

CT-derived liver and spleen volume accurately diagnose clinically significant portal hypertension in patients with hepatocellular carcinoma

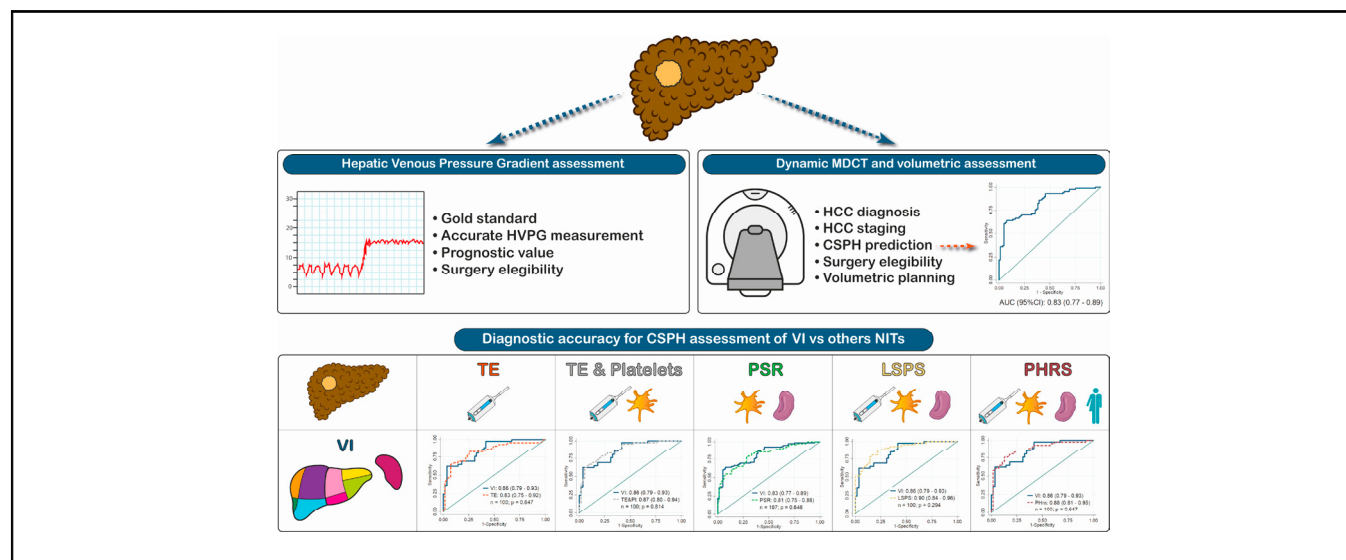
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Graphical abstract



Highlights

- The VI predicts the presence of CSPH and severe portal hypertension in patients with compensated cirrhosis and HCC.
- The accuracy of the VI for the prediction of CSPH is comparable to that of other widely used and validated NITs.
- Visceral volumetric assessment by MDCT is an accessible, affordable, easy-to-perform, and accurate test.
- A single imaging test can confirm the diagnosis/ stage of HCC and estimate the individual risk of different degrees of portal hypertension.

Impact and implications

An increase in portal pressure strongly impacts outcomes after surgery in patients with early hepatocellular carcinoma (HCC). Direct measurement through hepatic vein catheterization remains the reference standard for portal pressure assessment, but its invasiveness limits its application. Therefore, we evaluated the ability of CT scan-based liver and spleen volume measurements to predict portal hypertension in patients with HCC. Our results indicate that the newly described index, based on quantification of liver and spleen volume, accurately predicts portal hypertension. These results suggest that a single imaging test may be used to diagnose and stage HCC, while providing an accurate estimation of portal hypertension, thus helping to stratify surgical risks.

CT-derived liver and spleen volume accurately diagnose clinically significant portal hypertension in patients with hepatocellular carcinoma



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Background & Aims: Clinically significant portal hypertension (CSPH) is a landmark in the natural history of cirrhosis, influencing clinical decisions in patients with hepatocellular carcinoma (HCC). Previous small series suggested that splanchnic volume measurements may predict portal hypertension. We aimed to evaluate whether volumetry obtained by standard multidetector computerised tomography (MDCT) can predict CSPH in patients with HCC.

Methods: We included 175 patients with HCC, referred for hepatic venous pressure gradient (HVPG) evaluation, in whom contemporary MDCT was available. Liver volume, spleen volume (SV) and liver segmental volume ratio (LSVR: volume of the segments I-III/volume of the segments IV-VIII) were calculated semi-automatically from MDCT. Other non-invasive tests (NITs) were also employed.

Results: Volume parameters could be measured in almost 100% of cases with an excellent inter-observer agreement (intraclass correlation coefficient >0.950). SV and LSVR were independently associated with CSPH (HVPG ≥ 10 mmHg) and did not interact with aetiology. The volume Index (VI), calculated as the product of SV and LSVR, predicted CSPH (AUC 0.83; 95% CI 0.77–0.89). Similar results were observed in an external cohort (n = 23) (AUC 0.87; 95% CI 0.69–1.00). Setting a sensitivity and specificity of 98%, VI could have avoided 35.9% of HVPG measurements. The accuracy of VI was similar to that of other NITs. VI also accurately predicted HVPG greater than 12, 14, 16 and 18 mmHg (AUC 0.81 [95% CI 0.74–0.88], 0.84 [95% CI 0.77–0.91], 0.85 [95% CI 0.77–0.92] and 0.87 [95% CI 0.79–0.94], respectively).

Conclusions: Quantification of liver and spleen volumes by MDCT is a simple, accurate and reliable method of CSPH estimation in patients with compensated cirrhosis and HCC.

Impact and implications: An increase in portal pressure strongly impacts outcomes after surgery in patients with early hepatocellular carcinoma (HCC). Direct measurement through hepatic vein catheterization remains the reference standard for portal pressure assessment, but its invasiveness limits its application. Therefore, we evaluated the ability of CT scan-based liver and spleen volume measurements to predict portal hypertension in patients with HCC. Our results indicate that the newly described index, based on quantification of liver and spleen volume, accurately predicts portal hypertension. These results suggest that a single imaging test may be used to diagnose and stage HCC, while providing an accurate estimation of portal hypertension, thus helping to stratify surgical risks.

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Keywords: cirrhosis; hepatocellular carcinoma; portal hypertension; non-invasive test; cross-sectional imaging; predictive model; organ size.

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Introduction

The natural history of cirrhosis encompasses several stages associated with progressive histopathological, hemodynamic and morphologic alterations. Typically, the compensated stage is characterized by clinical stability and a good prognosis, with an estimated median survival of 12 years from diagnosis.¹ Clinically significant portal hypertension (CSPH), defined as an increase in the hepatic venous pressure gradient (HVPG) ≥ 10 mmHg, is the

key prognostic factor in compensated cirrhosis. CSPH is associated with an increased risk of decompensation and a greater probability of hepatocellular carcinoma (HCC) development.²⁻⁴ In the specific scenario of HCC, CSPH also affects the decision-making process, especially because surgery in patients with HVPG ≥ 10 mmHg has been associated with a greater risk of early decompensation and poorer outcomes.⁵

The gold standard procedure to assess CSPH is HVPG measurement through hepatic vein catheterization. However, this technique is invasive and not widely accessible in all centres. Not surprisingly, there is growing interest in the development of non-invasive tests (NITs) to estimate portal hypertension. Among them, the most widely used is transient elastography (TE). Either alone or in combination with platelet count, TE has shown high diagnostic accuracy for the detection of CSPH.⁶⁻⁸ Other NITs such as the PSR score (platelet count and spleen diameter by echography)⁹ and the LSPS score (TE, platelet count and spleen diameter by echography) have also shown high accuracy for predicting CSPH,¹⁰ albeit at the expense of higher complexity and reduced applicability.¹¹

Measurement of splanchnic organ volumes by conventional cross-sectional imaging is an easy and reliable technique available in most centres.¹² Current software is based on semi-automatic volume measurements, which improve reproducibility regardless of the operator's experience.^{13,14} Consequently, organ volume assessment by multidetector computerised tomography (MDCT) or magnetic resonance has become a validated and widely used method, especially for pre-operative evaluations in the context of liver tumour surgery and living donor liver transplantation.^{15,16}

Previous studies including a small number of patients suggested that spleen and liver volumes could reflect the presence and severity of portal hypertension.^{17,18} Moreover, some studies pointed to a role of liver and spleen volume as markers of progression in compensated chronic liver disease. The liver segmental volume ratio or LSVR (calculated as the volume of the liver segments I-III/volume of the segment IV-VIII), which represents the relative hypertrophy of left segments, has been considered as an imaging marker of cirrhosis and as a predictor of fibrosis severity.^{13,14} Moreover, a recent study has shown that the increase in LSVR during the compensated phase of cirrhosis is associated with CSPH, while the decrease in total liver volume (LV) and liver/spleen volume ratio (LV/SV) are associated with clinical decompensation.¹⁹ Therefore, liver and spleen volumetry may represent a novel approach to the non-invasive diagnosis of CSPH, but its role in this setting is still to be fully defined. We hypothesized that liver and spleen volumes may predict CSPH in patients with compensated cirrhosis and HCC. In these cases, a single cross-sectional dynamic imaging test that includes volumetric measurements would enable the diagnosis and staging of HCC as well as the evaluation of CSPH. On the grounds of this hypothesis, the main aims of our study were 1) to develop a predictive model for CSPH in patients with cirrhosis and HCC based on liver and spleen volumes assessed by MDCT; 2) to compare the diagnostic accuracy of this model with that of other reported NITs; and 3) to explore the ability of the model to predict other HVPG thresholds above 10 mmHg.

Patients and methods

Study design and data collection

In this cross-sectional study, we evaluated all consecutive patients with cirrhosis (diagnosed according to clinical and morphologic

criteria) and HCC who were referred to the Liver Unit of our institution for HVPG assessment between January 2012 and April 2019 (N = 203). In all cases, a recent imaging test was available (median interval [IQR] between HVPG and imaging test of 29 [15-58] days). The exclusion criteria were HCC occurring after liver transplantation (n = 4), previous liver resection (n = 8) or clinical decompensation⁷ at the time of HVPG measurement (n = 7). Four patients with imaging assessment by magnetic resonance instead of MDCT were also excluded. Finally, we did not include five patients who were receiving beta-blockers and had an HVPG value less than 10 mmHg in the analysis. After exclusions, a total of 175 patients were included in the study. The volumetric and hemodynamic assessment was fully conducted in 167 of them (Fig. 1). Importantly, 11 out of 30 patients (27%) with alcohol-related cirrhosis were in long-term abstinence at diagnosis. Likewise, 59 out of 108 patients (55%) with HCV-related cirrhosis had achieved a sustained virologic response to direct-acting antivirals (DAAs).

To assess the external validity of our findings, we included an independent external cohort, comprised of 23 consecutive patients referred to the Liver Unit of Hospital Universitario Ramón y Cajal (Madrid, Spain) for HVPG assessment between January 2017 and July 2020 who fulfilled the same inclusion and exclusion criteria.

Demographic, clinical and TE data were collected from electronic medical records. The validity of TE measurements was assessed as previously described.²⁰

Hemodynamic evaluation

After an overnight fast, a vascular introducer sheath was placed into the right internal jugular vein according to Seldinger's technique. Afterwards, a 7F balloon catheter was inserted into

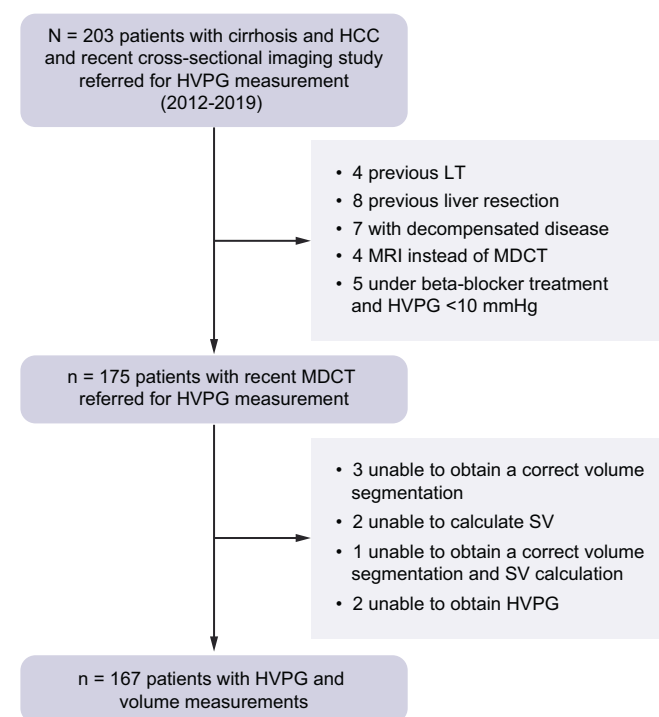


Fig. 1. Patient flowchart. HCC, hepatocellular carcinoma; HVPG, hepatic venous pressure gradient; LT, liver transplantation; MDCT, multidetector computerised tomography; SV, spleen volume.

the right hepatic vein to assess free and wedged hepatic venous pressures as previously described.²¹ The HVPG was calculated as the difference between the wedged and the free hepatic venous pressure. All hemodynamic measurements were recorded and performed at least in duplicate.

Calculation of non-invasive scores

NITs (PSR, LSPS and portal hypertension risk score) were calculated as previously described^{9,10,22} (see details in Table S1).

When necessary for the calculation of NITs, spleen diameter was obtained from the same MDCT used in volumetric assessment.

Liver and spleen volume evaluation

To measure splanchnic volumes, the portal venous phase was reconstructed with a 2 mm section thickness at 1 mm intervals. MDCT acquisition settings were based on patient size and study indication. Philips Intellispace V8 software was used for volumetric assessments as follows: after manual selection of anatomical reference points in the axial sections, this package provides automatized segmentation of the liver, including the Couinaud segments. When the initial segmentation is completed, organ margins are verified and adjusted by the operator when necessary. This technique has been extensively described elsewhere,^{13,23} providing reproducible measurements with high inter- and intra-reader agreement. All measurements were obtained by a radiologist (ER) with extensive expertise in abdominal imaging.

Total LV, and the volume of each liver segment and SV were expressed in cm³. The LSVR was calculated as previously described (ratio between the volume of the left lateral section and caudate [Couinaud segments I-III] and the volume of the right lobe and the medial left lobe [Couinaud segments IV-VIII]).^{13,14} Total LV and LSVR are surrogates of global liver atrophy and of the relative hypertrophy of left liver segments, respectively.

To assess the reproducibility of the method, the volumetric analysis was repeated in a random sample including 10% of the measured volumes by a second, independent, non-radiologist, operator (DR). Volume measurements in the validation cohort were calculated locally by an experienced radiologist (EC).

Statistical analysis

Quantitative variables were expressed as mean (SD) or median (range) as appropriate and categorical variables as n (%). The assumption of normality for the different volume measurements was tested by the construction of normal probability plots. Student's *t* test was used to compare continuous variables between groups, and the χ^2 or the Fisher exact tests were applied to analyse the relationship between categorical variables.

The intraclass correlation coefficient for absolute agreement (mixed effect model) was applied to assess the reproducibility of volume measurements obtained by the two different operators.

Univariate and multivariate logistic regression analyses were performed to identify the volumetric variables independently associated with the presence of CSPH. The volume parameters included were total LV, LSVR and SV. Age, sex and aetiology of liver disease were also included in the analysis. The backward stepwise method was used, setting $p < 0.05$ and $p > 0.10$ values as the criteria for the inclusion or exclusion of variables, respectively. To assess whether the aetiology of cirrhosis could modify the relationship between the volumetric parameters and the presence of CSPH, we assessed the significance of an interaction term composed of aetiology (viral, alcohol, metabolic dysfunction-associated fatty liver disease [MAFLD] and others) and the volume variables.

To evaluate internal validity, a bootstrapping analysis (bias-corrected confidence interval) generating 500 test datasets by random selection with replacement was used.

The calibration of the model was tested by the Hosmer-Lemeshow goodness-of-fit test, plotting the agreement between the predicted and observed probabilities of CSPH.

The discriminative ability of the predictive model was assessed by receiver-operating characteristic analysis. The AUC of the new index was compared with those obtained for other NITs by the DeLong test.

All the reported *p* values were two-sided; the type 1 error rate was set at 0.05. The analyses were performed with the software Stata version 17.0.

Ethical considerations

The study was approved by the local ethics Committee of Hospital General Universitario Gregorio Marañón (dated March 24, 2014).

Results

Patient characteristics and reproducibility of volume measurements

A total of 175 patients with cirrhosis and HCC referred for HVPG evaluation were included in the study (Fig. 1). The majority of patients had HCC within the Milan criteria (mostly unique tumours less than 5 cm) and no previous treatment. HVPG was successfully measured in 173 patients (98.9%). Ninety patients (52%) had CSPH.

Volume assessment including LV, LSVR and SV could be performed in nearly the whole cohort (100%, 97.7% and 98.3% of patients, respectively).

Baseline demographic data and characteristics of liver disease in the derivation cohort are summarized in Table 1.

Agreement between the two independent operators for the volume measurements was excellent (intraclass correlation coefficients of 0.999 [95% CI 0.997–0.999], 0.997 [95% CI, 0.984–0.999] and 0.976 [95% CI, 0.906–0.994] for total LV, SV and LSVR, respectively).

Development and diagnostic performance of a volume-based index for the prediction of CSPH

The prevalence of CSPH was 52%, similar to that previously reported.¹¹ Univariate and multivariate analyses identified that only LSVR and SV, but no other variables such as LV, age, sex or aetiology of liver disease, were independently associated with CSPH. Interactions between aetiology (viral, alcohol-related, MAFLD or others), and the volume variables were not significant, suggesting that the cause of liver disease did not modify the relationship between volume-derived parameters and CSPH.

According to these results, we defined a new volume index (VI; cm³) obtained from the product of both volume parameters ($volume\ index = LSVR\ (segments\ I-III/IV-VIII) * SV$). This approach, previously described for developing other NITs,¹⁰ maximizes the predictive effect of each parameter and simplifies the calculation of target thresholds with clinical applications. The capacity of VI to identify CSPH in the derivation cohort was high (AUC 0.83, 95% CI 0.77–0.89) (Fig. 2A), and importantly, greater than that observed for LSVR or SV separately (AUC [95% CI]: 0.83 [0.77–0.89] vs. 0.72 [0.64–0.80], $p = 0.001$, and 0.83 [0.77–0.89] vs. 0.79 [0.72–0.86], $p = 0.143$, respectively). Bootstrapping

Table 1. Characteristics of the derivation cohort (n = 175).

Characteristic	
Demographics	
Age (years)	62.24 (9.98)
Sex (male)	145/175 (82.86)
Aetiology of liver disease	
Viral	124/175 (70.86)
HCV	99/124 (79.84)
HBV	16/124 (12.90)
HCV + HBV	9/124 (7.26)
Alcohol-related	30/175 (17.14)
MAFLD	14/175 (8.00)
Other	7/175 (4.00)
Milan criteria	
1 tumour <5 cm	101/175 (57.71)
3 tumours <3 cm	35/175 (20.00)
Exceeding Milan criteria	39/175 (22.29)
Oesophageal varices [n = 146]	
No varices	76/146 (52.05)
Small	46/146 (31.51)
Large	24/146 (16.44)
Treatment with beta-blockers	32/175 (18.29)
Liver stiffness (kPa) (median [IQR])	13.9 [9.1-26.3]
Laboratory parameters	
Platelets ($10^3/\mu\text{l}$)	130.14 (56.06)
Bilirubin (mg/dl)	0.86 (0.53)
INR	1.14 (0.36)
Albumin (g/dl)	4.04 (0.47)
Haemodynamics	
HVPG (mmHg) [n = 173]	10.65 (5.11)
CSPH (yes)	90/173 (52.02)
Volumetric assessment by MDCT	
Total liver volume (cm^3)	1,607.02 (407.89)
LSVR	0.44 (0.23)
Spleen volume (cm^3)	519.38 (407.89)

Data are expressed as n/N (%), mean (SD) or median [IQR]. CSPH, clinically significant portal hypertension; HVPG, hepatic venous pressure gradient; INR, international normalized ratio; LSVR, liver segmental volume ratio (volume of segments I-III/segments IV-VIII); MAFLD, metabolic dysfunction-associated fatty liver disease; MDCT, multidetector computerised tomography.

analysis confirmed these results (bootstrap AUC 0.83; 95% CI 0.77–0.90), indicating appropriate internal validity.

The diagnostic performances of different VI cut-off values are shown in Table 2. When the sensitivity and specificity were set at 98%, the use of VI could have avoided 35.9% of invasive HVPG measurements (Fig. 3), accepting false-negative and false-positive proportions of only 2.3% and 2.5%, respectively.

No significant differences were found between the expected and observed probabilities in the different quintiles of risk ($p = 0.541$), indicating an appropriate calibration of the model. The calibration plot clearly showed that the reliability of the model for assessing individual absolute risk improves for probabilities of CSPH above 0.2 (Fig. 2B).

A nomogram for individual risk prediction of CSPH according to VI is shown in Fig. S1.

Comparison of the diagnostic accuracy of VI with that of other NITs

One hundred patients (59.9% of the overall series) had a coincident TE exam (median timeframe between the diagnostic procedures of 29 days [IQR 15–76]), allowing for calculation of NITs that include TE in their equations. In contrast, we were able to calculate the PSR and compare it with the VI in the whole cohort ($n = 167$). We did not find significant differences between the diagnostic accuracy of VI and the other predictive indexes (Fig. 4), suggesting that VI predicts CSPH similarly to the different validated NITs.

Finally, we compared the diagnostic performance of the VI with the recently published Baveno VII criteria to rule in (TE ≥ 25 kPa) and rule out CSPH (TE ≤ 15 kPa + platelet count $\geq 150 \times 10^9/L$).⁷ Using VI cut-off values of 194 and 111 cm^3 , could have saved a greater proportion of invasive studies compared to the Baveno VII criteria (59.5% vs. 42.2%), with comparable negative and positive predictive values to rule out and rule in CSPH, respectively (NPV 88.4% vs. 88.5%; PPV 90.3 vs. 84.6%) (Table S2).

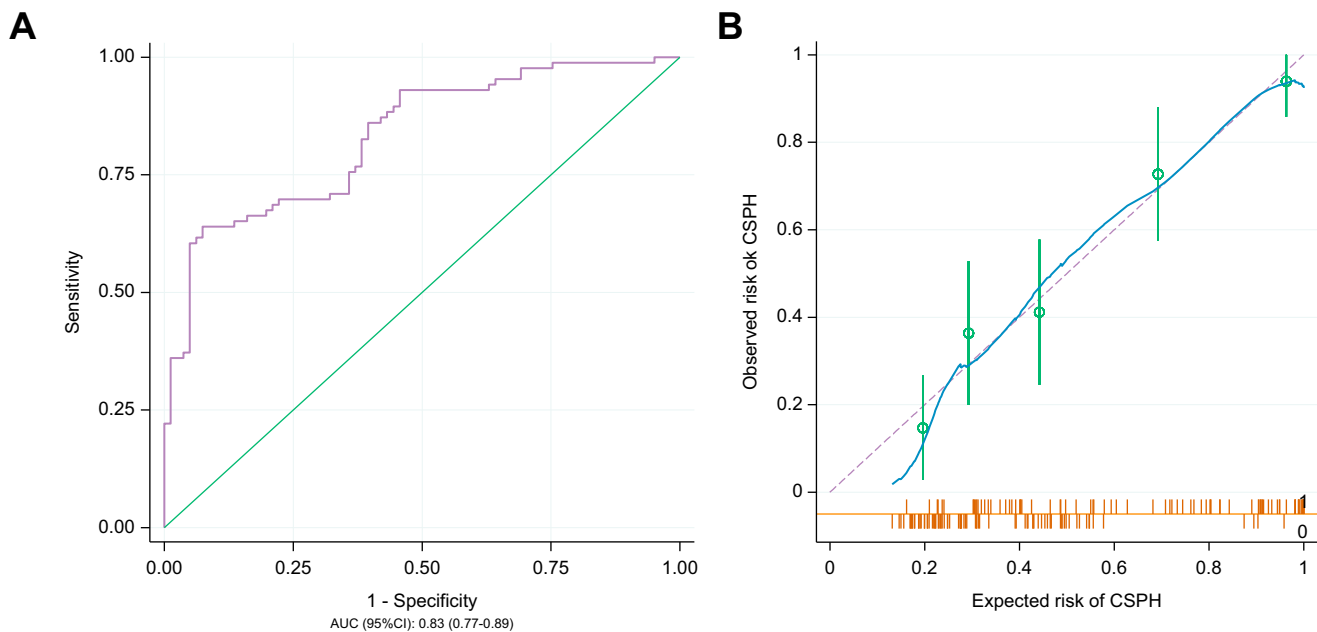


Fig. 2. Prediction of CSPH using the volume index (n = 167). (A) ROC curve and (B) calibration plot (Hosmer-Lemeshow goodness-of-fit test) for the prediction of CSPH using the volume index (n = 167). CSPH, clinically significant portal hypertension.

Table 2. Diagnostic performance of the Volume Index for the presence of CSPH at different sensitivity and specificity cut-offs and number of avoidable catheterizations in the derivation cohort (n = 167).

Sensitivity and specificity	Cut-off value (cm ³)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	FPP (1-Sp) (%)	FNP (1-Se) (%)	CSPH ruled-out (n)	CSPH ruled-in (n)	% of avoidable procedures*
98%	79	97.7	30.9	60.0	92.6	69.1	2.3	27	33	35.9%
	359	36.1	97.5	93.9	59.0	2.5	64.0			
95%	83	95.4	35.8	61.2	87.9	64.2	4.7	33	53	51.5%
	213	57.0	95.1	92.5	67.4	4.9	43.0			
90%	111	91.9	54.3	68.1	86.3	45.7	8.1	51	62	67.7%
	194	64.0	91.4	88.7	70.5	8.6	36.1			

CSPH, clinically significant portal hypertension; FNP, false-negative proportion; FPP, false-positive proportion; NPV, negative predictive value; PPV, positive predictive value; Se, sensitivity; Sp, Specificity. *(Ruled-out + ruled-in cases)/total cases.

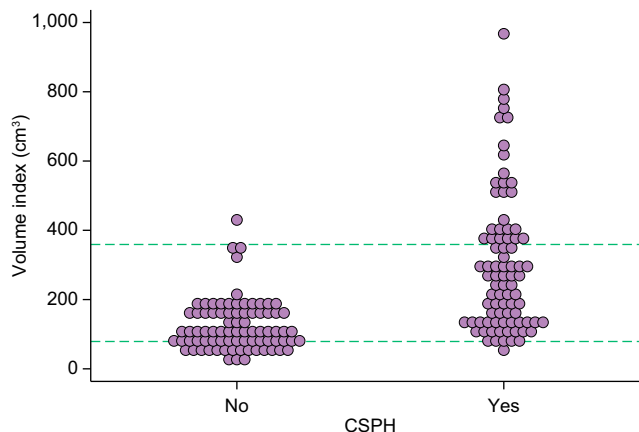


Fig. 3. Distribution of volume index according to the presence of CSPH (n = 167). Cut-off points of volume index (79.14 cc. and 359.48 cc) for sensitivity and specificity = 98%. CSPH, clinically significant portal hypertension.

External validation of VI for the prediction of CSPH

Overall, the external validation cohort (23 patients) was comparable to the derivation cohort (Table S3). Of note, in the validation cohort, a higher proportion of patients had a single tumour <5 cm.

The AUC of the VI for the prediction of CSPH in this cohort was 0.87 (95% CI 0.69–1.00), reinforcing its discriminative ability within a similar patient cohort (Fig. S2).

Diagnostic accuracy of VI for the prediction of different HVPG thresholds

A total of 64 (36.99%), 49 (28.32%), 30 (17.34%) and 16 (9.25%) patients had HVPG values greater than 12, 14, 16 and 18 mmHg, respectively.

The VI exhibited a solid discriminative ability across the entire spectrum of values explored: AUC 0.81 (95% CI 0.74–0.88), 0.84 (95% CI 0.77–0.91), 0.85 (95% CI 0.77–0.92) and 0.87 (95% CI 0.79–0.94) for the prediction of HVPG greater than 12, 14, 16 and 18 mmHg, respectively (Fig. S3).

Sensitivity analyses of VI performance for CSPH prediction in specific subgroups

Considering the variety and complexity of the target population, we performed a sensitivity analysis to explore the performance of the model in specific subgroups of patients: 1) patients without beta-blocker treatment; 2) patients without varices; and 3) patients with a BMI >30 kg/m², as a surrogate of MAFLD (with or without HCV). In all cases, the VI showed a similar diagnostic performance for the prediction of both CSPH (Fig. S4) and other HVPG thresholds (12, 14, 16 and 18 mmHg) (Table S4).

Discussion

CSPH is the main prognostic factor in patients with compensated cirrhosis, conferring a higher risk of clinical decompensation, HCC development and death. Moreover, the diagnosis of CSPH or higher thresholds of portal pressure strongly impacts the decision-making process, particularly in patients with potentially resectable HCC. HVPG measurement through hepatic vein catheterization is still the gold standard method to assess the presence of portal hypertension. However, the use of NITs has become an

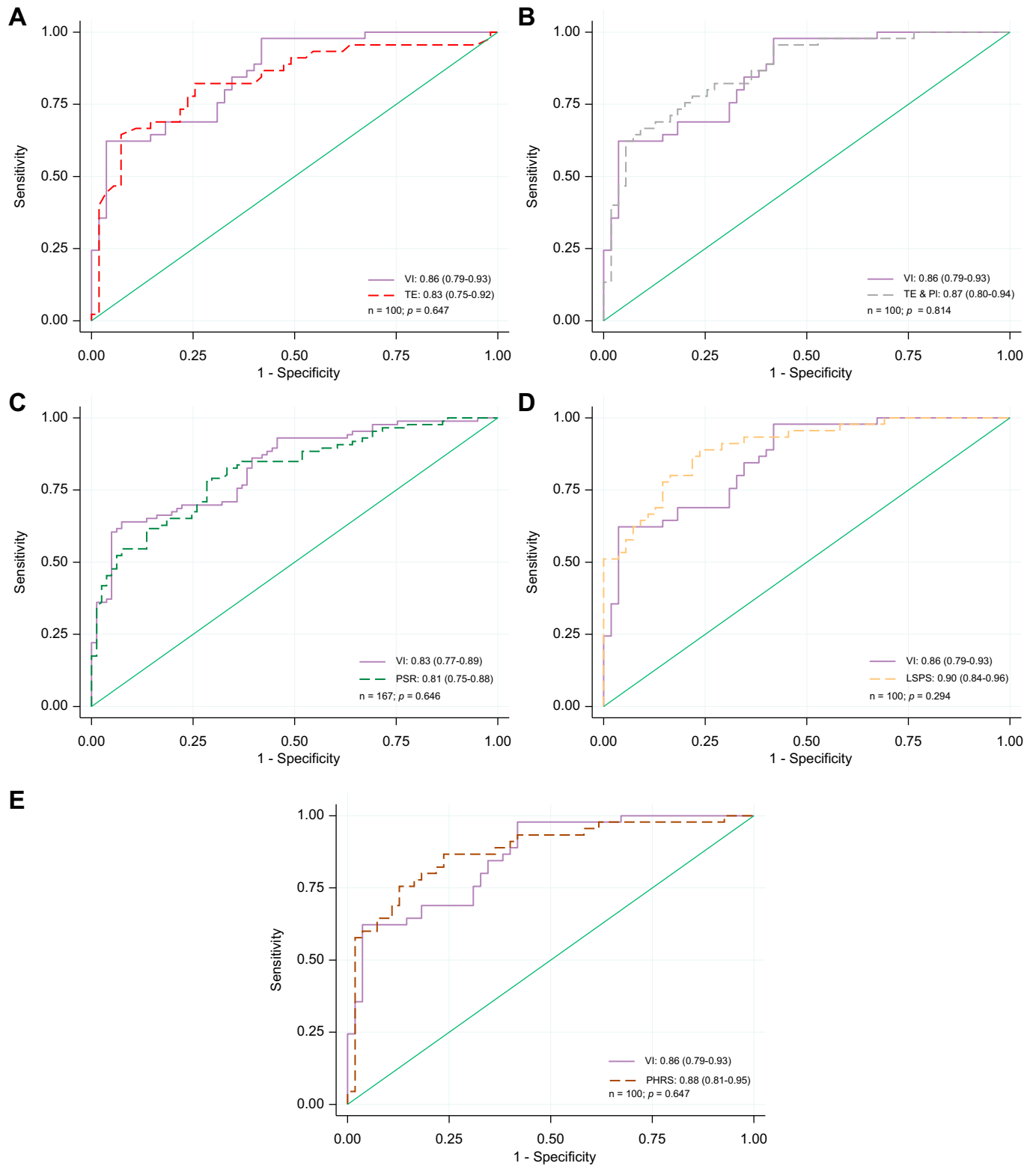


Fig. 4. Comparison of the diagnostic accuracy for clinically significant portal hypertension of the volume index and other non-invasive measures. Diagnostic accuracy (AUC [95% CI]) of the volume index and (A) transient elastography, (B) transient elastography and platelets, (C) PSR, (D) LSPS and (E) PHRS. (DeLong test for comparing AUCs). LSPS, liver stiffness-to-spleen platelet score; PHRS, portal hypertension risk score; PI, platelets; PSR, platelet-to-spleen ratio; TE, transient elastography; VI, volume index.

acceptable benchmark and widely used strategy to diagnose CSPH in clinical practice. Previous studies have suggested that visceral volumetry (liver and spleen) may be a surrogate marker of advanced liver disease and its complications.^{17,24} Nevertheless, the role of liver and spleen volumetry in the non-invasive diagnosis of CSPH in patients with chronic advanced liver disease, especially those with HCC, is not well-known.

Our study shows that liver and spleen volume assessment by MDCT is a reliable method to predict CSPH in patients with compensated cirrhosis and HCC. An important novelty introduced by our study is the use of regional intrahepatic volume changes as a predictor of CSPH. The VI (or volume index) includes the LSVR, a surrogate of the relative hypertrophy of left segments. LSVR has previously been shown to be related to the progression of liver disease, correlating with the stage of fibrosis.¹⁴ Although the mechanisms that drive the typical regional variations in chronic liver disease are not fully understood, it is reasonable to hypothesize that they are related to the severity of portal hypertension in the compensated phase of the disease. Therefore, these novel findings suggest that the VI is a robust and accurate tool for the prediction of CSPH.

Assessment of liver stiffness by TE is the non-invasive technique with the best proven accuracy for CSPH diagnosis in patients with compensated disease (reported AUCs up to 0.88).²² Such predictive capacity of TE further improved when combined with other parameters, such as platelet count or spleen diameter. In our series, the VI showed a similar non-inferior diagnostic accuracy to that observed for the most commonly used NITs. Notably, only one diagnostic test is required to calculate the VI, increasing its applicability compared to the other scores. Furthermore, it is well described that TE variability can reach rates up to 20%–30%,²⁵ even with experienced operators, which represents a major flaw for those values within the indeterminate 'grey zone'. By contrast, our study shows that liver and spleen volumetric assessment has excellent reproducibility across operators regardless of experience, confirming observations from other studies in the literature.^{14,15} Some previously reported models developed in small cohorts that include liver and spleen volumetric parameters, have been shown to have a high accuracy to predict different thresholds of portal hypertension.^{18,24} However, these models incorporated other variables such as endoscopic findings (*i.e.* oesophageal varices), radiological features unrelated to visceral volume (*i.e.* ascites) and laboratory determinations. This approach could help to improve the performance of the model, albeit at the expense of increasing the complexity and overestimating the diagnostic accuracy of the volumetric parameters when including findings typically present in patients with either clinically significant or severe portal hypertension.

The inclusion of additional novel characteristics increases the value of our predictive volumetric model. The data used to generate the VI were drawn from a large cohort of patients from a reference centre in the management of liver disease and HCC. The information collected was obtained in the setting of clinical practice and included a comprehensive set of diagnostic tests, all available in most of the patients, to generate the new index and calculate the most used NITs. Additionally, patients that comprised our cohort were consecutively included as opposed to previous studies based on volumetric assessments that included only patients with oesophageal varices.^{17,24} Comparatively, our approach granted an unbiased pre-test probability consistent with previous data (50%–70% prevalence of CSPH in compensated cirrhosis) and minimized the risk of selection bias.^{5,26}

Finally, we did not find statistically significant differences between the expected and observed probabilities in the different risk groups, and the performance of the model remained unchanged both in the bootstrapping analysis and when applied to an external validation cohort. Therefore, the model is adequately calibrated and holds internal and external validity that strengthen our results.

Several relevant findings arise from our study. The VI predicts the presence of CSPH in patients with compensated cirrhosis and HCC, and its accuracy is comparable to that of other widely used and validated NITs. In addition, the VI is reliable for predicting different HVPG thresholds above 10 mmHg, allowing for a continuous estimation of the severity of portal hypertension. This is of special relevance in patients with HCC who are candidates for surgery. The improvement in surgical techniques, along with careful patient selection, increases the safety margins of performing surgery in some patients with HCC and CSPH.²⁶ In line with the previously mentioned results, the model showed adequate calibration, suggesting that it is a reliable tool for continuous risk assessment in individual patients. It is important to note that the reliability of the model to assess the individual absolute risk improves for probabilities of CSPH above 0.2. A plausible explanation for this finding is that patients at earlier stages present fewer morphological changes, accounting for improved model performance to confirm rather than exclude the presence of CSPH.

Considering that visceral volumes may be influenced by the underlying aetiology,²⁷ we specifically addressed this issue by incorporating an interaction term including the VI and aetiology in the logistic regression model. The variables that independently predicted CSPH remained unchanged, suggesting that the cause of the liver disease does not influence the relationship between volumetric changes and outcome.

Therefore, a single imaging test provides the necessary information to 1) confirm the HCC diagnosis; 2) assess its stage; and 3) estimate the individual risk of different degrees of portal hypertension, identifying patients in whom invasive HVPG assessment may be warranted. The VI can be calculated in an accurate, fast, easy and reproducible manner with software to quantify liver and spleen volume by MDCT, available in most centres. Moreover, it is a reasonably priced examination that can be performed from an imaging test indicated for other reasons, without a significant increase in the consumption of technologic and human resources. This relatively simple processing technique provides valuable prognostic information that could be systematically incorporated into radiological reports. Validation of these results in other populations may assimilate an additional useful tool into clinical practice that improves the decision-making process and prevents unnecessary invasive procedures.

Our study has some limitations that deserve further discussion. A proportion of the patients included in the derivation cohort were under treatment with beta-blockers or had oesophageal varices. However, these patients are commonly seen in clinical practice. Consequently, not considering this subgroup for the analysis would have excluded cases with severe portal hypertension, impairing the implementation of the model in the full spectrum of patients with HCC and compensated cirrhosis. Interestingly, the VI preserved its diagnostic accuracy for the prediction of CSPH in the external cohort, in which none of the patients were under beta-blocker treatment. Furthermore, sensitivity analysis excluding patients with beta-blockers and patients with oesophageal varices, rendered similar results.

The aetiological distribution of liver disease in our series closely mirrors the current epidemiology of HCC in Europe, with 8% of cases secondary to MAFLD.²⁸ However, epidemiological models point to a significant increase in the disease burden over time associated with MAFLD, including HCC.²⁹ This means it will be necessary to specifically validate our model in patients with MAFLD-related liver disease. To partially overcome this matter, we performed a sensitivity analysis restricted to patients with a BMI >30 kg/m², as a possible surrogate diagnosis of MAFLD. The VI accurately predicted CSPH in this subset of patients. Concerning HCV-related cirrhosis, the successful implementation of DAAs has been shown to improve portal hypertension.³⁰ In our cohort, only 55% of cases had received specific therapy at the moment of diagnosis; thus, it is conceivable that future patients with HCC treated with DAAs will present with different HVPG values compared to our series. Considering that changes in HVPG after DAA therapy occur several weeks after sustained virological response,³⁰ this issue does not undermine our results since therapeutic decisions in the context of HCC must be made quickly. Whether our results are applicable in recompensated patients after DAA treatment, when HVPG changes are well established, remains to be elucidated.

Abbreviations

CSPH, clinically significant portal hypertension; DAAs, direct-acting antiviral agents; HVPG, hepatic venous pressure gradient; HCC, hepatocellular carcinoma; LSVR, liver segmental volume; LSPS, liver stiffness-spleen size-to-platelet ratio score; LV, liver volume; LV/SV, liver/spleen volume ratio; MAFLD, metabolic dysfunction-associated fatty liver disease; MDCT, multidetector computerised tomography; NITs, non-invasive tests; PSR, platelet count to spleen diameter ratio; SV, spleen volume; TE, transient elastography; VI, volume index.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Conceptualization: Mario Romero-Cristóbal, Ana Clemente-Sánchez, Rafael Bañares, Diego Rincón. Acquisition of data: Mario Romero-Cristóbal, Ana Clemente-Sánchez, Enrique Ramón, Olga Ortega-Lobete, Elena Velilla-Aparicio, Ana-María Matilla, Luis Ibáñez-Samaniego, María-Vega Catalina, Luis Téllez, Agustín Albillos, Elena Canales, María-Magdalena Salcedo, Rafael Bañares, Diego Rincón. Formal analysis and methodology: Mario Romero-Cristóbal, Ana Clemente-Sánchez, Rafael Bañares, Diego Rincón. Project administration: Rafael Bañares, Diego Rincón. Writing - original draft: Mario Romero-Cristóbal, Ana Clemente-Sánchez, Rafael Bañares, Diego Rincón. Writing - review and editing: Mario Romero-Cristóbal, Ana Clemente-Sánchez, Rafael Bañares, Diego Rincón.

Data availability statement

All data, materials and methods in this study can be made available from the corresponding author upon reasonable request.

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Another potential limitation is the relatively low number of patients included in the validation cohort. Although the discriminative ability of our predictive model remained similar, this observation needs further validation in larger well-characterized cohorts.

In conclusion, our results show that the quantification of liver and spleen volumes by MDCT is an accessible, affordable, easy-to-perform, accurate and reliable method to estimate the degree of portal hypertension in patients with compensated cirrhosis and HCC. In this clinical context, where an MDCT is mandatory for the diagnosis and staging of liver cancer, a simultaneous volumetric assessment may help to personalize treatment decisions based on the individual risk of CSPH and avoid unnecessary invasive procedures.

The potential utility of this tool for the entire spectrum of patients with liver disease rather than just compensated patients with HCC warrants further investigation. Corroborating these results in large populations where all the stages and aetiologies are well-represented might have a significant impact on the management of patients with liver disease in clinical practice.

Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhepr.2022.100645>.

References

Author names in bold designate shared co-first authorship

- [1] 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.
- [2] Sanchez Conde M, Pérez-Latorre L, Rincón D, Miralles P, Catalina M, López J, et al. Effect of eradication of HCV on hepatic venous pressure gradient in HIV-infected patients with compensated HCV-related cirrhosis. *J Acquir Immune Defic Syndr* 2015;69:142–144.
- [3] Ripoll C, Bañares R, Rincón D, Catalina M-V, Lo Iacono O, Salcedo M, et al. Influence of hepatic venous pressure gradient on the prediction of survival of patients with cirrhosis in the MELD Era. *Hepatology* 2005;42:793–801.
- [4] Ripoll C, Groszmann RJ, Garcia-tsao G, Bosch J, Grace N, Burroughs A, et al. Hepatic venous pressure gradient predicts development of hepatocellular carcinoma independently of severity of cirrhosis. *J Hepatol* 2009;50:923–928.
- [5] Bruix J, Castells A, Bosch J, Feu F, Fuster J, Garcia-Pagan JC, et al. Surgical resection of hepatocellular carcinoma in cirrhotic patients: prognostic value of preoperative portal pressure. *Gastroenterology* 1996;111:1018–1022.
- [6] Groszmann R, Bosch J, Grace N, Conn H, Garcia-Tsao G, Navasa M, et al. Hemodynamic events in a prospective randomized trial of propranolol versus placebo in the prevention of a first variceal hemorrhage. *Gastroenterology* 1990;99:1401–1407.
- [7] Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C, Abraldes JG, et al. Baveno VII – renewing consensus in portal hypertension. *J Hepatol* 2022;76:959–974.
- [8] Vizzutti F, Arena U, Romanelli RG, Rega L, Foschi M, Colagrande S, et al. Liver stiffness measurement predicts severe portal hypertension in patients with HCV-related cirrhosis. *Hepatology* 2007;45:1290–1297.
- [9] Giannini EG, Zaman A, Kreil A, Floreani A, Dulbecco P, Testa E, et al. Platelet count/spleen diameter ratio for the noninvasive diagnosis of esophageal varices: results of a multicenter, prospective, validation study. *Am J Gastroenterol* 2006;101:2511–2519.
- [10] Kim BK, Han KH, Park JY, Ahn SH, Kim JK, Paik YH, et al. A liver stiffness measurement-based, noninvasive prediction model for high-risk esophageal varices in B-viral liver cirrhosis. *Am J Gastroenterol* 2010;105:1382–1390.

- [11] Abralde J, Bureau C, Stefanescu H, Augustin S, Ney M, Blasco H, et al. Noninvasive tools and risk of clinically significant portal hypertension and varices in compensated cirrhosis: the “Anticipate” study. *Heptology* 2016;64:2173–2184.
- [12] Schiano TD, Bodian C, Schwartz ME, Glajchen N, Min A.D. Accuracy and significance of computed tomographic scan assessment of hepatic volume in patients undergoing liver transplantation. *Transplantation* 2000;69:545–550.
- [13] Furusato Hunt OM, Lubner MG, Ziemlewicz TJ, Muñoz del Rio A, Pickhardt PJ. The liver segmental volume ratio for noninvasive detection of cirrhosis. *J Comput Assist Tomogr* 2016;40:478–484.
- [14] Pickhardt PJ, Malecki K, Hunt OF, Beaumont C, Kloke J, Ziemlewicz TJ, et al. Hepatosplenic volumetric assessment at MDCT for staging liver fibrosis. *Eur Radiol* 2017;27:3060–3068.
- [15] Kishi Y, Abdalla EK, Chun YS, Zorzi D, Madoff DC, Wallace MJ, et al. Three hundred and one consecutive extended right hepatectomies. *Ann Surg* 2009;250:540–548.
- [16] Chen Y, Cheng Y, De Villa V, Wang C, Lin C, Huang T. Evaluation of liver living donors. *Transplantation* 2003;75:16–19.
- [17] **Yan S, Wu H**, Wang G, Chen Y, Zhang C, 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.
- [18] 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.
- [19] **Romero-Cristóbal M, Clemente-Sánchez A**, Peligros MI, Ramón E, Matilla AM, Colón A, et al. Liver and spleen volumes are associated with prognosis of compensated and decompensated cirrhosis and parallel its natural history. *United Eur Gastroenterol J* 2022;10:805–816.
- [20] Castera L, Forn X, Alberti A. Non-invasive evaluation of liver fibrosis using transient elastography. *J Hepatol* 2008;48:835–847.
- [21] Lebrec D, Hillon P, Muñoz C, Goldfarb G, Nouel O, Benhamou JP. The effect of propranolol on portal hypertension in patients with cirrhosis: a hemodynamic study. *Hepatology* 1982;2:523S–527S.
- [22] Berzigotti A, Seijo S, Arena U, Abralde JG, Vizzutti F, Carlos J, et al. Elastography, spleen size, and platelet count portal hypertension in patients with compensated cirrhosis. *Gastroenterology* 2013;144:102–111.e1.
- [23] Yoneyama T, Asonuma K, Okajima H, Lee K, Yamamoto H, Takeichi T, et al. Coefficient factor for graft weight estimation from preoperative computed tomography volumetry in living donor liver transplantation. *Liver Transpl* 2011;17:369–372.
- [24] **Tseng Y, Ma L**, Luo T, Zeng X, Li NA. Non-invasive predictive model for hepatic venous pressure gradient based on a 3-dimensional computed tomography volume rendering technology. *Exp Ther Med* 2018;15:3329–3335.
- [25] Nascimbeni F, Lebray P, Fedchuk L, Oliveira CP, Alvares-da-Silva MR, Varault A, et al. Significant variations in elastometry measurements made within short-term in patients with chronic liver diseases. *Clin Gastroenterol Hepatol* 2015;13:763–771.e6.
- [26] Cucchetti A, Cescon M, Golfieri R, Piscaglia F, Renzulli M, Neri F, et al. Hepatic venous pressure gradient in the preoperative assessment of patients with resectable hepatocellular carcinoma. *J Hepatol* 2016;64:79–86.
- [27] Kim I, Jang Y-J, Ryeom H, Lee SM, Lee HJ, Kim GC, et al. Variation in hepatic segmental volume distribution according to different causes of liver cirrhosis: CT volumetric evaluation. *J Comput Assist Tomogr* 2012;36:220–225.
- [28] Llovet JM, Kelley RK, Villanueva A, Singal AG, Pikarsky E, Roayaie S, et al. Hepatocellular carcinoma. *Nat Rev Dis Prim* 2021;7:6.
- [29] Estes C, Anstee QM, Arias-Loste MT, Bantel H, Bellentani S, Caballeria J, et al. Modeling NAFLD disease burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016–2030. *J Hepatol* 2018;69:896–904.
- [30] **Lens S, Baiges A**, Alvarado-Tapias E, Llop E, Martinez J, Fortea JI, et al. Clinical outcome and hemodynamic changes following HCV eradication with oral antiviral therapy in patients with clinically significant portal hypertension. *J Hepatol* 2020;73:1415–1424.