	0.005
Antiviral treatment before enrollment (yes compared with no)	0.70 (0.50–0.98)	0.04				
Antiviral treatment after enrollment (yes compared with no)	0.23 (0.17–0.31)	< 0.001	0.22 (0.16–0.31)	< 0.001	0.23 (0.16–0.32)	< 0.001

Numbers in parentheses are 95% confidence intervals. *Multivariable model 1 included Child-Pugh score and other variables except for MELD score, whereas multivariable model 2 included MELD score and other variables except for Child-Pugh score. ALT = alanine aminotransferase, AST = aspartate aminotransferase, DNA = deoxyribonucleic acid, HBeAg = hepatitis B viral e antigen, HBV = hepatitis B viral, HR = hazards ratio, INR = international normalized ratio, IU = international unit, MELD = Model for End Stage Liver Disease, PT = prothrombin time

https://doi.org/10.3348/kjr.2021.0348

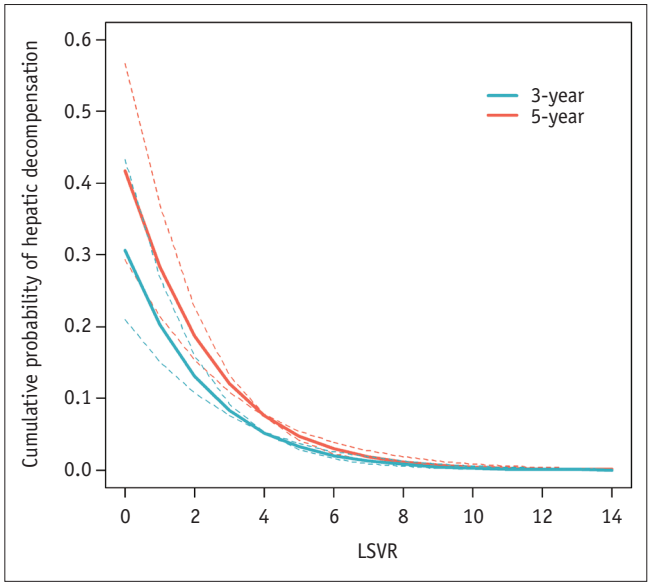

Fig. 2. Estimated 3- and 5-year cumulative probabilities of hepatic decompensation according to the LSVR. The solid lines indicate estimated values; dashed lines represent 95% confidence intervals. LSVR = liver-to-spleen volume ratio

of hepatic decompensation against LSVR are depicted in Figure 2, and they indicate an increasing probability of hepatic decompensation with decreasing LSVR. The optimal LSVR cut-off for predicting hepatic decompensation within 5 years was determined to be 2.9. This cut-off value stratified patients into two distinct prognosis groups (LSVR ≥ 2.9 [n = 646] vs. LSVR < 2.9 [n = 381]) with 3- and 5-year cumulative probabilities of hepatic decompensation of 2.5% vs. 16.7% and 4.6% vs. 21.9%, respectively (p < 0.001) (Supplementary Figs. 2, 3).

Secondary Outcome: Transplantation-Free Survival

The competing risk analysis with Fine and Gray multivariable regression revealed that LSVR was independently associated with transplantation-free survival (HR, 0.8; 95% CI, 0.72–0.89; p < 0.001 for the CPS model and HR, 0.77; 95% CI, 0.69–0.86; p < 0.001 for the MELD model) after accounting for other predictors (Table 3). The other independent predictors included sex,

Table 3. Univariable and Multivariable Fine and Gray Regression Analysis for Factors associated with Transplantation-Free Survival

Variables	Univariable		Multivariable Model 1*		Multivariable Model 2*	
	Unadjusted HR	*P*	Adjusted HR	*P*	Adjusted HR	*P*
Liver-to-spleen volume ratio (for increase by 1)	0.75 (0.67–0.84)	< 0.001	0.80 (0.72–0.89)	< 0.001	0.77 (0.69–0.86)	< 0.001
Sex (female compared with male)	0.69 (0.49–0.96)	0.027	0.54 (0.38–0.77)	0.001	0.54 (0.38–0.76)	< 0.001
Age (for 1 year)	1.04 (1.02–1.05)	< 0.001	1.04 (1.02–1.06)	< 0.001	1.05 (1.03–1.07)	< 0.001
AST (for 1 IU/L)	1.00 (1.00–1.00)	0.548				
ALT (for 1 IU/L)	1.00 (1.00–1.00)	0.121				
Bilirubin (for 1 mg/dL)	1.11 (1.03–1.20)	0.007				
PT (for 1 INR)	11.56 (4.37–30.62)	< 0.001				
Platelets (for 1 x 10^9/L)	0.99 (0.98–0.99)	< 0.001				
Creatinine (for 1 mg/dL)	1.22 (0.86–1.74)	0.254				
HBeAg (positive compared with negative)	1.44 (1.07–1.95)	0.017				
Serum HBV DNA level, IU/mL						
< 2000	Reference		Reference		Reference	
2000–200000	0.89 (0.55–1.44)	0.639	1.57 (1.05–2.34)	0.029	1.50 (1.01–2.23)	0.045
> 200000	1.56 (1.10–2.21)	0.012	2.06 (1.41–3.00)	< 0.001	2.08 (1.44–3.01)	< 0.001
Child-Pugh score (for increase by 1)	1.63 (1.41–1.89)	< 0.001	1.44 (1.23–1.70)	< 0.001	Not included	
MELD score (for increase by 1)	1.14 (1.08–1.21)	< 0.001	Not included		1.08 (1.01–1.17)	0.034
Antiviral treatment before enrollment (yes compared with no)	0.76 (0.55–1.04)	0.087				
Antiviral treatment after enrollment (yes compared with no)	0.48 (0.35–0.65)	< 0.001	0.48 (0.35–0.66)	< 0.001	0.50 (0.36–0.69)	< 0.001

Numbers in parentheses are 95% confidence intervals. *Multivariable model 1 included Child-Pugh score and other variables except for MELD score, whereas multivariable model 2 included MELD score and other variables except for Child-Pugh score. ALT = alanine aminotransferase, AST = aspartate aminotransferase, DNA = deoxyribonucleic acid, HBeAg = hepatitis B viral e antigen, HBV = hepatitis B viral, HR = hazards ratio, INR = international normalized ratio, IU = international unit, MELD = Model for End Stage Liver Disease, PT = prothrombin time

https://doi.org/10.3348/kjr.2021.0348

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Table 4. Risk of Liver-Related Events Stratified according to Liver Function and LSVR

Subgroups	No.	Cumulative Probability of Hepatic Decompensation		Cumulative Incidence of Liver-Related Death or Transplantation	
		3 Year	5 Year	3 Year	5 Year
Child-Pugh A	933	0.07 (0.05–0.08)	0.10 (0.08–0.12)	0.03 (0.02–0.05)	0.07 (0.06–0.09)
LSVR ≥ 2.9	617	0.02 (0.01–0.04)	0.05 (0.03–0.06)	0.01 (0–0.02)	0.04 (0.03–0.06)
LSVR < 2.9	316	0.16 (0.11–0.19)	0.20 (0.15–0.24)	0.08 (0.05–0.12)	0.14 (0.10–0.18)
Child-Pugh B–C	94	0.17 (0.08–0.24)	0.23 (0.14–0.31)	0.17 (0.11–0.27)	0.23 (0.16–0.33)
LSVR ≥ 2.9	29	0.03 (0–0.10)	0.03 (0–0.10)	0.1 (0.04–0.31)	0.14 (0.06–0.35)
LSVR < 2.9	65	0.23 (0.11–0.32)	0.31 (0.19–0.42)	0.20 (0.12–0.33)	0.27 (0.18–0.40)
MELD score < 10	828	0.05 (0.04–0.07)	0.08 (0.06–0.10)	0.03 (0.02–0.04)	0.06 (0.05–0.08)
LSVR ≥ 2.9	575	0.02 (0.01–0.04)	0.04 (0.03–0.06)	0.01 (0–0.02)	0.04 (0.03–0.06)
LSVR < 2.9	253	0.12 (0.08–0.16)	0.16 (0.11–0.21)	0.07 (0.04–0.11)	0.12 (0.09–0.17)
MELD score ≥ 10	199	0.19 (0.13–0.24)	0.25 (0.18–0.31)	0.12 (0.08–0.18)	0.17 (0.13–0.24)
LSVR ≥ 2.9	71	0.04 (0–0.09)	0.09 (0.02–0.16)	0.04 (0.01–0.13)	0.07 (0.03–0.17)
LSVR < 2.9	128	0.27 (0.19–0.34)	0.34 (0.25–0.42)	0.17 (0.11–0.25)	0.23 (0.17–0.32)

Numbers in parentheses are 95% confidence intervals. LSVR = liver-to-spleen volume ratio, MELD = Model for End Stage Liver Disease

age, HBeAg, HBV DNA, CPS, MELD, and antiviral treatment after enrollment. For the prediction of transplantation-free survival, LSVR showed a slightly higher C-index (0.64; 95% CI, 0.60–0.68) than CPS (0.61; 95% CI, 0.57–0.65; $p = 0.205$) and MELD (0.59; 95% CI, 0.55–0.63; $p = 0.050$) without statistical significance. Patients with an LSVR of ≥ 2.9 had a lower cumulative incidence of liver-related death or transplantation than those with an LSVR of < 2.9, with 3- and 5-year cumulative incidence of 1.1% vs. 10% and 4.2% vs. 15.7%, respectively ($p < 0.001$) (Supplementary Fig. 2).

Analysis Stratified by Liver Function

The probability of hepatic decompensation and the incidence of liver-related death or transplantation were lower in patients with Child-Pugh A than in those with Child-Pugh B–C ($p < 0.001$) and in those with MELD < 10 than in those with MELD ≥ 10 ($p < 0.001$) (Supplementary Fig. 4). When LSVR was used in combination with Child-Pugh and MELD stratifications, LSVR allowed further division of each Child-Pugh and MELD class into distinct prognostic subgroups (Table 4). An LSVR of < 2.9 was associated with a higher probability of hepatic decompensation than an LSVR of ≥ 2.9 for both Child-Pugh A ($p < 0.001$) and Child-Pugh B–C ($p = 0.003$), as well as MELD of < 10 and MELD of ≥ 10 ($p < 0.001$ for both groups). Similarly, an LSVR of < 2.9 was associated with a higher incidence of liver-related death or transplantation in both Child-Pugh ($p < 0.001$ for Child-Pugh A; $p = 0.045$ for Child-Pugh B–C) and MELD classifications ($p < 0.001$ for MELD score < 10; $p = 0.009$ for MELD score ≥ 10) (Fig. 3).

Clinical Feasibility of the Automatically Measured LSVR

The radiologist reviews of the deep learning-generated automated segmentation demonstrated no segmentation error for 922 (89.8%) of the 1027 patients. In the other 105 patients (10.2%), a minor segmentation error was observed, which required a short correction time (mean time for correction, 36.9 ± 42.8 seconds; range, 4–263 seconds) and was associated with a small change in LSVR (95% limit of agreement, -9.5% to 10.0% of measured LSVR; concordance correlation coefficient, 0.997 [95% CI, 0.996–0.998]) (Supplementary Table 1). The C-indices for the automatically measured LSVRs for predicting hepatic decompensation (C-index, 0.72 vs. 0.72; $p = 0.496$) and transplantation-free survival (C-index, 0.64 vs. 0.64; $p = 0.246$) were nearly identical to those of the radiologist-corrected LSVRs.

DISCUSSION

Our study demonstrated that LSVR can be used to predict the development of decompensation and transplantation-free survival in patients with HBV-compensated cirrhosis. Patients with HBV compensated cirrhosis and an LSVR of < 2.9 had an approximately 5-fold higher risk of hepatic decompensation and a 4-fold higher risk of liver-related death or transplantation in 5 years than those with an LSVR of ≥ 2.9.

Despite a significant correlation between LSVR and liver function indices, the associations of LSVR with hepatic decompensation and transplantation-free survival were

 https://doi.org/10.3348/kjr.2021.0348

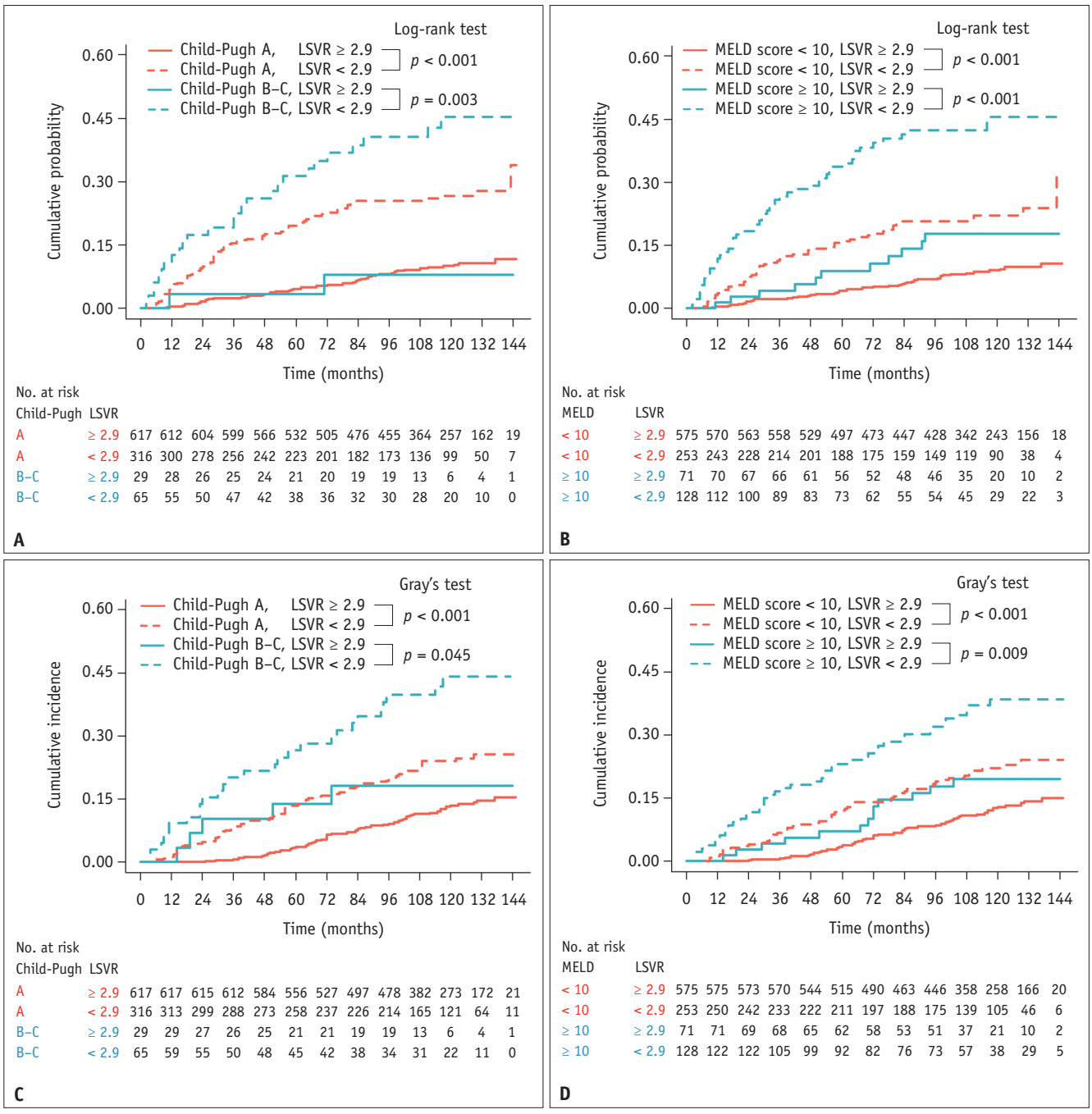

Fig. 3. Risks of liver-related events in patients stratified by liver function and LSVR.
A, B. Cumulative probability of hepatic decompensation estimated by Kaplan-Meier estimator in subgroups stratified by the Child-Pugh class and LSVR **(A)** and subgroups stratified by MELD score and LSVR **(B)**. **C, D.** Cumulative incidence of liver-related death and transplantation estimated by the Aalen-Johansen estimator in subgroups stratified by the Child-Pugh class and LSVR **(C)** and subgroups stratified by MELD and LSVR **(D)**.
LSVR = liver-to-spleen volume ratio, MELD = Model for End Stage Liver Disease

independent of both CPS and MELD scores, as well as other established prognostic factors for HBV cirrhosis. More importantly, the LSVR complemented the Child-Pugh or MELD classifications for predicting liver-related events. In patients with well-preserved liver function (Child-Pugh A or MELD score < 10), an LSVR of < 2.9, could identify patients with a high risk of liver-related events. This subset of patients may benefit from close surveillance and intense treatment. Similarly, the LSVR could be used to subdivide patients with diminished liver function (Child-Pugh B–C or MELD score ≥ 10) into two distinct groups with different risks of liver-related events. However, as shown in Figure 2,

https://doi.org/10.3348/kjr.2021.0348

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the estimated probability of hepatic decompensation varies with the LSVR. This indicates that patients in the same risk group by LSVR cut-off may have different risks of liver-related events. Therefore, patient management in clinical practice needs to be tailored by risk estimation based on LSVR values and liver function indices.

Liver volume decreases as cirrhosis progresses to end-stage liver disease [10,32], whereas spleen volume gradually increases with the progression of liver fibrosis, and this likely reflects portal hypertension [9,33]. As a composite index, LSVR may capture cirrhosis-related changes that are reflected in both liver and spleen volumes. An added advantage of the LSVR is that it is less dependent on anthropomorphic factors of patients such as height, bodyweight, and body surface area than liver and spleen volumes [10]. A few previous studies demonstrated the advantage of LSVR over the volume of the liver or spleen alone in the diagnosis of decompensated cirrhosis and the detection of clinically significant portal hypertension [8,18,27]. However, regarding the prognostic role of LSVR, only a single study with a small sample reported a correlation between LSVR and the survival of patients with primary biliary cirrhosis [11], which is in line with our results.

One aspect of our study that we wish to highlight is the use of a deep learning algorithm for automated liver and spleen volume measurement on CT images; previous studies relied on time-consuming manual organ segmentation [8,9,11,32]. The deep learning algorithm enables highly accurate measurement of the LSVR. Minor segmentation errors, which were rapidly corrected by the reviewing radiologists, were observed in only 10% of patients and associated with errors of < 10% for the measured LSVRs. Furthermore, such errors in the automatically measured LSVR did not affect its performance for predicting liver-related events, with nearly identical C-index values obtained for automatically measured and radiologist-corrected LSVRs. These findings indicate that LSVR automatically measured by deep learning analysis of CT images may be clinically applicable for the risk stratification of patients with HBV compensated cirrhosis, thereby adding valuable information to routine CT evaluations, without the requirement of additional time and effort from radiologists or clinicians.

We acknowledge some limitations of our study. One of the major limitations was its retrospective nature. CT is not a routine surveillance examination, and as our study included only those patients who underwent CT, it may be subject to selection bias. Cirrhotic patients with severe renal dysfunction and an allergy to iodine contrast agents were less likely to have been included in our study. Information such as results of endoscopy was not available for all patients. We did not evaluate the effect of acute hepatic inflammation on LSVR and the applicability of LSVR for risk prediction in patients with acute exacerbation of chronic HBV hepatitis. Our results were obtained from patients with HBV-compensated cirrhosis and cannot be generalized to patients with cirrhosis due to other etiologic causes. Finally, the results of our single-institution study need to be validated in future research.

In conclusion, LSVR can be used as a prognostic marker in patients with HBV-compensated cirrhosis. A lower LSVR was associated with higher future risks of hepatic decompensation, transplantation, and liver-related death independent of CPS or MELD and other well-known prognostic factors. Using the deep learning algorithm, the LSVR can be automatically measured on CT images, and this can be easily implemented in clinical practice, thereby providing a tool for risk stratification and decision-making in the management of patients with HBV compensated cirrhosis.

Supplement

The Supplement is available with this article at https://doi.org/10.3348/kjr.2021.0348.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

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REFERENCES

1. D'Amico G, Morabito A, D'Amico M, Pasta L, Malizia G, Rebora P, et al. Clinical states of cirrhosis and competing risks. *J Hepatol* 2018;68:563-576
2. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *J Hepatol* 2006;44:217-231
3. Fleming KM, Aithal GP, Card TR, West J. All-cause mortality in people with cirrhosis compared with the general population: a population-based cohort study. *Liver Int* 2012;32:79-84
4. de Franchis R. Expanding consensus in portal hypertension: report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. *J Hepatol* 2015;63:743-752
5. Forman LM, Lucey MR. Predicting the prognosis of chronic liver disease: an evolution from child to MELD. *Hepatology* 2001;33:473-475
6. Lee HW, Yoo EJ, Kim BK, Kim SU, Park JY, Kim DY, et al. Prediction of development of liver-related events by transient elastography in hepatitis B patients with complete virological response on antiviral therapy. *Am J Gastroenterol* 2014;109:1241-1249
7. Takuma Y, Morimoto Y, Takabatake H, Toshikuni N, Tomokuni J, Sahara A, et al. Measurement of spleen stiffness with acoustic radiation force impulse imaging predicts mortality and hepatic decompensation in patients with liver cirrhosis. *Clin Gastroenterol Hepatol* 2017;15:1782-1790.e4
8. Yan SP, Wu H, Wang GC, Chen Y, Zhang CQ, Zhu Q. A new model combining the liver/spleen volume ratio and classification of varices predicts HVPG in hepatitis B patients with cirrhosis. *Eur J Gastroenterol Hepatol* 2015;27:335-343
9. Iranmanesh P, Vazquez O, Terraz S, Majno P, Spahr L, Poncet A, et al. Accurate computed tomography-based portal pressure assessment in patients with hepatocellular carcinoma. *J Hepatol* 2014;60:969-974
10. Son JH, Lee SS, Lee Y, Kang BK, Sung YS, Jo S, et al. Assessment of liver fibrosis severity using computed tomography-based liver and spleen volumetric indices in patients with chronic liver disease. *Eur Radiol* 2020;30:3486-3496
11. Murata Y, Abe M, Hiasa Y, Azemoto N, Kumagi T, Furukawa S, et al. Liver/spleen volume ratio as a predictor of prognosis in primary biliary cirrhosis. *J Gastroenterol* 2008;43:632-636
12. Park HJ, Park B, Lee SS. Radiomics and deep learning: hepatic applications. *Korean J Radiol* 2020;21:387-401
13. Ahn Y, Yoon JS, Lee SS, Suk HI, Son JH, Sung YS, et al. Deep learning algorithm for automated segmentation and volume measurement of the liver and spleen using portal venous phase computed tomography images. *Korean J Radiol* 2020;21:987-997
14. Wang K, Mamidipalli A, Retson T, Bahrami N, Hasenstab K, Blansit K, et al. Automated CT and MRI liver segmentation and biometry using a generalized convolutional neural network. *Radiol Artif Intell* 2019;1:180022
15. Liang TJ. Hepatitis B: the virus and disease. *Hepatology* 2009;49:S13-S21
16. Wong GL, Chan HL, Wong CK, Leung C, Chan CY, Ho PP, et al. Liver stiffness-based optimization of hepatocellular carcinoma risk score in patients with chronic hepatitis B. *J Hepatol* 2014;60:339-345
17. Shiffman ML. Approach to the patient with chronic hepatitis B and decompensated cirrhosis. *Liver Int* 2020;40:22-26
18. Sinn DH. Natural history and treatment indications of chronic hepatitis B. *Korean J Gastroenterol* 2019;74:245-250
19. Yuen MF, Tanaka Y, Fong DY, Fung J, Wong DK, Yuen JC, et al. Independent risk factors and predictive score for the development of hepatocellular carcinoma in chronic hepatitis B. *J Hepatol* 2009;50:80-88
20. Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology* 2003;38:518-526
21. Wiesner R, Edwards E, Freeman R, Harper A, Kim R, Kamath P, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology* 2003;124:91-96
22. Cholongitas E, Papatheodoridis GV, Vangeli M, Terreni N, Patch D, Burroughs AK. Systematic review: the model for end-stage liver disease--should it replace Child-Pugh's classification for assessing prognosis in cirrhosis? *Aliment Pharmacol Ther* 2005;22:1079-1089
23. Child CG, Turcotte JG. Surgery and portal hypertension. *Major Probl Clin Surg* 1964;1:1-85
24. Idezuki Y. General rules for recording endoscopic findings of esophagogastric varices (1991). Japanese Society for Portal Hypertension. *World J Surg* 1995;19:420-422

https://doi.org/10.3348/kjr.2021.0348

25. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;94:496-509
26. Schafer JL. *Analysis of incomplete multivariate data*. London: Chapman & Hall, 1997
27. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996;15:361-387
28. Kang L, Chen W, Petrick NA, Gallas BD. Comparing two correlated C indices with right-censored survival outcome: a one-shot nonparametric approach. *Stat Med* 2015;34:685-703
29. Bewick V, Cheek L, Ball J. Statistics review 13: receiver operating characteristic curves. *Crit Care* 2004;8:508-512
30. Aalen O. Nonparametric estimation of partial transition probabilities in multiple decrement models. *Ann Stat* 1978;6:534-545
31. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat* 1988;16:1141-1154
32. Liu P, Li P, He W, Zhao LQ. Liver and spleen volume variations in patients with hepatic fibrosis. *World J Gastroenterol* 2009;15:3298-3302
33. Berzigotti A, Seijo S, Arena U, Abraldes JG, Vizzutti F, García-Pagán JC, et al. Elastography, spleen size, and platelet count identify portal hypertension in patients with compensated cirrhosis. *Gastroenterology* 2013;144:102-111.e1

 https://doi.org/10.3348/kjr.2021.0348