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HEPATOBILIARY-PANCREAS

Hepatosplenic volumetric assessment at MDCT for staging liver fibrosis

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Abstract

Purpose To investigate hepatosplenic volumetry at MDCT for non-invasive prediction of hepatic fibrosis.

Methods Hepatosplenic volume analysis in 624 patients (mean age, 48.8 years; 311 M/313 F) at MDCT was performed using dedicated software and compared against pathological fibrosis stage (F0 = 374; F1 = 48; F2 = 40; F3 = 65; F4 = 97). The liver segmental volume ratio (LSVR) was defined by Couinaud segments I–III over segments IV–VIII. All pre-cirrhotic fibrosis stages (METAVIR F1-F3) were based on liver biopsy within 1 year of MDCT.

Results LSVR and total splenic volumes increased with stage of fibrosis, with mean(±SD) values of: F0: 0.26 ± 0.06 and 215.1 ± 88.5 mm^3; F1: 0.25 ± 0.08 and 294.8 ± 153.4 mm^3; F2: 0.331 ± 0.12 and 291.6 ± 197.1 mm^3; F3: 0.39 ± 0.15 and 509.6 ± 402.6 mm^3; F4: 0.56 ± 0.30 and 790.7 ± 450.3 mm^3, respectively. Total hepatic volumes showed poor discrimination (F0: 1674 ± 320 mm^3; F4: 1631 ± 691 mm^3). For discriminating advanced fibrosis (≥F3), the ROC AUC values for LSVR, total liver volume, splenic volume and LSVR/spleen combined were 0.863, 0.506, 0.890 and 0.947, respectively.

Conclusion Relative changes in segmental liver volumes and total splenic volume allow for non-invasive staging of hepatic fibrosis, whereas total liver volume is a poor predictor. Unlike liver biopsy or elastography, these CT volumetric biomarkers can be obtained retrospectively on routine scans obtained for other indications.

Key Points

- *Regional changes in hepatic volume (LSVR) correlate well with degree of fibrosis.*
- *Total liver volume is a very poor predictor of underlying fibrosis.*
- *Total splenic volume is associated with the degree of hepatic fibrosis.*
- *Hepatosplenic volume assessment is comparable to elastography for staging fibrosis.*
- *Unlike elastography, volumetric analysis can be performed retrospectively.*

Keywords MDCT · Cirrhosis · Liver fibrosis · Volume · Volumetric analysis

Introduction

Liver damage from a variety of underlying causes may result in hepatic fibrosis. Although this damage is irreversible when end-stage fibrosis results in cirrhosis, earlier stages of fibrosis may be reversible. Liver biopsy can confirm and stage hepatic fibrosis, but is invasive, expensive, somewhat subjective and only samples a tiny fraction of the liver parenchyma [1, 2]. Given these drawbacks, non-invasive diagnostic means for the detection and staging of liver fibrosis have received considerable attention [2], most notably the elastography techniques that measure liver stiffness.

Both ultrasound (US) and magnetic resonance (MR) elastography have repeatedly shown good correlation between parenchymal stiffness and degree of underlying liver fibrosis [3–12]. In particular, MR elastography has proven to be more effective than US techniques, including fewer technical

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failures in obese patients [13]. However, MR elastography may still be unsuccessful in over 5 % of cases even in expert hands [11], and considerable overlap in stiffness exists between early fibrosis and inflammation (e.g. steatohepatitis) [14, 15], which may coexist. Furthermore, elastography requires specific equipment and must be prospectively applied.

To address these issues, we have become interested in the non-invasive assessment of morphological hepatosplenic changes at cross-sectional imaging (CT or MR) that may correlate with the degree of underlying fibrosis, as these non-invasive features do not require prospective planning. If successful, these changes could be assessed retrospectively on CT scans performed for other indications. Our preliminary work [16] has shown that intrahepatic changes demonstrable at CT, specifically the decreased volume of Couinaud segments IV–VIII relative to compensatory changes in segments I–III, can reliably distinguish normal from cirrhotic livers. Furthermore, we found that volumetric assessment accentuates and better reflects morphological changes compared with linear measures (e.g. the caudate-to-right lobe ratio), which may fail to account for changes in the left lateral segment (Couinaud II and III). In addition, splenic size increase can also effectively distinguish normal from cirrhotic patients but may be a less specific finding given other potential causes of splenomegaly. However, it is unknown if these morphological hepatosplenic changes can differentiate intermediate degrees of hepatic fibrosis from both normal (F0) and cirrhotic states (F4), including discrimination of significant (≥F2) and advanced (≥F3) fibrosis. Therefore, the purpose of this study was to investigate whether relative changes in segmental hepatic volume and total splenic volume at CT can predict the degree of underlying hepatic fibrosis.

Material and methods

This HIPAA-compliant retrospective study was approved by our institutional review board; the need for signed informed consent was waived.

Patient population

The final cohort consisted of 624 patients (mean age, 48.8 years; 311 M/313 F). Patients were primarily categorized according to pathological METAVIR stage of liver fibrosis (F0-F4), ranging from no fibrosis (F0) to end-stage cirrhosis (F4), separated by varying degrees of intermediate stages of liver fibrosis (F1-F3). A primary inclusion criterion for the entire cohort was an abdominal CT scan available within our PACS, in addition to placement into a proper fibrosis category as defined below.

The patient population (n = 624) consisted of discrete subcohorts including: (1) patients with chronic end-stage liver disease (cirrhosis) undergoing potential liver transplant evaluation (F4; n = 97); (2) patients with varying degrees of pre-cirrhotic liver fibrosis (F1: n = 48; F2: n = 40; F3: n = 65); and (3) an asymptomatic group without known liver disease undergoing CT for potential renal donation (F0: n = 374). Liver biopsy within 1 year of CT was required for all patients in the early (F1), intermediate (F2) and advanced (F3) fibrosis cohorts. Within the end-stage cirrhotic cohort (F4), liver histology was available in 46 patients. Liver biopsy is not always pursued in cirrhotic patients by our hepatologists when the following conditions are met: clear cause for cirrhosis, clinical evidence for chronic end-stage liver disease and/or complications of portal hypertension, and clear-cut imaging evidence of cirrhosis. Chart review confirmed these conditions were met for all cirrhotic patients without biopsy. For the cirrhotic cohort, mean Model for End-Stage Liver Disease (MELD) scores (± SD) were 15.32 ± 6.14. For the normal controls (F0) without evidence off underlying liver disease, biopsy was generally not performed and not required.

For patients with liver fibrosis or cirrhosis, the most common causes of the underlying liver disease was chronic hepatitis C, alcoholism and non-alcoholic fatty liver disease (NAFLD). Other minor contributors included primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), cryptogenic cirrhosis, hepatitis B virus, autoimmune hepatitis and alpha-1 antitrypsin deficiency. A number of patients had more than one aetiology (e.g. hepatitis C and alcoholism). Patients with large liver tumours (e.g. hepatocellular carcinoma (HCC)) that might affect volume measurements were excluded from analysis.

MDCT technique

All CT scans were acquired on 16- or 64-detector row scanners (GE Healthcare, Waukesha, WI). Specific CT technique varied somewhat based on the patient cohort, but multiphasic protocols were applied to most patients (triphasic for pre-transplant evaluation, biphasic for pre-cirrhotic liver evaluation and multiphasic for renal donor evaluation). For volumetric analysis, the portal venous phase was utilized, reconstructed at 5-mm slice thickness at 3-mm intervals. Previous work has shown that thin (1.25-mm) versus a thick (5-mm) slice thickness does not significantly impact volume measurement [17]. Specific kV and mA settings were based on patient size and study indication. In general, volumetric analysis is relatively resistant to the specific phase of contrast, kV/mA settings, slice thickness and reconstruction algorithm.

Quantitative morphological liver analysis at CT

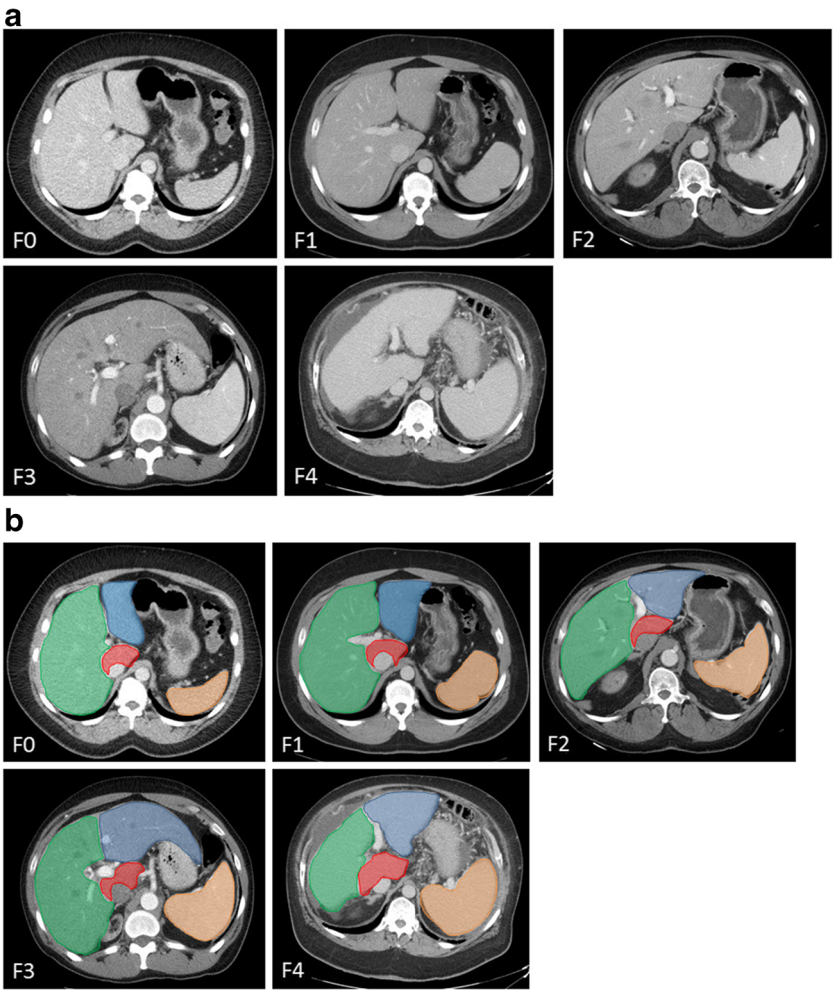
Morphological liver analysis was performed by co-authors blinded to the specific clinical data utilizing a dedicated CT software tool (Liver Analysis application, Philips IntelliSpace

Portal, Philips, Best, The Netherlands). This package provides automated segmentation of the liver and spleen. After the initial automated segmentation, the organ margins were verified and adjusted if needed with digital brush and eraser tools to add and subtract tissue volume, respectively. Total hepatic and splenic volumes were then recorded. Subsequently, Couinaud segments I–III (caudate and left lateral lobe) were isolated from segments Couinaud IV–VIII to derive the separate volumes of each component (Fig. 1). These measurements allow for derivation of the 'liver segmental volume ratio' or LSVR, which we have previously defined as the volume ratio of Couinaud segments I–III to segments IV–VIII [16]. The LSVR accentuates the changes of volume loss in segments IV–VIII against compensatory hypertrophy of segments I–III and along with total hepatic and splenic volume is a reproducible measure with good agreement [16].

The primary volumetric measurements were performed by three of the co-authors (K.M., O.H. and C.B.), who were trainees with varying experience in CT (range, 1–5 years). These readers were trained and monitored by three other co-authors (P.J.P, M.G.L. and T.M.Z.), all of whom were abdominal radiologists with over 10 years of experience. Our previous work has demonstrated that these volumetric measurements, including the LSVR, are reproducible across readers with varying CT experience levels [16]. Examples of hepatosplenic segmentation at MDCT with the typical changes seen as fibrosis (and portal hypertension) progresses are illustrated in Fig. 1.

Statistical analysis

All volume measurements were recorded with summary statistics (mean, standard deviation and quartiles), calculated separately for each patient cohort according to stage of liver fibrosis. A Kruskal-Wallis test was used to assess differences between F0–F4 cohorts for each measured parameter.



	F0	F1	F2	F3	F4
LSVR	0.26	0.29	0.33	0.39	0.60
Total Liver	1684	2197	1942	1738	1985
Spleen	149	212	261	412	978

Fig. 1 Examples of liver segmental volume ratio (LSVR), total liver volume and splenic volume for each stage of pathological liver fibrosis (F0-F4). Contrast-enhanced CT images without (**A**) and with (**B**) segmentation of the liver and spleen are shown for each fibrosis stage. In addition total volumes of the segmented liver and spleen (orange), Couinaud segments I (red), II/III (blue) and IV-VIII (green) are derived to obtain the liver segmental volume ratio (LSVR; I–III/IV–VIII). The table inset shows a progressive increase in both LSVR and splenic volume with increasing fibrosis (F0–F4), whereas total liver volume shows no clear correlation. For the case of cirrhosis (F4), there are other imaging clues of end-stage liver disease including surface nodularity and portal hypertension (ascites and portosystemic collaterals)

Emphasis was placed on the clinically relevant distinctions of significant (≥F2) and advanced (≥F3) hepatic fibrosis. Receiver operating characteristic (ROC) curves were obtained for each candidate metric, and areas under the curve (AUCs) were calculated, with a DeLong 95 % confidence interval (CI). Sensitivity and specificity results were obtained using cut-off values derived from the ROC curve analysis. The cut-off values were determined by the point on the ROC curve closest to the upper left hand corner of the plot (i.e. minimum distance from the point (1, 1). Logistic regression was used to predict liver fibrosis stage as a function of LSVR and splenic volume combined. A p-value <0.05 (two-sided) was the criterion for statistical significance. R 3.2.2 (R Core Team 2014) was used for all statistical analyses.

Results

Summary statistics for the LSVR are shown in Table 1, with the corresponding box plots of LSVR values according to fibrosis stage shown in Fig. 2. Little or no difference was seen in LSVR between categories F0 and F1, but notable differences were seen with fibrosis stages above F1, with a progressive increase in separation between cohorts as the degree of fibrosis increased from F1 to F4. The relative contributions of Couinaud segments I (caudate), II and III (left lateral segment), and IV–VIII (right lobe and left medial segment) to total liver volume are illustrated for each stage of fibrosis in Fig. 1. Diagnostic performance of the LSVR for discriminating between stages of liver fibrosis is shown in Table 2, and the most relevant ROC curves are shown in Fig. 3. For the clinically relevant distinction of advanced fibrosis (F3–F4 vs. F0–F2), the ROC AUC value for the LSVR was 0.880, with a sensitivity of 72.2 % and a specificity of 88.1 % using a threshold ratio of 0.347. For distinguishing significant fibrosis (F2–F4 vs. F0–F1), the ROC AUC was 0.854, with a sensitivity of 68.3 % and a specificity of 87.9 % with an LSVR threshold of 0.336.

Mean total liver volume varied relatively little across the fibrosis spectrum, as shown in Table 1 and Fig. 2. Consequently, total liver volume was a very poor predictor of fibrosis stage, with ROC AUC values near 0.500 (Table 2). Specifically, for the relevant distinctions of significant fibrosis (≥F2) and advanced fibrosis (≥F3), the ROC AUC values for total liver volume were 0.512 and 0.506, respectively. Using a liver volume threshold of 1,926 cm^3, the sensitivity for both significant and advanced fibrosis was only 35–36 % with specificity above 80 %. Figure 1 demonstrates the intrahepatic changes that occur as the degree of liver fibrosis increases, resulting in a relatively static overall volume.

Summary statistics for splenic volume are also shown in Table 1. As with the LSVR, splenic volume generally increased with stage of fibrosis, with more substantial changes beyond the F2 level (Fig. 2). Diagnostic performance of splenic volume for discriminating between stages of liver fibrosis is shown in Table 2. For distinguishing significant (≥F2) fibrosis, the ROC AUC value was 0.848, with a sensitivity of 71.6 % and a specificity of 85.9 % using a threshold volume of 311.5 cm^3. For distinguishing advanced fibrosis (≥F3), the ROC AUC was 0.901, with a sensitivity of 81.4 % and a specificity of 85.2 % using a threshold of 315.2 cm^3.

Combined assessment of LSVR and splenic volume data resulted in further diagnostic improvement for staging liver fibrosis. The complementary information provided by these two parameters led to ROC AUC values of 0.908 for determining significant fibrosis, 0.947 for advanced fibrosis and

Table 1 Summary statistics for the main variables of liver segmental volume ratio (LSVR), total liver volume, and splenic volume according to stage of liver fibrosis

Variable		Pathological fibrosis stage				
		F0 (n = 374)	F1 (n = 48)	F2 (n = 40)	F3 (n = 65)	F4 (n = 97)
LSVR	Mean	0.26	0.25	0.33	0.39	0.56
	SD	0.06	0.08	0.12	0.15	0.30
	Median	0.25	0.24	0.31	0.35	0.51
	IQR	0.09	0.12	0.15	0.16	0.25
Total liver volume (cm^3)	Mean	1,658.5	1,815.3	1,718.5	1,992.6	1,630.7
	SD	303.6	441.0	359.8	602.0	690.8
	Median	1,624.3	1,689.8	1,661.2	1,939.0	1,456.8
	IQR	364.2	439.1	538.8	708.7	748.0
Splenic volume (cm^3)	Mean	215.1	294.8	291.6	509.6	790.7
	SD	88.5	153.4	197.1	402.6	450.3
	Median	195.4	248.4	251.9	390.8	743.1
	IQR	103.2	155.1	160.9	306.8	507.9

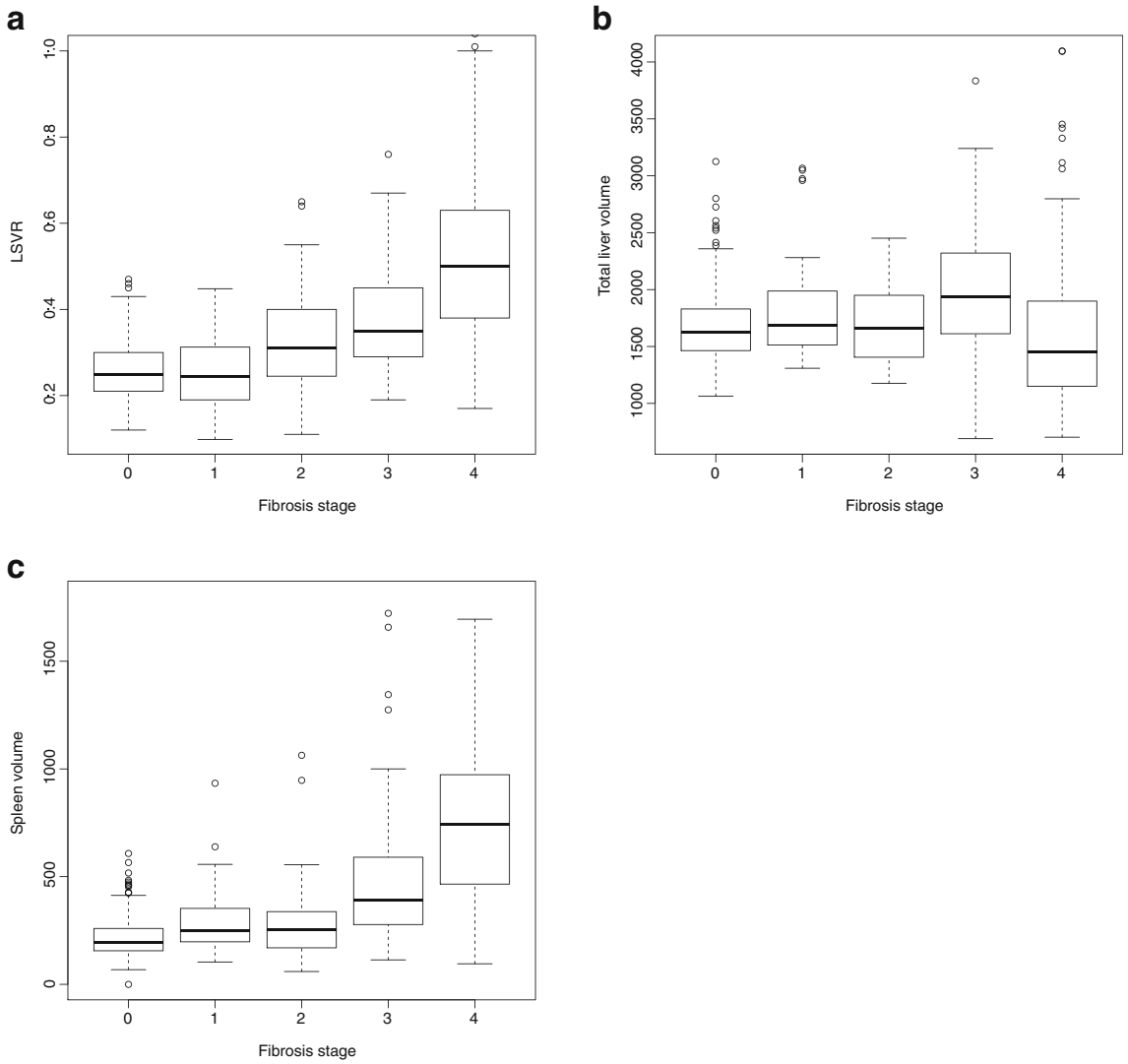


Fig. 2 Box plots of liver segmental volume ratio (LSVR), total liver volume and splenic volume according to liver fibrosis stage (F0–F4). Box plots of LSVR (**A**), total liver volume (**B**) and splenic volume (**C**) according to liver fibrosis stage (F0–F4) demonstrate a progressive overall increase in LSVR and splenic volume, whereas total liver volume demonstrates no such pattern. The boxes represent the middle 50 % or interquartile range (IQR) of the data. The line within the box represents the median of the data. Whiskers extend to the minimum and maximum values unless there are outliers represented by dots (defined as being further from the median than a multiple of the size of the box/IQR). Of note, some outliers for F4 in **A** and **B** extend above the visualized range

0.965 for cirrhosis (Table 3 and Fig. 4). Inclusion of total liver volume did not improve performance.

Discussion

We found that relative changes in CT-derived segmental liver volumes, as reflected by the LSVR, and total splenic volume both allow for non-invasive staging of hepatic fibrosis. In comparison, we also found that total liver volume was a poor predictor of the degree of underlying hepatic fibrosis. Unlike liver biopsy or elastography techniques, these CT volumetric biomarkers can be obtained retrospectively on routine scans obtained for other indications, and could also allow for serial monitoring over time.

Non-invasive techniques that can provide a more global assessment of liver status are desirable, either as a pre-screen for appropriate biopsy selection or as a standalone measure [2]. Serum-based biomarkers, including both routine liver function tests and other laboratory-based fibrosis biomarkers, are of some clinical value but are relatively ineffective for distinguishing amongst different fibrosis stages [2]. Measurement of liver stiffness with US and MR elastography techniques as a means to predict the degree of liver fibrosis is widely utilized but must be planned and performed prospectively.

Table 2 Diagnostic performance of the liver segmental volume ratio (LSVR), total liver volume and splenic volume for predicting stage of liver fibrosis at pathology

LSVR				
Fibrosis score*	ROC AUC (95 % CI)	Cut-off Value	Sensitivity (%)	Specificity (%)
F0 vs. F1–F4	0.782 (0.742–0.822)	0.340	58.8	88.5
F0–1 vs. F2–4	0.854 (0.819–0.889)	0.336	68.3	87.9
F0–2 vs. F3–4	0.880 (0.848–0.912)	0.347	72.2	88.1
F0–3 vs. F4	0.904 (0.869–0.939)	0.347	85.6	83.1
Total liver volume				
Fibrosis score	ROC AUC (95 % CI)	Cut-off Value	Sensitivity (%)	Specificity (%)
F0 vs. F1–F4	0.533 (0.484–0.583)	1924.9	33.2	84.8
F0–1 vs. F2–4	0.512 (0.457–0.567)	1926.3	34.7	83.6
F0–2 vs. F3–4	0.506 (0.444–0.568)	1926.3	36.4	82.7
F0–3 vs. F4	0.617 (0.542–0.692)	1259.8	37.1	93.0
Splenic volume				
Fibrosis score	ROC AUC (95 % CI)	Cut-off Value	Sensitivity (%)	Specificity (%)
F0 vs. F1–F4	0.825 (0.790–0.860)	266.7	73.8	79.0
F0–1 vs. F2–4	0.848 (0.812–0.884)	311.5	71.6	85.9
F0–2 vs. F3–4	0.901 (0.871–0.931)	315.2	81.4	85.2
F0–3 vs. F4	0.920 (0.889–0.952)	413.9	83.5	90.2

* F0–1 vs. F2–4 refers to significant fibrosis and F0–2 vs. F3–4 refers to advanced fibrosis

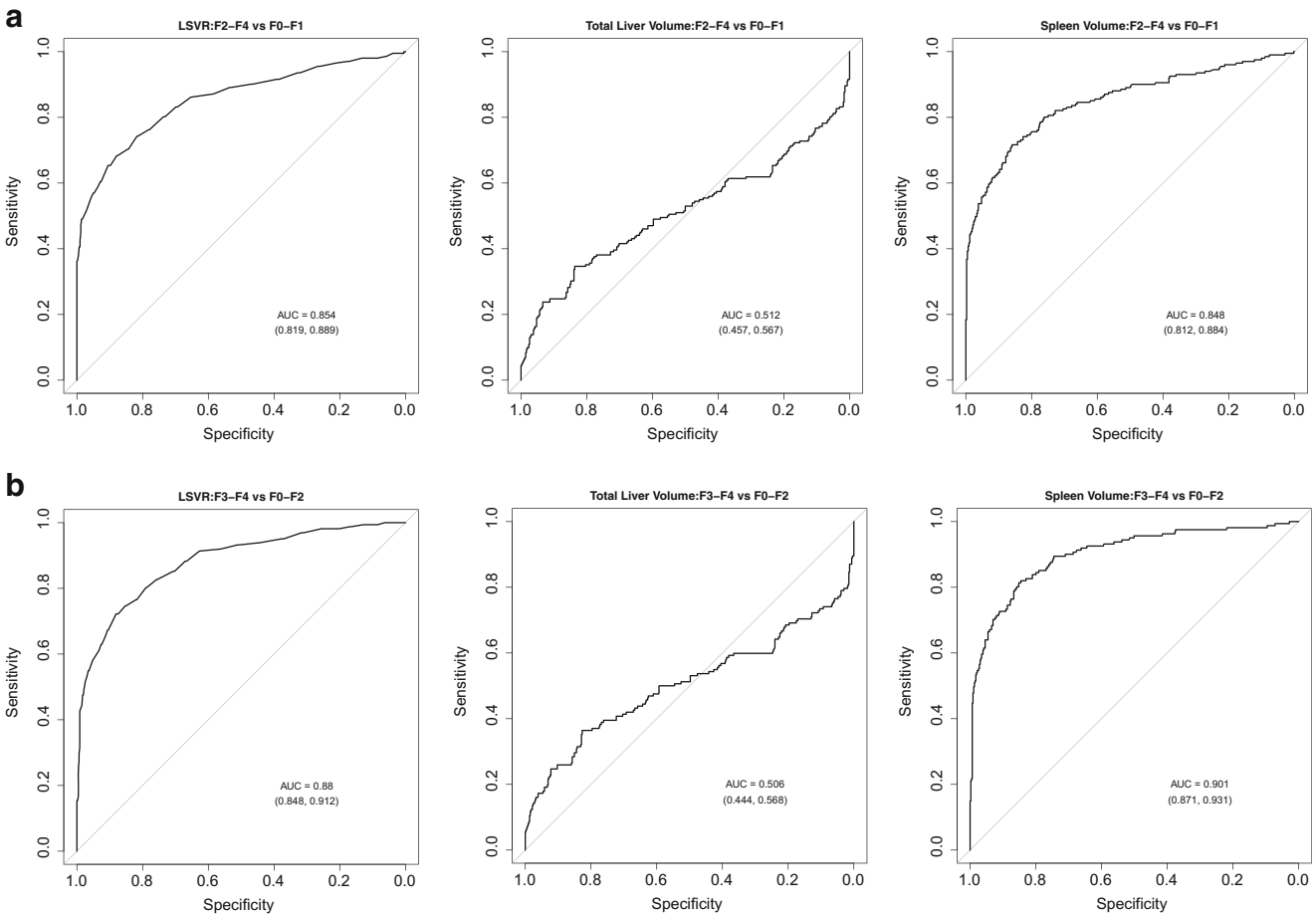


Fig. 3 Receiver operating characteristic (ROC) curves for performance of the liver segmental volume ratio (LSVR), total hepatic volume and splenic volume for distinguishing significant and advanced liver fibrosis. ROC curves for distinguishing significant fibrosis (≥F2; **A**) and advanced fibrosis (≥F3; **B**) demonstrate good performance using LSVR and splenic volume measurements, with AUC values ranging between 0.854 and 0.901, whereas total liver volume is ineffective, with AUC values around 0.500

Table 3 Combined diagnostic performance of the liver segmental volume ratio (LSVR) and splenic volume for predicting stage of liver fibrosis at pathology

LSVR and splenic volume combined	
Fibrosis score	ROC AUC (95 % CI)
F0 vs. F1–F4	0.865 (0.833–0.897)
F0–1 vs. F2–4	0.908 (0.879–0.937)
F0–2 vs. F3–4	0.947 (0.926–0.968)
F0–3 vs. F4	0.965 (0.950–0.981)

The utilization of cross-sectional CT and MR imaging features to predict the degree of hepatic fibrosis is appealing since this information can be extracted retrospectively from pre-existing scans performed for a wide variety of indications. Our results show that retrospective assessment of hepatosplenic volume on routine CT scans (i.e. LSVR and splenic volume) is comparable to US elastography for staging liver fibrosis. Previous attempts at harnessing other aspects of inherent imaging data from CT and MR studies without the use of elastography have shown mixed results. Examples include analysis of parenchymal enhancement on the equilibrium phase at CT [18], optical analysis of CT images [19], diffusion-weighted imaging (DWI) at MR [20–22], hepatobiliary phase at gadoxetic acid-enhanced MR [23] and early work using a multiparametric MR approach [24]. We are also investigating other retrospective CT imaging parameters, including liver surface nodularity and parenchymal texture analysis [25]. Because individual response to liver fibrosis and portal hypertension appears to be so variable in terms of the imaging features (e.g. degree of liver nodularity, splenic enlargement, portosystemic collaterals, ascites, etc), a multi-parametric approach seems prudent. Furthermore, since our CT volumetric assessment is based solely on anatomical changes, comparable measures could presumably be obtained at MR.

The LSVR attempts to accentuate the known volume loss that primarily affects Couinaud segments IV–VIII in cirrhosis, coupled with the compensatory hypertrophy in segments I–III. Other studies that have assessed liver volume in cirrhosis have either focused on the caudate or left lateral segments separately [26–28] or total liver volume [29]. Our results indicate that total liver volume is a very poor predictor of the degree of underlying hepatic fibrosis, which is perhaps not unexpected as changes related to volume loss and compensation cancel each other out. Importantly, the current study now shows that this volume ratio progressively differs for the pre-cirrhotic stages of fibrosis (F1–F3), which is much more relevant to clinical practice.

Previously, some have assumed that splenomegaly resulting from portal hypertension would largely apply only to cirrhosis (F4), rendering it less useful for detecting pre-cirrhotic stages of fibrosis [2]. However, our

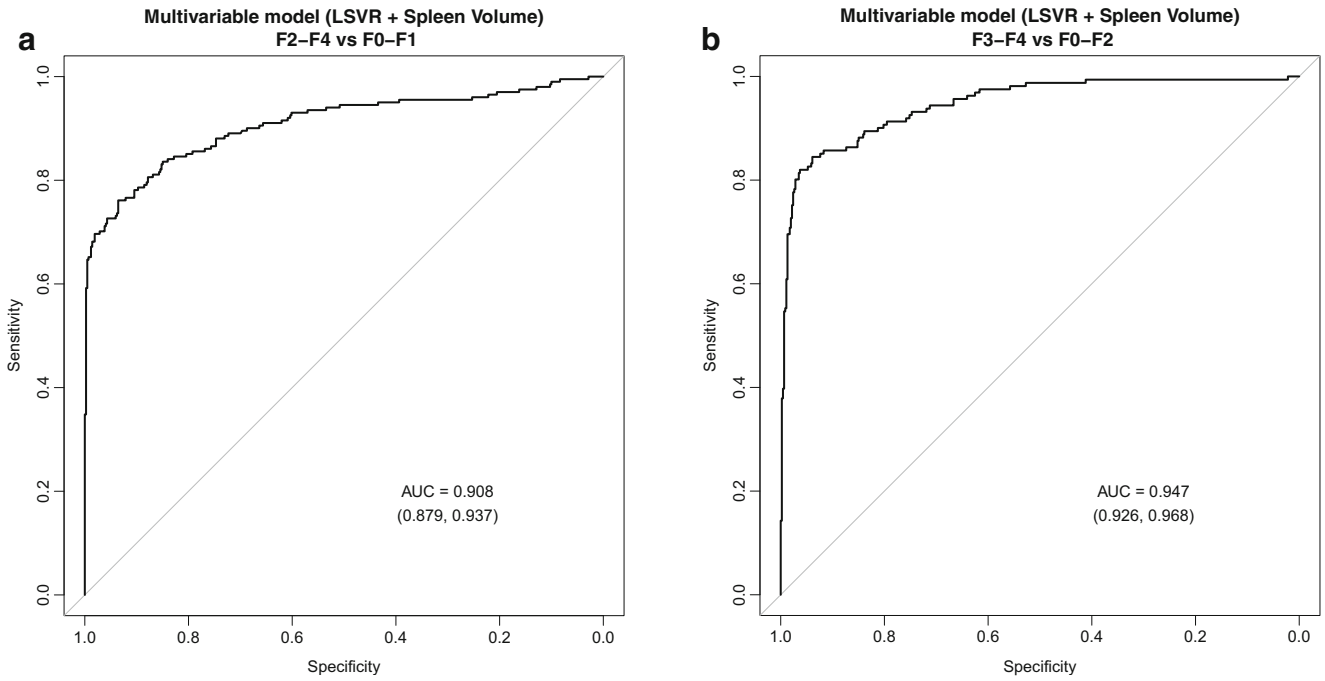


Fig. 4 Receiver operating characteristic (ROC) curves for the combined performance of liver segmental volume ratio (LSVR) and splenic volume for distinguishing significant and advanced liver fibrosis. ROC curves for distinguishing significant fibrosis (≥F2; **A**) and advanced fibrosis (≥F3; **B**) by combining LSVR and splenic volume using logistic regression analysis shows complementary performance of these two variables, with AUC values (0.908 and 0.947, respectively) that improve upon either variable alone

study shows the potential utility of assessing splenic volume alone for predicting earlier stages of liver fibrosis. Of note, a prior study investigating a smaller patient cohort found a correlation with linear splenic size [30]. Although splenic volume showed less distinction between fibrosis stages F1 and F2 compared with LSVR, we found that these measures were complementary as splenic volume showed more separation between F0 and F1, and the two measures taken together showed improved performance, with ROC AUC values matching or exceeding typical elastography levels. With continued improvements in automated segmentation by CT software packages, splenic volume could become a very easy and reproducible measure to obtain in routine practice. In comparison, our findings confirm that total liver volume is a poor predictor of fibrosis, even for distinguishing between normal and cirrhotic livers [29]. This is likely due to the compensatory increase in segments I–III, which offsets much of the volume loss seen in segments IV–VIII (both of which increase the LSVR).

We acknowledge limitations to our study. First, although all patients with pre-cirrhotic fibrosis (F1–F3) had histological confirmation, we did not require liver biopsy for our normal controls and a well-defined subset with known cirrhosis. Conceivably, some of the normal controls might have unsuspected early hepatic fibrosis, which may account in part for the relative lack of differences in LSVR between F0 and F1 cohorts. However, it is also quite possible that no significant volumetric changes have yet occurred at the F1 stage. In addition, the histological reference standard is prone to sampling error and inter-reader variability. Second, there were a variety of causes for the underlying hepatic fibrosis, for which we did not perform a sub-analysis. Of greatest current interest is staging patients with hepatitis C, where expensive pharmacological therapy requires accurate assessment of fibrosis stage, particularly for F2/F3 and above. Additional studies focusing on specific aetiologies for chronic liver disease would help to identify any unique changes occurring with hepatosplenic volumes. Lastly, the objective method used for determining cut-off values from the ROC curves precluded effective discrimination between fibrosis stages for the LSVR based on cut-off values alone. Other approaches to choosing a threshold value might have allowed for better distinction.

In conclusion, relative changes in segmental liver volumes (as reflected by the LSVR) and total splenic volume allow for non-invasive staging of hepatic fibrosis. In comparison, total liver volume is a poor predictor of fibrosis, as it fails to account for the dynamic intrahepatic changes between Couinaud segments I–III and IV–VIII. Hepatosplenic volume assessment at CT can serve as a useful biomarker for staging hepatic fibrosis and, unlike elastography or biopsy, can be obtained either retrospectively or prospectively. Further investigation is warranted, including confirmation by other groups, and assessment of other retrospective imaging features in a multi-parametric approach.

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