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Original Article

Noncontrast-enhanced MRI-based Noninvasive Score for Portal Hypertension (CHESS1802): An International Multicenter Study

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Abstract

Background and Aims: This study aimed to determine the performance of the non-invasive score using noncontrast-enhanced MRI (CHESS-DIS score) for detecting portal hypertension in cirrhosis. ***Methods:*** In this international multicenter, diagnostic study (ClinicalTrials.gov, NCT03766880), patients with cirrhosis who had hepatic venous pressure gradient (HVPG) measurement and noncontrast-enhanced MRI were prospectively recruited from four university hospitals in China (n=4) and Turkey (n=1) between December 2018 and April 2019. A cohort of patients was retrospectively recruited from a university hospital in Italy between March 2015 and November 2017. After segmentation of the liver on fat-suppressed T1-weighted MRI maps, CHESS-DIS score was calculated automatically by an in-house developed code based on the quantification of liver surface nodularity. ***Results:*** A total of 149 patients were included, of which 124 were from four Chinese hospitals (training cohort) and 25 were from two international hospitals (validation cohort). A positive correlation between CHESS-DIS score and HVPG was found with the correlation coefficients of 0.36 (p<0.0001) and 0.55 (p<0.01) for the training and validation cohorts, respectively. The area under the receiver operating characteristic curve of CHESS-DIS score in detection of clinically significant portal hypertension (CSPH) was 0.81 and 0.9 in the training and validation cohorts, respectively. The intraclass correlation coefficients for assessing the inter- and intra-observer agreement were 0.846 and 0.841, respectively. ***Conclusions:*** A non-invasive score using noncontrast-enhanced MRI was developed and proved to be significantly correlated with invasive HVPG. Besides, this score could be used to detect CSPH in patients with cirrhosis.

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Abbreviations: AAR, aspartate aminotransferase to alanine aminotransferase ratio; APRI, aspartate aminotransferase to and platelet ratio index; AUC, area under the receiver operating characteristic curve; CI, confidence interval; CSPH, clinically significant portal hypertension; CT, computed tomography; FIB-4, fibrosis index based on four factors; GPR, gamma glutamyl trans-peptidase to platelet ratio; HVPG, hepatic venous pressure gradient; ICC, Intraclass correlation coefficient; LR+, positive likelihood ratio; LR-, negative likelihood ratio; LSN, liver surface nodularity; MRI, magnetic resonance imaging; NPV, negative predictive value; PPV, positive predictive value; ROI, region of interest.

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Introduction

In patients with cirrhosis, the presence of portal hypertension is an important event in the natural history of the disease, characterized by a significantly higher risk of clinical complications such as variceal bleeding and ascites.[1] The reference standard for portal hypertension is hepatic venous pressure gradient (HVPG), measured by an invasive hepatic vein catheterization.[2] A patient with an HVPG value higher than 5 mmHg is considered as having portal hypertension and the diagnosis of clinically significant portal hypertension (CSPH) is made when the value is equal to or higher than 10 mmHg.[3] A recent multicenter double-blind randomized controlled trial suggested that therapy with β-blockers should be started once CSPH is detected to prevent decompensation of cirrhosis.[4] Therefore, an early identification of CSPH, ideally before complications have occurred, should be one of the key aspects of management of cirrhosis. Because of the invasiveness, requirement of a specific expertise, and relatively high cost, the HVPG measurement is not highly accepted by patients with cirrhosis, especially those in early stage without clinical symptoms. Consequently, the development of a simple and reliable non-invasive surrogate for HVPG has been a hot topic in this area.[5]

Liver surface nodularity (LSN) increases parallel with cirrhosis severity.[6,7] Besides, on liver histology, patients without CSPH are more likely to have thin fibrous septa than patients with CSPH, who characteristically have thicker septa and small nodules.[6,7] Based on this, Smith *et al*.[8] have developed a software to quantify LSN from routine computed tomography (CT) images for detection and evaluation of cirrhosis, and studies have demonstrated that it could allow the detection of CSPH and prediction of decompensation events and death in patients with cirrhosis.[9,10] Latter studies have reported the possibility and feasibility of quantification of LSN using magnetic resonance imaging (MRI) for identification of fibrosis stage, cirrhosis, and CSPH.[11–13] These studies were limited by relatively small sample size. Thus, further studies need to be undertaken in a larger population with different etiological categories to evaluate and validate the feasibility of MRI-based LSN quantification. So far, there has been no study on the performance of LSN using noncontrast-enhanced MRI images for diagnosing portal hypertension. In this study, we aimed to develop a non-invasive score by quantification of LSN from noncontrast-enhanced MRI images and to study the correlation between LSN-based score and portal pressure as well as its performance for detecting CSPH in patients with liver cirrhosis.

Methods

Participants and study design

This multicenter, diagnostic study prospectively included patients from four university hospitals in China (The Fifth Medical Center of Chinese PLA General Hospital, Beijing; Xingtai People's Hospital, Xingtai; Shandong Provincial Hospital, Jinan; The First Hospital of Lanzhou University, Lanzhou) and one university hospital in Turkey (Ankara University School of Medicine, Ankara) from December 2018 to April 2019. Besides, patients from a university hospital in Italy (S. Orsola-Malpighi Hospital, University of Bologna, Bologna) were retrospectively collected to validate the diagnostic performance of the proposed non-invasive model. Study participants with cirrhosis were prospectively included, according to the following criteria: (1) age 18–75 years; (2) liver cirrhosis diagnosed by the combination of clinical, biochemical, imaging, and/or histological criteria; (3) scheduled to undergo clinically-indicated transjugular HVPG measurement; (4) underwent abdominal MRI scanning within 14 days of the HVPG measurement; (5) no hepatic-portal vein interventional therapy between the time of MRI and hepatic vein catheterization; and (6) provided written informed consent. The exclusion criteria were: (1) contraindications to MRI scanning; (2) inability to comply with breathing or other imaging-related instructions, resulting in inability to obtain diagnostic quality MRI studies; (3) prior transjugular intrahepatic portosystemic stent-shunt surgery; (4) prior devascularization operation; (5) receipt of a liver transplant; or (6) presence of any active, serious, life-threatening disease. The reference standard was transjugular HVPG measurement. CSPH was defined as an HVPG value equal to or higher than 10 mmHg. This study was registered with ClinicalTrials.gov (03766880) and was performed according to the Helsinki Declaration, with approval by the institutional review board of First Hospital of Lanzhou University. The researchers only analyzed de-identified data of the patients.

HVPG measurement

Clinical measurement of HVPG is indicated for the precise evaluation of portal pressure, and the risk stratification of participants with cirrhosis. Transjugular HVPG measurement (reference standard) was performed according to the standard protocol[14] using a balloon catheter (Fogarty by Edwards Lifesciences, Irvine, CA, USA; Armada by Abbott Vascular, Temecula, CA, USA; or Occluder Occlusion Balloon Catheter by Boston Scientific, Marlborough, MA, USA) with a pressure transducer at the tip. A zero measurement with transducer open to air was required before the transjugular catheterization. The free hepatic venous pressure was measured in the right hepatic vein, and the wedged hepatic venous pressure was measured as the balloon was inflated for total occlusion of the right hepatic vein. Continuous recording was necessary until the pressure reached a plateau. HVPG represents the difference between free venous hepatic pressure and wedged hepatic pressure. All measurements were performed in duplicate at least and then averaged.

MRI acquisition

MRI scans were performed following the routine upper abdominal imaging protocols, with one of the following systems: Ingenia 3.0 T (Philips Healthcare, Best, Netherlands); Achieva 3.0 T (Philips Healthcare); MAGNETOM Skyra 3.0 T (Siemens Healthcare, Erlangen, Germany); MAGNETOM Aera 1.5T (Siemens Healthcare); MAGNETOM Verio 3.0T (Siemens Healthcare); or Signa HDxt 1.5 T (GE Healthcare). The T1-weighted images (T1WIs) were acquired with three-dimensional T1 High-resolution Isotropic Volume Excitation pulse sequence or Volumetric Interpolated Breath-hold Examination pulse sequence or Liver Acquisition with Volume Acceleration pulse sequence.

Image processing and development of the non-invasive score from MRI

Fat-suppressed noncontrast enhanced T1-weighted sequence

was used to investigate the liver surface characteristics for each participant. Technicians who performed the image processing and model development were blinded to the clinical data of the patients. The MRI images (DICOM format) were imported into an open source software platform (3D slicer, version 4.10.2; https://www.slicer.org/)[15] and a segmentation of region of interest (ROI) was conducted to cover the edge of the left lobe of the liver, with 10 mm in diameter and 50–100 mm in length. The T1WIs as well as the according ROIs were exported as NIFTI format to be processed in the next step, with an in-house developed code based on MATLAB software (version R2013a; Mathworks, Natick, MA, USA). The calculation of the CHESS-DIS score was performed with the following steps: (1) noise removal using a fast Fourier transformation and inverse fast Fourier transformation; (2) iteration based on the histogram of the target voxels to determine a proper threshold and segmentation of the liver tissue with the detected threshold; (3) conduction of a connection map based on eight-connected voxels within the segmented images; (4) selection of the largest cluster and transformation of the cluster into binary images; (5) detection of the edge of the segmented images using edge detection function based on the Prewitt method; (6) surface matching using polynomial curve fitting, with x, x^2 and x^3 based on the voxels of the edges with least squares method; and (7) calculation of the minimum distance of each edge voxel to the surface (Supplementary Fig. 1). Of note, for each case, seven different slices were applied based on the same ROI (the original slice as well as three slices upper and three slicers underneath). The CHESS-DIS score was the average of the five largest values among the seven measurements.

Reliability of the CHESS-DIS score

The inter-observer reliability was analyzed with 30 randomly and equiprobably chosen cases in a blind fashion by two independent technicians for ROI segmentation and CHESS-DIS score calculation. Besides, to study the intra-observer agreement, one technician repeated the above procedures twice on 30 cases with at least 1-week interval to reduce the recall bias. Intraclass correlation coefficient (ICC) and Bland-Altman plot were used to evaluate the intra- and inter-observer agreement.

Calculation of conventional non-invasive scores

The diagnostic performance of eight serum-based scores, including aspartate aminotransferase to alanine aminotransferase ratio (AAR), aspartate aminotransferase to and platelet ratio index (APRI), CSPH risk score, fibrosis index based on four factors (FIB-4), Fibrosis Index, gamma glutamyl trans-peptidase to platelet ratio (GPR), King's score, and Lok score, were studied.[16–23] The serum tests were conducted during the hospitalization of the transjugular HVPG measurement. Calculation formulas for these models are summarized in Supplementary Table 1. Besides, three imaging-based parameters including liver stiffness by transient elastography, portal vein diameter, and portal vein velocity by Doppler ultrasound were collected to study the accuracy for detecting CSPH.

Statistical analysis

Continuous variables were expressed as mean (standard deviation) or median (interquartile range), and categorical data was expressed as numbers (percentages). Spearman correlation coefficient analysis (R value) was used to assess the correlation between the CHESS-DIS score and transjugular HVPG. The Mann-Whitney *U* test was used to analyze the differences in the mean values of the CHESS-DIS score between patients with and without CSPH. The diagnostic performance was assessed by area under the receiver operating characteristic curve (AUC), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), and negative likelihood ratio (LR-). Youden's index was used to determine the optimal cutoff. A p-value of <0.05 indicated statistical significance. The statistical analyses were conducted using R Language (5.1.2, R Core Team, 2019) and SPSS statistical software (version 20.0; IBM Corp., Armonk, NY, USA).

Results

Study population

A total of 186 patients with cirrhosis were screened, with 174 prospectively recruited from five centers (The Fifth Medical Center of Chinese PLA General Hospital, n=119; Xingtai People's Hospital, n=15; Shandong Provincial Hospital, n=9; The First Hospital of Lanzhou University, n=8; Ankara University School of Medicine, n=23) and 12 were retrospectively collected from S. Orsola-Malpighi Hospital using the same inclusion and exclusion criteria. Thirty-seven patients were excluded due to either ineligible images for further analysis including image artifacts, indistinct image border of liver, and missing fat-suppression images or post-hepatectomy. As a result, 149 patients were included, among which 124 were from four Chinese centers, serving as the training cohort, and 25 were from two international centers, serving as the validation cohort. The prevalence of CSPH in both cohorts were 84.7% and 48.0%, respectively. The study flow chart is shown in Figure 1. Baseline characteristics of the enrolled participants are summarized in Table 1.

Correlation between the CHESS-DIS score and HVPG

All the cases achieved valid CHESS-DIS score calculation. Two examples of CHESS-DIS score calculation are shown in Figure 2. The mean time to calculate CHESS-DIS score once the ROI was placed was 2.36±0.97 s. CHESS-DIS score was significantly correlated with transjugular HVPG value in the training cohort (R=0.36, p<0.0001) (Fig. 3A). In the validation cohort, the correlation coefficient was 0.55 (p=0.005) (Fig. 3B).

Reproducibility of the CHESS-DIS score

ICC values for assessing the inter- and intra-observer agreement were 0.846 (95% confidence interval [CI]: 0.702–0.924) and 0.841 (95% CI: 693–0.921), respectively. Bland-Altman plots also revealed good inter- and intra-observer reliability (Fig. 3C, D).

Diagnostic performance of the CHESS-DIS score for CSPH

The performance of CHESS-DIS score for detection of CSPH was also studied. The overall CHESS-DIS score was higher in participants with CSPH than in those without CSPH (8.00±3.18 vs. 4.79±1.41, p<0.0001). In the training cohort, AUC of the CHESS-DIS score for detecting CSPH was 0.81 (95% CI: 0.72–0.90) (Fig. 4A). Additionally, the diagnostic performance of the CHESS-DIS score was validated in patients recruited

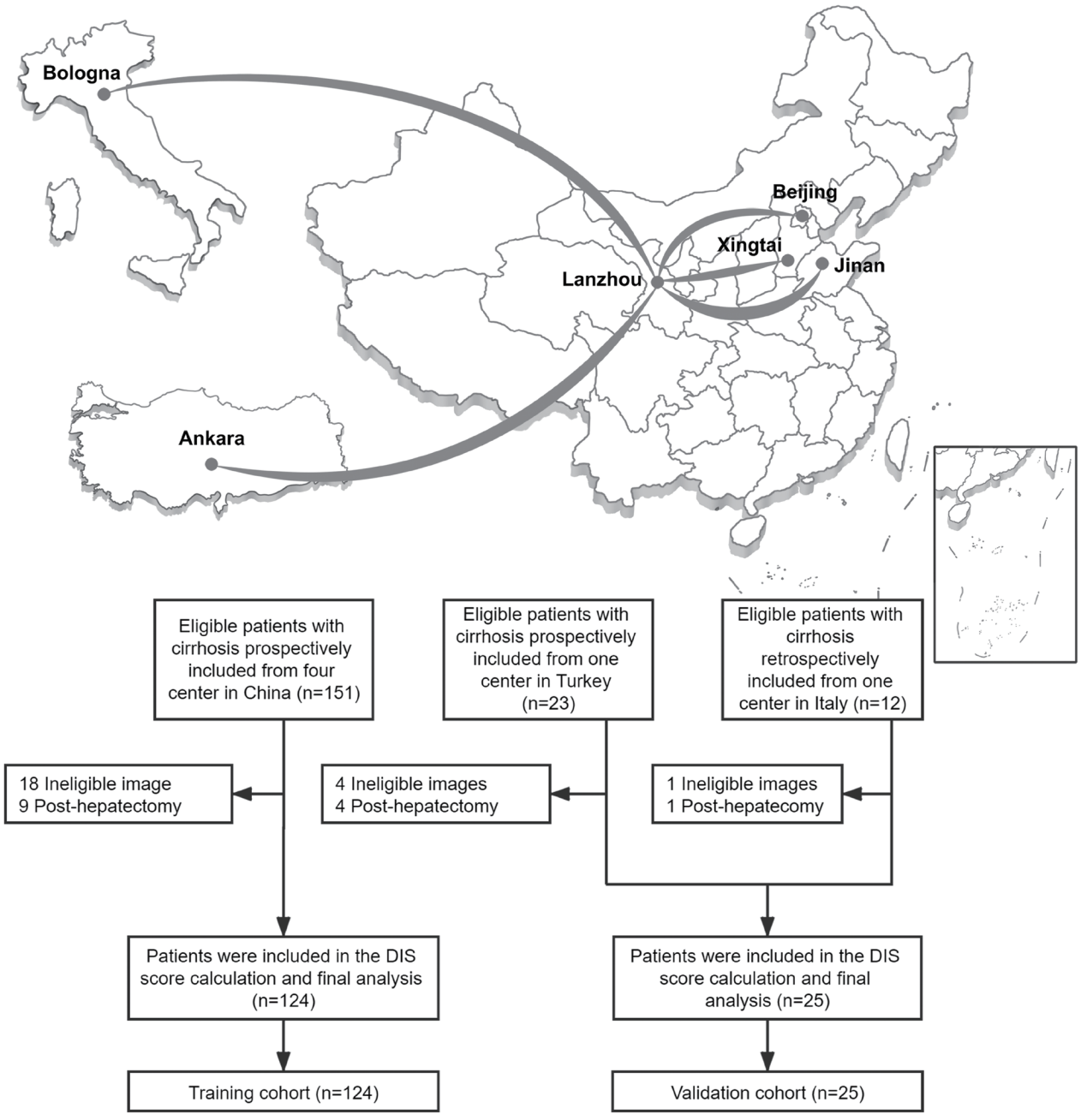

Fig. 1. Flow chart for the study's enrollment.

from two external international centers with an AUC value of 0.91 (95% CI: 0.78–1.00) (Fig. 4A). The specificity, sensitivity, PPV, NPV, LR+, and LR- values of the CHESS-DIS score in the validation cohort were 0.92 (0.77–1.00), 0.92 (0.75–1.00), 0.92 (0.77–1.00), 0.92 (0.79–1.00), 11.92 (1.80–78.94), and 0.09 (0.01–0.59), respectively (Table 2).

Performance of conventional non-invasive tools for detecting CSPH

Among 11 studied conventional non-invasive models (AAR, APRI, CSPH risk score, FIB-4, Fibrosis Index, GPR, King's score, Lok score, liver stiffness, portal vein diameter, and portal vein velocity), GPR showed the highest performance for detecting CSPH, with an AUC of 0.64 (95% CI: 0.54–0.75), followed by liver stiffness, with an AUC of 0.59 (95% CI: 0.40–0.78) (Fig. 4B, C). The values for AUC, specificity, sensitivity, PPV, NPV, LR+, and LR- of all the above conventional non-invasive models are presented in Table 3.

Discussion

We developed a non-invasive score based on the quantification of LSN using noncontrast-enhanced MRI, which we

Table 1. Baseline characteristics of the included patients

Variables	All patients, *n*=149	Training cohort, *n*=124	Validation cohort, *n*=25	*p* value
Age (year), mean (SD)	52 (11.7)	50 (11.1)	61 (11.0)	<0.0001
Male, *n* (%)	105 (70.5)	91 (73.4)	14 (56.0)	0.082
HVPG (mmHg), mean (SD)	14.5 (6.0)	15.3 (5.7)	10.7 (6.3)	0.0003
Etiology, *n* (%)				<0.0001
Hepatitis B virus	82 (55.0)	77 (62.1)	5 (20.0)	–
Alcohol	17 (11.4)	17 (13.7)	0	–
Hepatitis C virus	17 (11.4)	9 (7.3)	8 (32.0)	–
Autoimmune hepatitis	9 (6.0)	6 (4.8)	3 (12.0)	–
NAFLD	4 (2.7)	0	4 (16.0)	–
Primary biliary cholangitis	3 (2.0)	3 (2.4)	0	–
Drug-induced liver disease	1 (0.7)	1 (0.8)	0	–
Amyloidosis	1 (0.7)	1 (0.8)	0	–
Unknown	15 (10.1)	10 (8.1)	5 (20.0)	–
Child-Pugh score, *n* (%)				0.087
Class A	97 (65.1)	77 (62.1)	20 (80.0)	–
Class B	52 (34.9)	47 (37.9)	5 (20.0)	–
AST (IU/L), mean (SD)	41.0 (26.2)	40.0 (22.7)	46.7 (25.7)	0.271
ALT (IU/L), mean (SD)	33.0 (25.9)	30.9 (20.4)	44.7 (26.1)	0.362
Albumin (g/L), mean (SD)	35.1 (4.5)	34.8 (4.3)	37.0 (5.7)	0.111
TBil (μmol/L), mean (SD)	20.9 (12.1)	20.8 (11.5)	21.0 (15.4)	0.829
INR, mean (SD)	1.19 (0.17)	1.17 (0.16)	1.25 (0.20)	0.067
Platelet count (10^9/L), median (IQR)	70 (55.3)	66 (48.0)	102 (75.5)	0.005

Comparisons between the cirrhosis group and the non-cirrhosis group were analyzed using Fisher's exact test or Mann-Whitney *U* test, where appropriate. A two-sided *p*-value of less than 0.05 was considered statistically significant. SD, standard deviation; IQR, interquartile range; HVPG, hepatic venous pressure gradient; NAFLD, nonalcoholic fatty liver disease; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TBil, total bilirubin; INR, international normalized ratio.

termed "CHESS-DIS score". The result suggested that the CHESS-DIS score was significantly correlated with the invasive HVPG value. Besides, the score showed a potentiality for detection of CSPH in patients with cirrhosis.

Due to the invasiveness, high cost, and requirement for specific expertise of HVPG measurement, developing a non-invasive and reliable tool for estimation of portal pressure has persisted as an unmet need in the field.[5,24] LSN quantification reflects the lobulated liver surface margin that develops as liver fibrosis and cirrhosis progresses.[25] Histologic studies have shown that patients without CSPH are more likely to have thin fibrous septa than patients with CSPH, who characteristically have thicker septa and small nodules;[6,7] thus, LSN was considered a candidate for non-invasive assessment of portal hypertension. Quantification of LSN based on routine CT scans was initially put forward for the diagnosis of liver fibrosis, and studies reported on the satisfactory performance of this method.[8,26] In recent years, studies have demonstrated the benefit of this method to predict CSPH, decompensating events, and death in patients with cirrhosis.[9,10] Besides using CT images for LSN quantification, MRI-based measurements were also reported to be accurate in distinguishing fibrosis stages F1 and F2-F3 in patients with nonalcoholic fatty liver disease, with AUC, sensitivity and specificity values of 0.788, 0.833 and 0.727, respectively.[11] However, the feasibility of developing MRI-based LSN quantification needed further evaluation and validation in studies with larger sample size and more etiological categories. A recent study reported that MRI-based LSN quantification correlated significantly with the invasive HVPG value and was capable for accurate detection of CSPH.[13] However, that study was limited by use of contrast-enhanced images. Besides, the previous studies on MRI-based LSN quantification[11–13] were retrospective and based upon patient data from a single center; moreover, the included sample size was small.

The present international multicenter study was the first to investigate the correlation between noncontrast-enhanced MRI-based LSN quantification score and HVPG value, and its accuracy for detection of CSPH in patients with cirrhosis. Besides, this was the largest study on MRI-based LSN quantification so far. Moreover, the major etiologies of fibrosis or cirrhosis in the previous studies[11–13] were nonalcoholic fatty liver disease (42%, 30/72) and hepatitis C virus infection (24%), when taking all these published data together. In the present study, the training cohort was recruited from China, so that more than half of the participants (62%) had hepatitis B virus-related cirrhosis; in the validation cohort, which involved two countries outside Asia-Pacific region, hepatitis C virus infection (32%) remained the most common cause of cirrhosis, the etiology characteristics of which were similar to that in western countries.[27,28] The wider spectrum of etiology in our population might add value. Nevertheless, considering the small sample size of patients with nonalcoholic fatty liver disease-, alcohol-related liver disease-, and autoim-

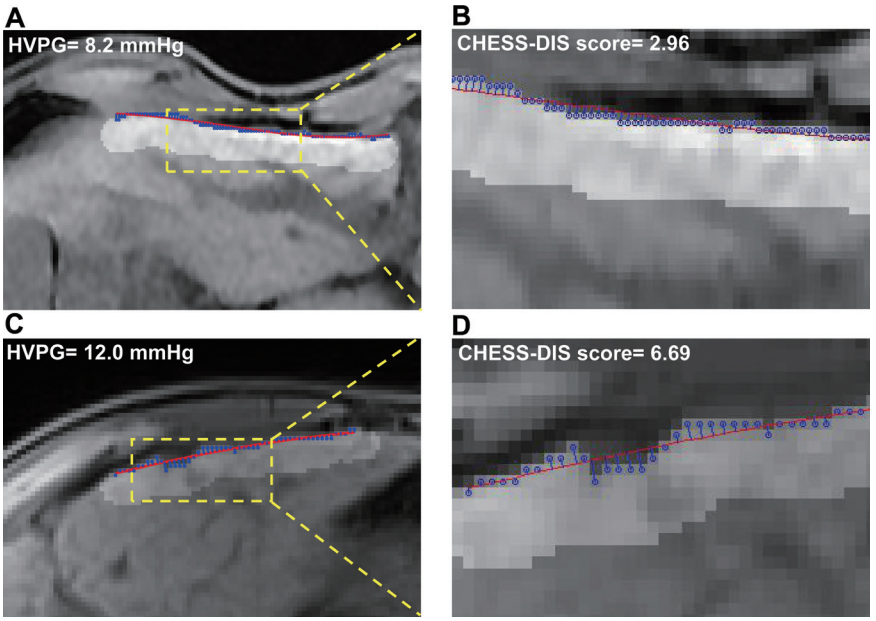

Fig. 2. Interpretation of the CHESS-DIS score. (A) MRI image of a patient without CSPH, with an HVPG value of 8.2 mmHg. (B) Magnified ROI of the patient in panel A for calculation of the CHESS-DIS score (blue lines), with the value of 2.96. (C) MRI image of a patient with CSPH, with an HVPG value of 12.0 mmHg. (D) Magnified ROI of the patient in panel C for calculation of the CHESS-DIS score (blue lines), with the value of 6.69. CSPH, clinically significant portal hypertension; HVPG, hepatic venous pressure gradient; ROI, region of interest.

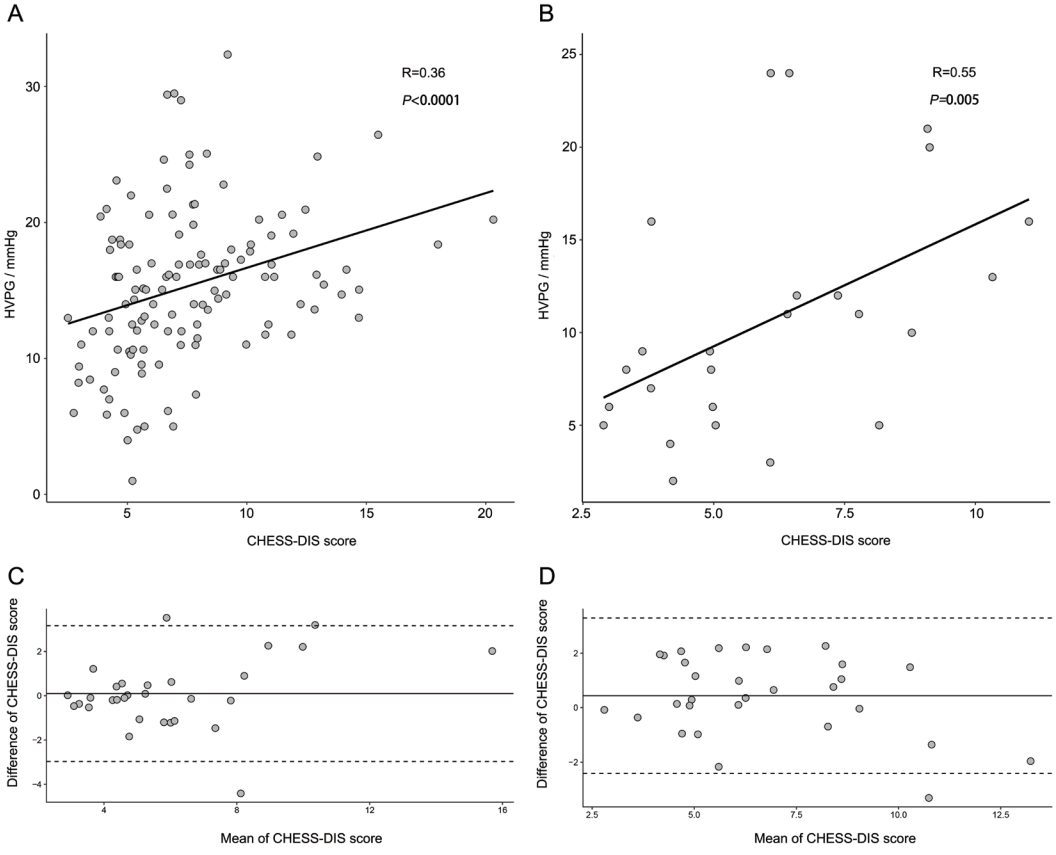

Fig. 3. Correlation between the CHESS-DIS score and HVPG. Scatterplot graph showing the correlation between CHESS-DIS score and HVPG in the training cohort (A) (*n*=124) and validation cohort (B) (*n*=25). Bland-Altman plots for assessment of inter- (C) (*n*=30) and intra- (D) (*n*=30) observer agreement. HVPG, hepatic venous pressure gradient.

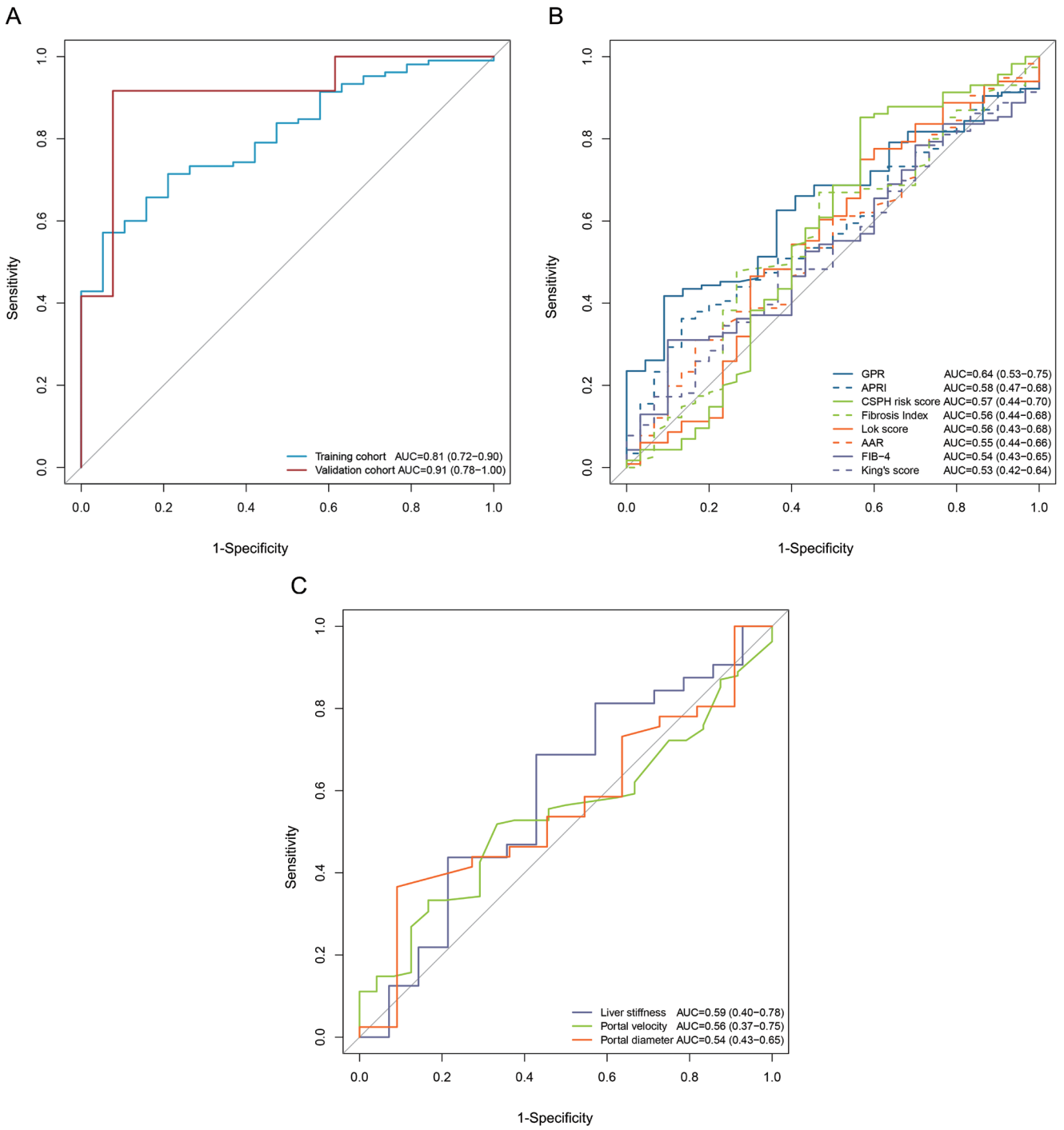

Fig. 4. Receiver operating characteristics curves. (A) CHESS-DIS score in the training and validation cohorts (*n*=124 and 25, respectively). Conventional serum-based (B) and image-based (C) non-invasive models for detection of CSPH. AUC, area under receiver operating characteristics curve; CSPH, clinically significant portal hypertension.

mune liver disease-related cirrhosis included in the present study, the accuracy and reliability of the CHESS-DIS score in patients with other etiologies should be further validated.

Compared to the study by De Vos *et al.*,[13] the correlation between MRI-based LSN score and HVPG, and diagnostic performance for CSPH, were both comparable. In the previous study,[13] the correlation coefficients between MRI-based LSN score and HVPG ranged from 0.43 to 0.51 and AUC values for detection of CSPH ranged between 0.801 and 0.908, depending on different sequences and phases of the MRI images.[13] In our study, with larger sample size and more centers involved, the correlation coefficient between CHESS-DIS score and HVPG was 0.55 in the validation cohort from

Table 2. Diagnostic performance of the CHESS-DIS score for CSPH

	Training cohort, *n*=124	Validation cohort, *n*=25
AUC (95% CI)	0.81 (0.72–0.90)	0.91 (0.78–1.00)
Cutoff	6.94	6.08
Specificity (95% CI)	0.95 (0.84–1.00)	0.92 (0.77–1.00)
Sensitivity (95% CI)	0.57 (0.48–0.67)	0.92 (0.75–1.00)
PPV (95% CI)	0.98 (0.95–1.00)	0.92 (0.77–1.00)
NPV (95% CI)	0.29 (0.24–0.34)	0.92 (0.79–1.00)
LR+ (95% CI)	10.86 (1.60–73.68)	11.92 (1.80–78.94)
LR- (95% CI)	0.45 (0.35–0.58)	0.09 (0.01–0.59)

AUC, area under the receiver operating characteristic curve; CI, confidential interval; CSPH, clinically significant portal hypertension; PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR-, negative likelihood ratio.

Table 3. Diagnostic performance of conventional non-invasive models for CSPH

	AUC (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	PPV (95% CI)	NPV (95% CI)
Serum-based models					
GPR, *n*=137	0.64 (0.53–0.75)	0.91 (0.77–1.00)	0.42 (0.33–0.51)	0.96 (0.90–1.00)	0.23 (0.20–0.27)
APRI, *n*=146	0.58 (0.47–0.68)	0.87 (0.73–0.97)	0.36 (0.28–0.44)	0.91 (0.83–0.98)	0.26 (0.22–0.30)
CSPH risk score, *n*=145	0.57 (0.44–0.70)	0.43 (0.27–0.60)	0.85 (0.78–0.91)	0.85 (0.81–0.90)	0.44 (0.29–0.59)
Fibrosis Index, *n*=145	0.56 (0.44–0.68)	0.73 (0.57–0.87)	0.48 (0.39–0.57)	0.88 (0.80–0.94)	0.27 (0.21–0.32)
Lok score, *n*=146	0.56 (0.43–0.68)	0.43 (0.27–0.60)	0.75 (0.67–0.83)	0.84 (0.79–0.88)	0.31 (0.20–0.42)
AAR, *n*=146	0.55 (0.44–0.66)	0.83 (0.70–0.93)	0.31 (0.23–0.39)	0.88 (0.79–0.96)	0.24 (0.20–0.27)
FIB-4, *n*=146	0.54 (0.44–0.65)	0.90 (0.77–1.00)	0.31 (0.23–0.40)	0.93 (0.84–1.00)	0.25 (0.22–0.28)
King's score, *n*=146	0.53 (0.42–0.64)	0.63 (0.47–0.80)	0.48 (0.39–0.57)	0.84 (0.76–0.91)	0.24 (0.18–0.30)
Imaging-based models					
Liver stiffness, *n*=46	0.59 (0.40–0.78)	0.57 (0.29–0.79)	0.69 (0.53–0.84)	0.79 (0.68–0.89)	0.44 (0.29–0.64)
Portal venous velocity, *n*=52	0.56 (0.37–0.75)	0.91 (0.73–1.00)	0.37 (0.22–0.54)	0.94 (0.80–1.00)	0.27 (0.22–0.34)
Portal diameter, *n*=132	0.54 (0.43–0.65)	0.67 (0.46–0.83)	0.52 (0.43–0.62)	0.88 (0.81–0.94)	0.23 (0.17–0.30)

CSPH, clinically significant portal hypertension; CI, confidential interval; AUC, area under the receiver operating characteristic curve; PPV, positive predictive value; NPV, negative predictive value; AAR, aspartate aminotransferase to alanine aminotransferase ratio; APRI, aspartate aminotransferase to platelet ratio index; FIB-4, fibrosis index based on 4 factors; GPR, gamma glutamyl trans-peptidase to platelet ratio.

two international centers. The AUC value of the CHESS-DIS score in the validation cohort was 0.91. Notably, the LR+ of the CHESS-DIS score for detection of CSPH in the training and validation cohorts were both higher than 10, indicating the excellent rule-in performance of the CHESS-DIS score. However, the sensitivity (57%) and NPV (28%) were low in the training cohort, mainly because of population bias, since 84.9% of patients in this cohort had CSPH. In the validation cohort, with a balanced population (CSPH ratio: 48%), the sensitivity, specificity, PPV, and NPV values were all higher than 90%. Regarding the noncongruence between the excellent diagnostic performance of the LSN-based score for CSPH and the relatively poor correlation between LSN and HVPG, we think that MRI-based LSN quantification is good classifier for the disease, CSPH; yet, its ability to monitor HVPG still needs to be improved.

Serum markers and traditional Doppler ultrasound have the advantages of low-cost and feasibility of repeated testing, both of which are important for monitoring disease progression and therapy response. However, so far, serum markers and Doppler ultrasound have shown limited diagnostic accuracy for portal hypertension and are not recommended by the current guidelines.[3,29] In the present study, we investigated eight serum-based non-invasive models, including AAR, APRI, CSPH risk score, FIB-4, Fibrosis Index, GPR, King's score, and Lok score,[16–23] and three imaging-based parameters, including liver stiffness, portal vein diameter and portal vein velocity. However, all of the above parameters showed poor diagnostic performance for identifying CSPH. The unsatisfactory accuracy of liver stiffness might due to the limited sample size (*n*=46) and varied range of etiology in our study. Thus, comparison between the proposed CHESS-DIS score and liver stiffness measurement should be further studied. As reported by Sartoris *et al*.,[10] the AUC values of the CT-based LSN score for detecting CSPH in patients with cirrhosis were 0.88 and 0.87 in

the training and validation cohorts, respectively. The diagnostic values of the CT-based LSN score and MRI-based LSN score seem to be comparable. This also has clinical value since MRI examination are performed in patients with cirrhosis. Also, compared with CT-based LSN, the CHESS-DIS score has the advantage of being free of radiation exposure, since it can be derived from noncontrast-enhanced MRI.

Our study has several limitations. First, despite having a balanced ratio of CSPH, the sample size in the validation cohort was relatively small, which might have compromised our results. Further studies on diagnostic performance of LSN quantification based on noncontrast-enhanced MRI images in well characterized patients with compensated cirrhosis are needed. Second, the prognostic value of the CHESS-DIS score, such as for predicting decompensated events and death, was not studied, which should be our next goal.

In conclusion, a non-invasive score based on noncontrast-enhanced MRI, namely the CHESS-DIS score, was developed and validated to correlate positively with the invasive HVPG value. The CHESS-DIS score could also be used to detect CSPH in patients with cirrhosis.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study concept and design (QX, JS), supervision of the study (QX, GR, JS), acquisition of data and technique support (GR, ÖN, HY, WJ, LX, LZ, AW, LD, ZC, LCC, LJ, LC, WG, CM, AC, AB, SA, EC, EU, SB, EZ, AÖÖ, LL, ZH, KN, XD, HR, WY, BY, GY), analysis and interpretation of data (LY, TT), and drafting of the manuscript (LY, TT). All authors revised the manuscript critically and approved the version to be published.

Data sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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