



Liver and spleen volumes are associated with prognosis of compensated and decompensated cirrhosis and parallel its natural history

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Abstract

Objective: Cirrhosis is characterized by the complex interplay among biological, histological and haemodynamic events. Liver and spleen remodelling occur throughout its natural history, but the prognostic role of these volumetric changes is unclear. We evaluated the relationship between volumetric changes assessed by multidetector computerised tomography (MDCT) and landmark features of cirrhosis.

Methods: We included consecutive cirrhotic patients who underwent liver transplantation (LT) or hepatocellular carcinoma (HCC) resection in whom dynamic MDCT was available. Different volumetric indices were calculated. Fibrosis was evaluated by the collagen proportional area and Laennec sub-stages. Correlation and logistic regression analysis were performed to explore associations of volumetric indexes and fibrosis with key prognostic features across the clinical stages of cirrhosis.

Results: 185 patients were included (146 LT; 39 HCC); the predominant aetiology was viral hepatitis (51.35%); 65.9% had decompensated disease and 85.08% clinically significant portal hypertension (CSPH). The standardised liver volume and liver-spleen volume ratio negatively correlated with Model for End-stage Liver Disease (MELD), albumin and hepatic venous pressure gradient (HVPG) and were significantly lower in decompensated patients. The liver segmental volume ratio (segments I–III/segments IV–VIII) best captured the characteristic features of the compensated phase, showing a positive correlation with HVPG and a good discrimination between patients with and without CSPH and varices. Volumetric changes and fibrosis severity were independently associated with key prognostic events, with no association between these two parameters.

Mario Romero-Cristóbal and Ana Clemente-Sánchez share first authorship.

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Conclusions: Liver and spleen volumetric indices evolve differently along the natural history of cirrhosis and are associated with key prognostic factors in each phase, regardless of fibrosis severity and portal hypertension.

KEYWORDS

cirrhosis, fibrosis, natural history, portal hypertension, tomography

INTRODUCTION

Cirrhosis is a complex disease characterised by progressive replacement of the normal parenchyma by abnormal nodules and fibrous septa¹ leading to architectural distortion and parenchymal extinction.^{2,3} These histopathological changes contribute to the development of portal hypertension which is variably followed by clinical decompensation and worsening of prognosis.⁴ In recent decades, knowledge about the prognostic value of clinical, haemodynamic and histological findings and their respective interconnections has greatly increased.⁵⁻⁷ Moreover, several sub-stages integrating these different features have been defined in order to stratify risk.⁸

On the other hand, some characteristic morphological changes such as left liver lobe hypertrophy, atrophy of the whole liver and splenomegaly occur along the natural history of cirrhosis.^{9,10} These changes can be easily quantified with imaging techniques such as multidetector computerised tomography (MDCT). In fact, the estimation of liver volume (LV) by MDCT is widely used for assessing the feasibility of tumour resection¹¹⁻¹³ or living donor transplantation.^{14,15} However, to what extent these morphological changes could be related to key events in cirrhosis has not been fully addressed. The aim of this study was to explore the relationship between landmark histological, haemodynamic, and clinical features of cirrhosis and changes in liver and spleen volumes.

MATERIALS AND METHODS

Patients

This cross-sectional study included all cirrhotic patients who consecutively underwent liver transplantation (LT, $n = 179$) or resection of hepatocellular carcinoma (HCC, $n = 41$) during a 6-year period (2009–2015) at the Hospital General Universitario Gregorio Marañón (Madrid, Spain), and in whom a cross-sectional imaging study was available. Patients who received LT for acute liver failure ($n = 14$), amyloidosis ($n = 1$) or a history of liver resection prior to LT ($n = 1$) were excluded from the study as well as 13 patients (12 LT; 1 HCC) evaluated with magnetic resonance instead of MDCT and 6 patients (5 LT, 1 HCC) because MDCT was performed without intravenous contrast medium. The final study population comprised 185 patients (LT, $n = 146$; HCC, $n = 39$). Despite the potential bias generated by these criteria, we chose this population to obtain large histological samples, accurately

Key summary

Established knowledge

- Cirrhosis evolution is driven by a complex interplay among biological, histological, haemodynamic and clinical changes.

New Findings

- Liver and spleen volumes change in a characteristic and quantifiable manner along the natural history of cirrhosis and are related to its clinical and haemodynamic landmarks.
- This relationship between visceral volumes and prognosis in cirrhosis is independent of the extent of fibrosis. Assessment of liver and spleen volume by computerised tomography is easy and accessible, and may contribute to risk stratification in cirrhosis.

accounting for the heterogeneous changes observed in cirrhosis (flowchart in Supplementary Figure S1).

Demographic, clinical, and haemodynamic data were obtained from electronic medical records.

Volumetric assessment

For volumetric analysis, the portal venous phase was reconstructed at 2 mm section thickness at 1 mm intervals. Multidetector computerised tomography acquisition settings were based on patient size and study indication. The Philips Intellispace V8 software was used for volumetric assessments. After manual selection of anatomical reference points, this package provides automatised segmentation of the liver. When the initial segmentation is completed, organ margins are verified and adjusted by the operator when necessary. This technique has been extensively described elsewhere^{16,17} providing reproducible measurements with high inter- and intra-reader agreement. All measurements were obtained by a radiologist (ER) with extensive experience in abdominal imaging. To assess the reproducibility of the method, volumetric analysis was repeated in a random sample of 10 cases by a second, independent, non-radiologist, operator (DR).

The total LV and the volume of each liver segment and spleen volume (SV) were calculated and expressed in cm^3 . Previous population-based studies have shown that anthropometric variability

determines liver size regardless of the presence of liver disease,^{18,19} therefore, we used several methods to standardise the total LV. We calculated for each patient the following volumetric ratios (Supplementary Figure S2):

- (1) SdLV (standardised LV by height and weight)²⁰: the measured total LV/theoretical standard LV according to height and weight.
- (2) SdLV-TD (standardised LV by thoracic diameter (TD))²¹: the measured total LV/theoretical standard LV according to TD.

A value of 1 for these ratios indicates that the patient has a normal LV standardised for a healthy person of the same anthropometric parameters, while a value less than 1 would indicate a decrease in LV as compared to the standard volume.

- (3) The standardisation of LV on body weight (SdLV-BW) (standardised LV by body weight): the measured total LV (cm³)/body weight (Kg).
- (4) The liver segmental volume ratio (LSVR)²²: the ratio between the volume of segments I to III and the segments IV to VIII. This ratio is considered as a radiological sign of cirrhosis²³
- (5) The LV/SV (liver to SV ratio): the ratio between liver and spleen volumes. This ratio has previously been associated with the severity of fibrosis and the presence of portal hypertension.²⁴⁻²⁶

Histological assessment

Conventional histopathological analysis

Histological samples were obtained from the right lobe (except in seven patients with left lobe resection). Five micrometre sections were prepared and stained with haematoxylin and eosin and Masson-trichrome. Samples were analysed by a pathologist expert in liver histology (IP) according to a pre-specified semi-quantitative scale (Supplementary Table 1). Sub-classification of cirrhosis was made according to Laennec sub-stages.⁶

Digital image analysis for quantification of fibrosis

Digital image analysis after Sirius red staining was used to quantify fibrosis as previously described.²⁷ For this purpose, we used a digital camera (Olympus SZ.17) connected to a compatible personal computer. The ImageJ® processing software was used to calculate the collagen proportional area (CPA) following the methodology described elsewhere.²⁷⁻²⁹

Fibrosis-free liver volume

To estimate the proportion of liver parenchyma free of fibrosis, we combined the data obtained by MDCT and CPA into a single variable, following the square-cube mathematical principle first described by Galileo Galilei in 1638.³⁰ To calculate the total volume of fibrosis we

considered each individual CPA as a representative two-dimensional estimation of the amount of fibrosis. Then, we transformed this factor from a quadratic to a cubic scale raising it to the power of 3/2. This factor was applied to the total LV obtained in the MDCT. Finally, we obtained the standardised fibrosis-free liver volume (Ff-LV) by removing the estimated fibrosis volume from the total LV and dividing this result by the standard LV (real example in Supplementary Figure S3).

Statistics

Quantitative variables are expressed as mean (standard deviation) or median (range) as appropriate. Categorical variables are shown as proportions (percent). The correlation between the total LV calculated by MDCT and the liver weight in those patients who underwent LT was analysed by Pearson correlation test.

To explore the association between visceral volumes and key features of the disease, the Spearman correlation test was used for continuous variables (scatterplots and 95% confidence level density ellipses were plotted for these bivariate distributions) whilst the Student's *t*, or ANOVA (with Bonferroni correction) tests were used for categorical variables. The χ^2 or the Fisher tests were applied to analyse the relationship between categorical variables.

Univariate and multivariate logistic regression analysis were performed to investigate variables independently associated with clinically significant portal hypertension (CSPH: HVPG ≥ 10 mmHg³¹) or clinical decompensation. A modelling strategy was followed including the aetiology of liver disease, volumetric changes and histological findings as explanatory variables. A backward stepwise method was used ($p < 0.05$ and $p < 0.10$ values as inclusion and exclusion criteria). We repeated this analysis including obesity (defined as body mass index [BMI] > 30 kg/m²) as an explanatory variable representing a surrogate of non-alcoholic steatohepatitis (NASH).

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.

Significance testing was two-sided, and type 1 error rates were set at 0.05. All the calculations were performed with Stata version 14.0.

Ethical issues

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

RESULTS

Characteristics of the patients

The study population comprised mostly male patients (161/185, 87%) with a mean age of 55.39 (8.48) years. The aetiology of cirrhosis was predominantly viral hepatitis (113/185, 61.08%) and alcohol (53/185, 28.65%). The spectrum of cirrhosis severity was homogeneously represented (Child-Pugh A, B and C: 37.50%, 32.95% and 29.55%,

TABLE 1 Characteristics of study population

Demographics		
Age (years)	55.39	(8.48)
Male sex	161/185	(87.03)
Weight (kg)	77.43	(13.04)
Height (m)	1.68	(0.07)
BMI (Kg/m ²)	27.24	(3.82)
Weight of the liver in patients with LT (gr) ^a	1301.30	(408.89)
Cardiovascular risk factors		
Diabetes mellitus	53/185	(28.65)
Arterial hypertension	47/185	(25.41)
Dyslipidemia	21/185	(35.35)
History of active or previous smoking	111/177	(62.71)
Aetiology of liver disease		
Hepatitis C virus	95/185	(51.35)
Alcohol	53/185	(28.65)
Hepatitis B virus	18/185	(9.73)
NASH	8/185	(4.32)
Autoimmune hepatitis	4/185	(2.16)
Primary biliary cholangitis	3/185	(1.62)
Primary sclerosing cholangitis	3/185	(1.62)
Haemochromatosis	1/185	(0.54)
Hepatocellular carcinoma		
All cases	116/185	(62.70)
1 nodule	78/116	(67.24)
2 nodules	29/116	(25.00)
3 or more nodules	9/116	(7.76)
Oesophageal varices		
No varices	41/178	(23.03)
Small	77/178	(43.26)
Large	58/178	(32.56)
Isolated gastric varices	2/178	(1.12)
Previous variceal bleeding	42/185	(22.70)
Previous hepatic encephalopathy		
No	110/185	(59.46)
Grade I–II	67/185	(36.22)
Grade III–IV	8/185	(4.32)
Ascites		
No	71/185	(38.38)
Diuretic-responsive	66/185	(35.68)
Refractory	48/185	(25.95)
Previous spontaneous bacterial peritonitis	44/185	(23.78)

TABLE 1 (Continued)

Laboratory values		
Platelets (x10 ³ /μl)	92.79	(56.35)
Bilirubin (mg/dl)	3.54	(5.31)
INR	1.31	(0.40)
Creatinine (mg/dl)	0.91	(0.38)
Sodium (mmol/L)	137	(4.9)
Albumin (g/dl)	3.45	(0.69)
Volumetric calculations (cm ³)		
Total liver volume	1423.14	(449.97)
Segment I	39.8	(35.47)
Segment II	177.86	(97.81)
Segment III	213.80	(160.57)
Segment IVa	109.39	(54.49)
Segment IVb	52.14	(40.66)
Segment V	225.93	(112.14)
Segment VI	168.44	(84.82)
Segment VII	213.47	(95.65)
Segment VIII	228.24	(92.71)
Spleen volume	779.22	(458.38)

Note: Data are expressed as mean (SD) or as proportion (%).

Abbreviations: BMI, body mass index; INR, international normalized ratio; LT, liver transplantation; NASH, non-alcoholic steatohepatitis.

^aThe weight of the whole liver in patients with LT was available in 140/146 cases.

respectively). Twenty-seven (14.92%), 32 (17.68%) and 122 (67.40%) patients had compensated cirrhosis without CSPH, compensated cirrhosis with CSPH and decompensated cirrhosis, respectively (HVPG was not available in 4 compensated patients). The median Model for end-stage liver disease (MELD) score was 11 (6–40) points, and the median HVPG was 16 mmHg (2.5–41.5 mmHg). The mean area of the histological samples used for CPA analysis was 2.43 (0.84) cm². The cohort distribution according to the Laennec sub-classification was 32.76%, 41.80% and 26.44% for stages 4a, 4b and 4c, respectively. Upper gastrointestinal endoscopy, HVPG and cardiac index, all performed close to MDCT, were available in 178, 147 and 105 cases, respectively. The median time between surgery (LT or resection) and MDCT, endoscopy and the haemodynamic study was less than 10 months.

The demographic data, and the characteristics of liver disease and visceral volumes are shown in Table 1.

Correlation between liver volume and liver weight and reproducibility of the volume measurements

Overall, there was a strong correlation between liver weight and LV estimated by MDCT ($r = 0.92$; $p < 0.01$) which was similar

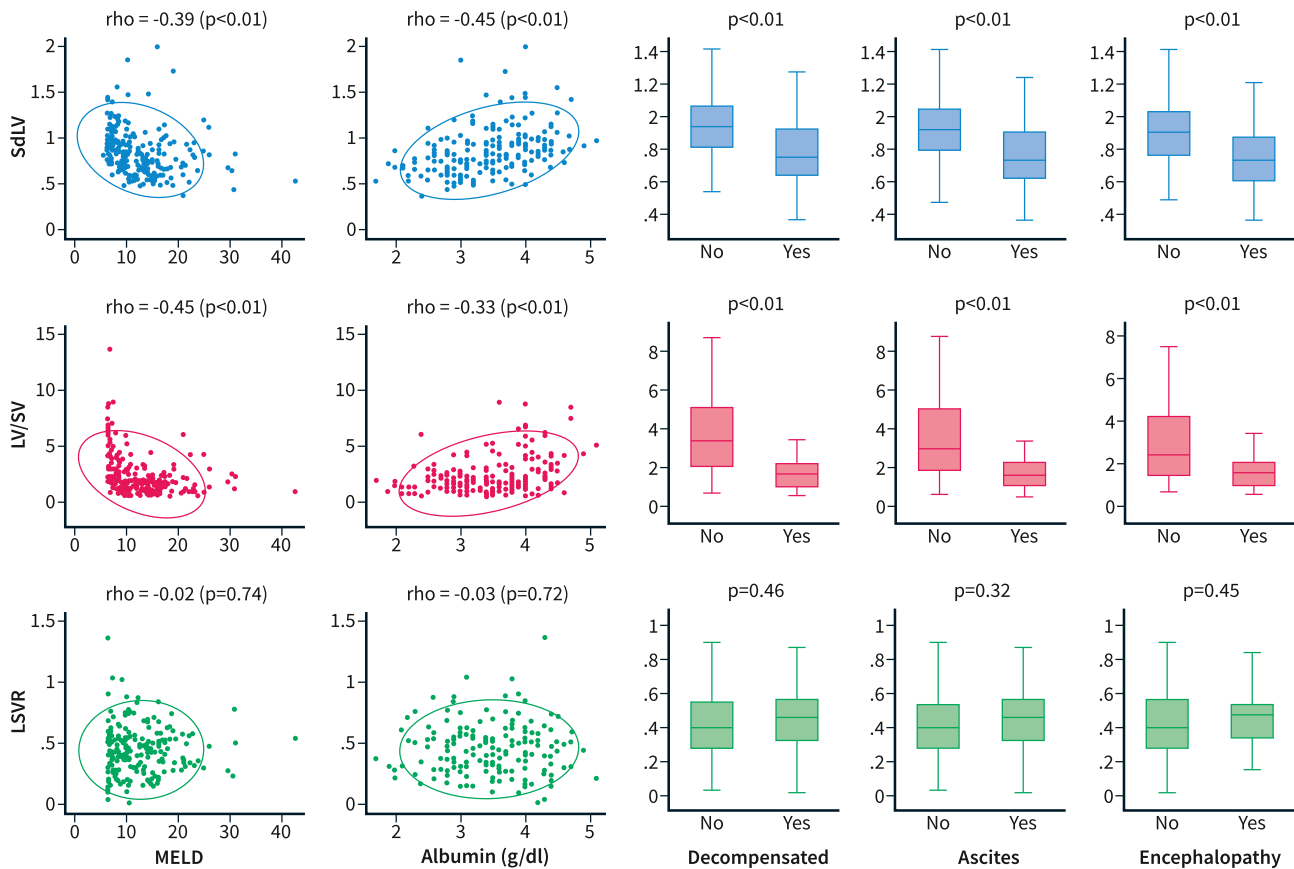


FIGURE 1 Association between visceral volume indices, clinical events and variables related to liver failure. LSVR, liver segmental volume ratio (segments I-III/segments IV-VIII); LV/SV, liver to spleen volume (SV) ratio; MELD, model for end stage liver disease; SdLV, standardised liver volume (LV) according to height and weight

among the different Child-Pugh classes ($r = 0.88$, $p < 0.01$; $r = 0.96$, $p < 0.01$; and $r = 0.84$, $p < 0.01$; for Child A, B and C, respectively) and aetiologies ($r = 0.95$, $p < 0.01$; $r = 0.83$, $p < 0.01$; and $r = 0.93$, $p < 0.01$; for viral, alcoholic and other aetiologies, respectively).

Agreement between the two independent operators in volume measurements was excellent [intraclass correlation coefficient (95% confidence interval of 0.9991 (0.9965–0.9997), 0.9970 (0.9835–0.9993) and 0.9757 (0.9056–0.9939) for total LV, SV and LSVR, respectively].

Association between visceral volumes and severity of liver disease

The SdLV and the LV/SV but not the LSVR, showed a significant correlation with the MELD score and serum albumin. Furthermore, the SdLV and LV/SV were significantly lower in decompensated patients (overall and for each specific decompensation). Conversely, the LSVR was similar in patients with and without previous decompensation (Figure 1).

Association between visceral volumes and portal hypertension hallmarks

We found a positive correlation between the HVPG and LSVR. Conversely, the HVPG was negatively correlated with the SdLV and LV/SV. Furthermore, patients with CSPH had a significantly lower SdLV and LV/SV and a higher LSVR. Similar findings were observed for the presence of oesophageal varices (Figure 2).

If considering only compensated patients, a significant correlation in the same direction was found between the HVPG and the LSVR and LV/SV. The presence of CSPH or gastroesophageal varices was also associated with a significant variation in LSVR and LV/SV. However, we did not find association between the SdLV and the HVPG, the presence of CSPH or varices in this subgroup of patients (Supplementary Figure S4).

Association between visceral volumes and fibrosis

None of the volumetric ratios were associated with the intensity of fibrosis, estimated by the Laennec sub-classification or CPA (Figure 3).

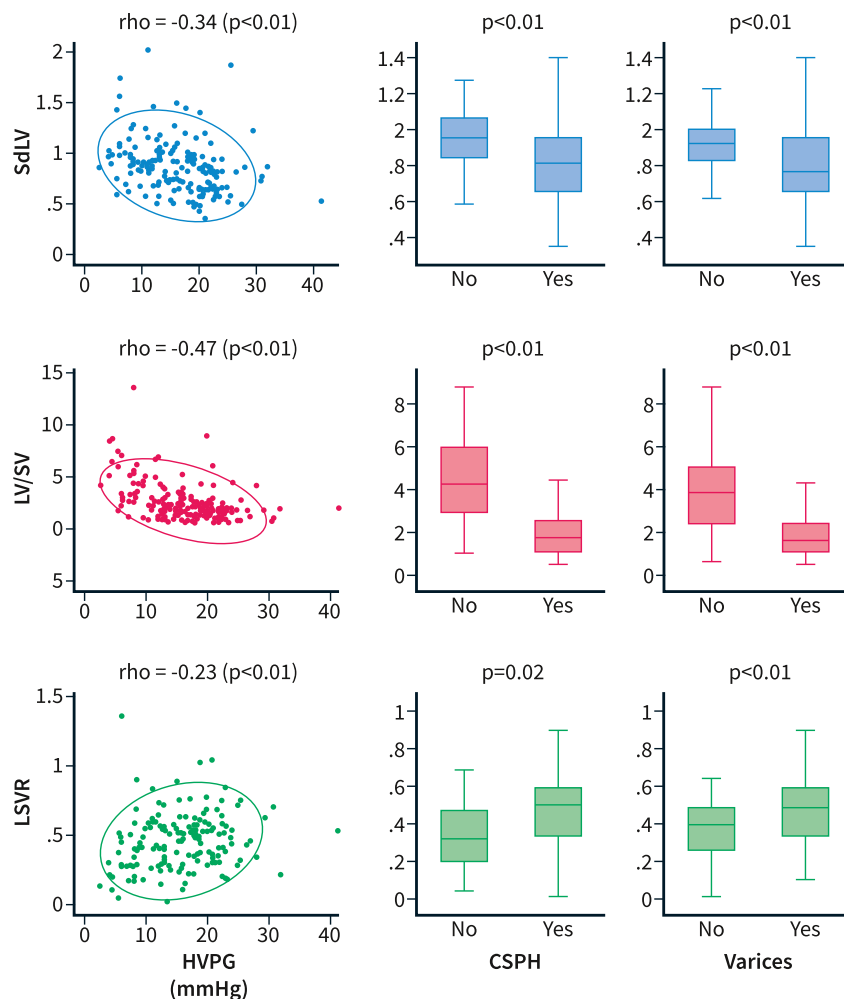


FIGURE 2 Association between visceral volume indices and variables related to portal hypertension. CSPH, clinically significant portal hypertension; HVPG, hepatic venous pressure gradient; LSVR, liver segmental volume ratio (segments I-III/segments IV-VIII); LV/SV, liver to spleen volume (SV) ratio; SdLV, standardised liver volume (LV) according to height and weight

As expected, fibrosis deposition was significantly greater in patients with decompensated disease and its severity increased in accordance with the prognostic scores (Child-Pugh, MELD score) and the clinical, haemodynamic or endoscopic findings (Supplementary Table S2).

The associations between other histological findings and splanchnic volumes are summarised in Supplementary Table S3.

Relationship between liver volume, fibrosis and prognostic events

As shown previously, liver and spleen volumes and the severity of fibrosis, individually, are clearly associated with key features of the disease and its severity. Nevertheless, no association was found between visceral volumes and fibrosis. We next explored the association of these variables with the development of CSPH or clinical decompensation when considered simultaneously.

(A) Relationship between LV changes and clinical decompensation across the fibrosis severity spectrum.

As shown in Figure 4, the SdLV was significantly lower in decompensated patients along the different degrees of fibrosis (Laennec substages or quartiles of CPA).

To evaluate the independent contribution of volumetric liver indices (SdLV and LSVR) and the severity of fibrosis to the presence of CSPH or clinical decompensation, different explicative models were developed (Table 2). The aetiology of liver disease, SdLV, LSVR and CPA were independently associated with the presence of CSPH. On the other hand, the aetiology, SdLV and CPA but not the LSVR were found to be independent factors associated with clinical decompensation. Interestingly, when the HVPG was included as a covariate in the last model, only the HVPG and the SdLV remained as independent variables. Additionally, when we included in the model the presence of obesity (BMI >30 kg/m²) as a surrogate of NASH, the results were similar (Supplementary Table S4).

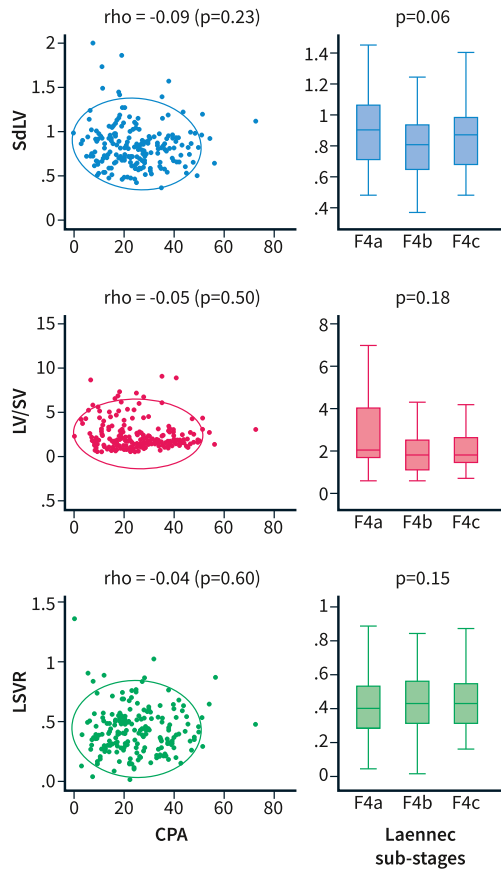


FIGURE 3 Association between volume indices and severity of fibrosis. CPA, collagen proportional area; LSVR, liver segmental volume ratio (segments I-III/segments IV-VIII); LV/SV, liver to spleen volume (SV) ratio; SdLV, standardised liver volume (LV) according to height and weight

(B) Relationship between standardised Ff-LV and disease severity

The Ff-LV discriminated better than CPA or SdLV across the different Child-Pugh classes or HVPG strata (Supplementary Figure S5). Additionally, the reduction of portal tracts and central veins, two histological changes closely related to parenchymal extinction, were associated with a reduction in Ff-LV (Figure 5). We found that a differential contribution of CPA and SdLV changes may lead to a similar reduction of Ff-LV, and eventually, to a similar clinical scenario (Supplementary Figure S6).

The Table 3 provides a comprehensive summary of the histological, haemodynamic, biochemical and splanchnic volume changes according to the different clinical stages of cirrhosis.

All the previous analyses were also performed using the standardisations of LV based on thoracic diameter and on body weight (SdLV-BW), showing similar results (Supplementary Tables S5 and S6).

DISCUSSION

Cirrhosis is a heterogeneous disease driven by a complex interplay among biological, histological, haemodynamic and clinical changes. All these events define the natural history of the disease and allow its stratification in terms of severity and prognosis.⁸ The pathophysiological and prognostic role of volumetric changes throughout the different stages is unclear. In this study we aimed to explore the relationship between changes in the liver and spleen volumes and the landmark histological, haemodynamic, and clinical features of cirrhosis.

First, our results demonstrate that liver and spleen volumetric changes evaluated by MDCT can be detected across the different

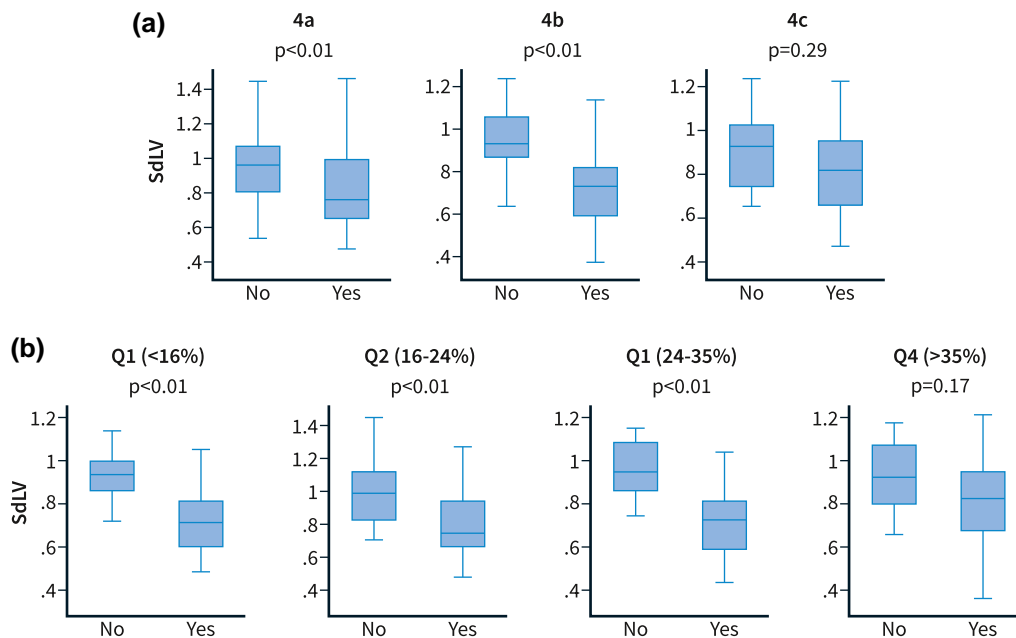


FIGURE 4 Comparison of SdLV distribution in patients with and without clinical decompensation across fibrosis stages according to the Laennec classification (a) and consecutive quartiles of collagen proportional area (CPA) (%) (b). CPA, collagen proportional area; SdLV, standardised liver volume (LV) according to height and weight

TABLE 2 Logistic regression analysis for the presence of clinically significant portal hypertension (CSPH) or clinical decompensation

Dependent variable: Presence of CSPH			
Variable	Univariate OR (95% CI)	p	Multivariate OR (95% CI)
Aetiology (viral as reference)			
-Alcoholic versus viral	2.71 (0.87–8.47)	0.086	5.78 (1.38–24.25)
-Others versus viral	0.79 (0.25–2.47)	0.684	2.42 (0.52–11.33)
SdLV	0.18 (0.04–0.73)	0.016	0.07 (0.01–0.51)
LSVR	15.15 (1.63–140.62)	0.017	16.52 (1.36–200.38)
CPA (%)	1.08 (1.04–1.14)	0.001	1.09 (1.03–1.15)
Dependent variable: Presence of clinical decompensation			
Variable	Univariate OR (95% CI)	p	Multivariate OR (95% CI)
Aetiology (viral as reference)			
-Alcoholic versus viral	2.35 (1.09–5.04)	0.029	3.64 (1.42–9.37)
-Others versus viral	0.68 (0.26–1.81)	0.444	2.60 (0.71–9.54)
SdLV	0.06 (0.02–0.24)	0.000	0.02 (0.00–0.11)
LSVR	1.80 (0.39–8.44)	0.453	
CPA (%)	1.06 (1.03–1.10)	0.000	1.06 (1.03–1.10)
Dependent variable: Presence of clinical decompensation (considering HVPG in the model)			
Variable	Univariate OR (95% CI)	p	Multivariate OR (95% CI)
Aetiology (viral as reference)			
-Alcoholic versus viral	2.35 (1.09–5.04)	0.029	1.78 (0.54–5.84)
-Others versus viral	0.68 (0.26–1.81)	0.444	2.01 (0.37–10.87)
SdLV	0.06 (0.02–0.24)	0.000	0.07 (0.01–0.59)
LSVR	1.80 (0.39–8.44)	0.453	
CPA (%)	1.06 (1.03–1.10)	0.000	1.01 (0.97–1.06)
HVPG (mmHg)	1.33 (1.21–1.46)	0.000	1.28 (1.16–1.42)

Abbreviations: CPA, collagen proportional area; LSVR, liver segmental volume ratio (Couinaud segments I-III to Couinaud segments IV- VIII); SdLV, liver volume standardised by height and weight.

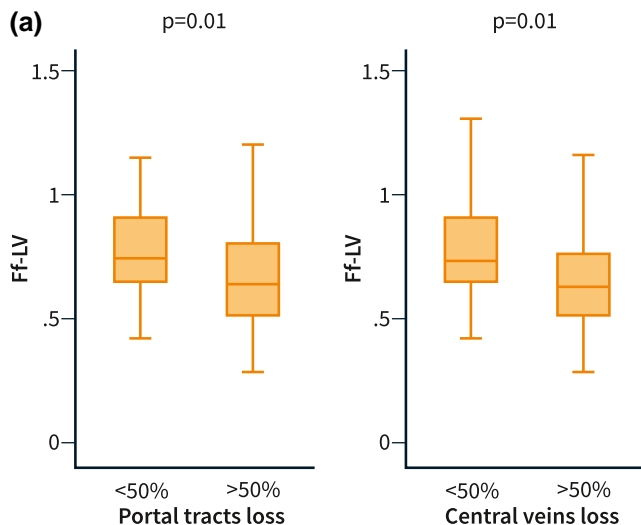


FIGURE 5 Variation of fibrosis-free liver volume (Ff-LV) according to the loss of portal tracts and central veins. Ff-LV, standardised fibrosis-free liver volume

stages mirroring the natural history of cirrhosis. Second, we showed that these volumetric changes do not evolve homogeneously over time, but rather specific volumetric changes are related to different phases (compensated without CSPH, compensated with CSPH and decompensated). It is of note that the volumetric changes are related to these evolutive phases of cirrhosis independently of the intensity of fibrosis.

We found two pivotal changes in the volumetric indices that closely correlated with each of the clinical phases: (1) a relative atrophy of the right lobe and medial sector of the left lobe (segments IV–VIII) along with hypertrophy of the left lateral sector and caudate lobe (segments I–III). This phenomenon seems to begin in the pre-cirrhotic stages and evolves along the compensated phase. The underlying drivers of this process still remain to be elucidated, but several mechanisms have been proposed.^{32,33} The LSVR is the volumetric index that best captures this pathophysiological process. The LSVR showed a positive correlation with HVPG, the most robust prognostic factor in compensated cirrhosis. Moreover, it discriminated between patients with CSPH (i.e. at risk of decompensation) and those without it, regardless of the whole LV or the extent of fibrosis. Importantly, this is the first study that demonstrates that the LSVR does not undergo significant changes during the decompensated phase. (2) the second pivotal change was a progressive atrophy of the whole liver. This phenomenon occurs during the decompensated phase. The SdLV was significantly correlated with well-known prognostic factors of decompensated cirrhosis. We hypothesised that SdLV changes are mainly secondary to parenchymal extinction. This histopathological event is a key feature in disease progression resulting in loss of functioning parenchyma.³ The reduction in LV was associated with the development of decompensation independently of the intensity of fibrosis, thereby supporting our hypothesis.

Another remarkable finding of our study was that LV changes and fibrosis severity independently contribute to prognosis. In fact, decompensated patients showed a significantly lower LV than

compensated patients across the different Laennec stages. Although speculative, it may be possible that fibrosis deposition and parenchymal extinction are partially overlapped mechanisms that impact disease progression: (a) fibrosis is mainly implicated in the development of architectural distortion during the compensated phase, and the relative hypertrophy of segments I–III would be a compensatory mechanism in response to the atrophy of segments IV–VIII; and (b) progressive extinction of functioning parenchyma would be responsible for the loss of hepatic volume, the progressive increase in portal hypertension, and eventually, the development of clinical decompensation. Therefore, the results of our investigation challenge the current histopathological sub-classification of cirrhosis and its correlation with the key events within the decompensated phase of the disease. Certainly, and in line with previous data,⁶ decompensated patients had a greater fibrosis deposition. However, this finding does not unequivocally imply that fibrosis severity triggers the development of clinical decompensation, but rather that other factors easily evaluated by visceral volumetry, such as functional parenchymal collapse, are more relevant in this phase. A recent study showed that the severity of fibrosis assessed by CPA correlates with the clinical severity until a decompensation occurs but not with subsequent decompensating events.³⁴ Overall, these findings could explain that some patients could have less severe fibrosis, concomitantly with marked parenchymal extinction, leading to decrease LV.

The methodology followed confers additional strength to the results. We included a large and well-characterised cohort, partially representative of the entire spectrum of cirrhosis severity. Importantly, in contrast with previous studies using small needle samples,^{6,7,27} we included high quality histological specimens from hepatic surgical procedures. Finally, and considering that population-based studies have shown that anthropometric variability determines the size of the liver,^{18,19} we standardised the volumetric determinations. We have shown that standardisation using TD leads to identical results; thus, LV can be measured and standardised just with MDCT-related information.

Therefore, visceral volumetry by MDCT is an easy, reproducible and non-invasive tool which provides valuable prognostic information in cirrhosis. Our results invite prospective investigation of the ability of liver and spleen volumetry to predict histological, haemodynamic and clinical events in order to provide a point-of-care risk assessment in both compensated and decompensated patients.

Our study has some limitations. We only included cirrhotic patients who underwent LT or liver resection, which might introduce selection bias. However, the characteristics of the patients regarding demographics, liver disease severity and haemodynamic findings, are similar to those reported in other series.³⁵ Our cohort comprised mostly patients with hepatitis C or alcohol-related cirrhosis and less than 5% of the cases were secondary to NASH, an aetiology that is highly prevalent nowadays.³⁶ To overcome this limitation, we adjusted the volume indexes to the anthropometric condition of the patients and included a sub-analysis incorporating the BMI as a surrogate of NASH. Additionally, there is evidence showing that the amount of steatosis (a possible influencing factor on LV

TABLE 3 Distribution of histological, haemodynamic, biochemical and volume changes according to the different clinical risk groups in cirrhosis

		Clinical Risk Group			P value
		I	II	III	
FIBROSIS	CPA (%)	15.14 [10.17]	25.29 [13.02]	28.29 [11.91]	<0.001
	% Portal tracts lost (<50/>50) (% patients)	64/36	55.17/44.83	31.95/68.05	<0.001
HAEMODYNAMIC CHANGES	HVPG (mmHg)	6.90 [1.86]	14.42 [3.48]	19.19 [5.94]	<0.001
	Cardiac index (l/min.m ²)	3.21 [0.77]	3.57 [1.02]	4.25 [1.09]	0.006
LABORATORY DATA	Albumin (g/dl)	4.23 [0.40]	3.79 [0.48]	3.16 [0.60]	<0.000
	Sodium (mmol/l)	141.41 [3.69]	140.75 [2.58]	136.08 [4.90]	<0.000
	MELD	7.70 [2.47]	9.33 [3.42]	14.98 [6.09]	<0.000
VOLUME CHANGES	Liver volume (SdLV)	1.00 [0.24]	0.98 [0.27]	0.80 [0.24]	<0.000
	Left hypertrophy (LSVR)	0.37 [0.27]	0.49 [0.22]	0.46 [0.18]	0.057
	Spleen volume (LV/SV)	5.11 [2.58]	2.91 [1.62]	1.88 [1.16]	<0.000

Note: Group I: compensated without risk (HVPG <10 mmHg); Group II: compensated at risk (HVPG ≥10 mmHg); Group III: Decompensated. Data are expressed as means [SD] or as proportions (%). ANOVA for mean comparison among groups and Chi-squared test for comparison of categorical variables. A different intensity colour between categories represents a p-value <0.05.

Abbreviations: CPA, collagen proportional area; HVPG, hepatic venous pressure gradient; LSVR, liver segmental volume ratio (segments I–II /segments IV–VIII); LV/SV, liver to spleen volume ratio; MELD, model for end stage liver disease; SdLV, standardised liver volume according to height and weight.

measurements), decreases in advance NASH disease.³⁷ However, whether our findings are equally valid in NASH patients should be specifically explored in further studies. The inherent retrospective nature and cross-sectional design of our study precluded the evaluation of longitudinal changes in individual patients. Although a longitudinal study with prolonged follow-up and repeated

measurements would be ideal to fully confirm our findings, such a study is very difficult to perform considering the invasive nature of obtaining repeated liver samples and HVPG measurements.

In conclusion, liver and spleen volumetric changes parallel the natural history of cirrhosis, correlate with the clinical stages and are associated with its prognostic factors, regardless of the severity of

fibrosis. These volumetric indices can be easily obtained and reproduced by MDCT and provide relevant prognostic information in patients with cirrhosis across the entire spectrum of the disease.

AUTHOR CONTRIBUTIONS

Conceptualization: Mario Romero-Cristóbal, Ana Clemente-Sánchez, Rafael Bañares, Diego Rincón. Acquisition of data: Mario Romero-Cristóbal, Ana Clemente-Sánchez, María-Isabel Peligros, Enrique Ramón, Ana-María Matilla, Arturo Colón, Sonia Alonso, María-Vega Catalina, Ainhoa Fernández-Yunquera, Rita García, Jose Ángel López-Baena, María-Magdalena Salcedo, Rafael Bañares, Diego Rincón. Formal analysis and methodology: Mario Romero-Cristóbal, Ana Clemente-Sánchez, María-Isabel Peligros, Enrique Ramón, 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.

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CONFLICT OF INTEREST

No conflict of interest to declare.

DATA AVAILABILITY STATEMENT

Data generated or analysed during the study are available from the corresponding author by request.

ETHICS APPROVAL

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. Institutional Review Board approval was obtained. Written informed consent was waived by the Institutional Review Board.

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