The Role of Liver Segment-to-Spleen Volume Ratio in the Staging of Hepatic Fibrosis in Patients with Hepatitis C Virus Infection

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ABSTRACT: **Background:** Accurate assessment of liver fibrosis is crucial for the management of patients with hepatitis C virus (HCV) infection.

Objectives: To evaluate the performance of liver segment-to-spleen volume ratio in predicting the severity of liver fibrosis.

Methods: Sixty-four consecutive HCV patients were enrolled in this retrospective study. All patients underwent contrast-enhanced computed tomography (CT) and were divided into three groups based on their hepatic fibrosis stage evaluated by shear-wave elastography (SWE): non-advanced (F0–F1, n=29), advanced (F2, n=19) and severe (F3–F4, n=16). Using semi-automated liver segmentation software, we calculated the following liver segments and spleen volumes for each participant: total liver volume (TLV), caudate lobe (CV), left lateral segment (LLV), left medial segment (LMV), right lobe (RV) and spleen (SV), as well as their ratios: CV/SV, RV/SV, LLV/SV, LMV/SV and TLV/SV.

Results: RV/SV was found to discriminate between patients with non-advanced and advanced fibrosis ($P = 0.001$), whereas SV, CV, RV, TLV/SV, LMV/SV and RV/SV discriminated between patients with advanced and severe fibrosis ($P < 0.05$). RV/SV ≤ 3.6 and RV ≤ 2.9 were identified as the best cutoff values to differentiate non-advanced from advanced fibrosis and advanced from severe fibrosis with sensitivities of 72.2% and 92.7%, specificities of 72.7% and 77.8%, and with an area under the receiver operating characteristic (ROC) curve of 0.797 and 0.847, respectively ($P \leq 0.002$).

Conclusions: RV/SV may be used for the assessment and monitoring of liver fibrosis in HCV patients prior to the administration of antiviral therapy, considering SWE as the reference method.

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KEY WORDS: liver volume, liver fibrosis, spleen volume, hepatitis C virus (HCV), computed tomography (CT)

Hepatitis C virus (HCV) affects 130 to 210 million people worldwide and is a major cause of liver fibrosis [1]. New antiviral agents, approved recently for the treatment of chronic HCV infection [2-4], provide the tools for cure in many patients and may reverse hepatic fibrosis [5]. Therefore, assessment of the liver fibrosis burden can provide useful information not only for diagnosis but also for antiviral treatment planning, for prognosis, as well as for evaluating patients prior to hepatic resection and living-donor liver transplantation.

Although liver biopsy is currently considered the best-accepted standard for the staging of liver fibrosis, its limitations – namely its invasive nature, potential complications, sampling errors, and associated interobserver variability – have motivated research towards non-invasive alternatives. Furthermore, because of its invasive nature, liver biopsy may not be the ideal method for monitoring disease progression. The non-invasive methods used for the evaluation of liver damage are either biological tests (which use biological markers to estimate the severity of fibrosis) or elastographic methods [6,7]. Among them, shear-wave elastography (SWE) is a promising method with early data suggestive of equivalence with transient elastography for diagnosing liver fibrosis [8-10] and a high diagnostic accuracy in differentiating lower from higher stages of fibrosis [11].

Studies have shown that clinical volumetric measurements using computed tomography (CT) are highly relevant in staging liver fibrosis and diagnosing cirrhosis [12-16]. Li et al. [12] showed that variations in liver and spleen volume measured by CT correlated with the stage of liver fibrosis in 87 patients with chronic hepatitis B virus (HBV) infection. Others investigated liver lobe volumes and the ratios of liver lobe volumes to spleen volume measured with magnetic resonance imaging (MRI) for quantitatively monitoring and staging liver fibrosis in a mini-pig model [17]. Our study was the first attempt, to our knowledge, to utilize semi-automated liver segmentation software for the evaluation of total liver, liver segments and spleen volume and their ratio, measured by CT, in predicting the severity of liver fibrosis stage in patients with HCV.

PATIENTS AND METHODS

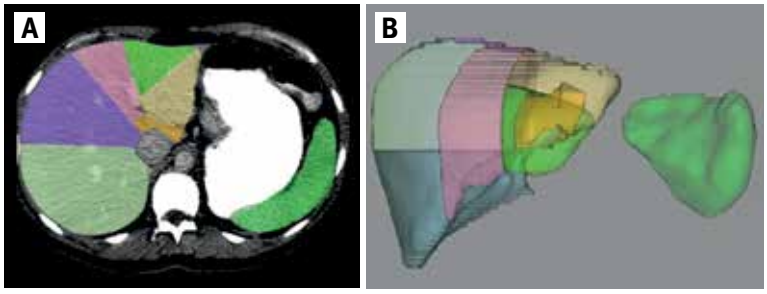
STUDY DESIGN AND SETTINGS

This single-institution study was approved by the institutional review board. Informed consent was waived due to the retrospective review of data. Imaging and clinical data were obtained from the picture archive and communication system (PACS, Carestream Health 11.0, Rochester, NY, USA) and the computerized medical records at our hospital, respectively. CT volumetric measurement of the liver, spleen, and liver segments was obtained using semi-automated liver segmentation clinical software (Liver™, Philips Corporation, Einthoven, Netherlands).

STAGING OF LIVER FIBROSIS

In our medical institution every HCV patient is referred to SWE (SuperSonic Imagine, Aix-en-Provence, France) for the detection and staging of hepatic fibrosis. It is performed with a convex broadband probe (SC6-1) by a skilled radiologist (Y.K.) who has more than 15 years experience in abdominal ultrasound imaging and more than 3 years in real-time elastography examinations. The technology measures the speed of shear-wave propagation, which is then used to compute tissue stiffness, also known as Young's modulus of elasticity, in kiloPascals (KPa). SWE measurements were performed on the right upper lobe of the liver through intercostal spaces with the patient lying in the supine position with the right arm in maximal abduction. Young's modulus < 7.1 KPa denotes non-advanced fibrosis (F0–F1), 7.1 to 8.6 KPa denotes advanced disease (F2) and > 8.6 KPa denotes severe fibrosis (F3–F4) [8].

Figure 1. [A] Axial image of a segmented liver and spleen of a patient with non-advanced fibrosis. **[B]** Three-dimensional reconstruction image of the liver and spleen. **[C]** Values are the volumes of the total liver, spleen, liver segments and their normalized volume out of the total liver volume (Liver™, Philips Corporation, Einthoven, Netherlands)



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Liver	Volume			% of total		
Functional liver	1337.1 ml			96.8%		
Total liver	1380.6 ml			100.0%		
Segments	**Total volume**			**% of total**		
Segment 1	11.5 ml			0.8%		
Segment 2	141.9 ml	205.9 ml	330.9 ml	10.3%	14.9%	24.0%
Segment 3	64.0 ml			4.6%		
Segment 4	125.0 ml			9.1%		
Segment 5	216.9 ml	510.6 ml	1037.9 ml	15.7%	37.0%	75.2%
Segment 8	293.7 ml			21.3%		
Segment 6	199.9 ml	527.3 ml		14.5%	38.2%	
Segment 7	327.4 ml			23.7%		
Findings	**Volume**			**% of total**		
Spleen	188.1 ml			0.0%		

STUDY POPULATION

Ninety-five consecutive HCV patients were enrolled in the study between November 2012 and February 2014 based on their performance of contrast-enhanced CT in tandem with SWE, not more than 3 months apart. Patients were excluded if portal vein thrombosis (n = 2), hepatocellular carcinoma (n = 8) or primary hematologic disorders (e.g., lymphoma or leukemia, n = 2) were detected, or if they had a history of treatment for portal hypertension and liver/circulatory dysfunction, including splenectomy, partial spleen embolization or transjugular intrahepatic portosystemic shunt placement, recurrent variceal hemorrhage and ascites (n = 19). The final patient population (n=64, 34 men, mean age 55 ± 12, range 27–75 years) was divided into three groups based on their fibrosis stage: 29 patients with non-advanced fibrosis (F0–F1), 19 patients with advanced fibrosis (F2), and 16 patients with severe fibrosis (F3–F4).

CT IMAGING

All patients underwent contrast-enhanced scans in the supine position with either a 256-multidetector CT scanner (VCT LightSpeed, GE Healthcare, Buckinghamshire, UK) or a 64-multidetector CT scanner (iCT, Philips Healthcare, Best, Netherlands). The scanning parameters were as follow: 120 kVp, 240 mAs, section thickness 2.5 mm, section reconstruction interval 2.5 mm.

LIVER AND SPLEEN VOLUMETRIC MEASUREMENTS

Contiguous portal venous phase or delayed phase images of 2.5 mm thickness were used for the image analysis. The software outlined the boundaries of the liver and the spleen, allowed for manual correction in three planes, and calculated their volumes. Liver segments were delimited by the software on the basis of hepatic vascular anatomy [18] [Figure 1 A and B]. For each patient, hepatic vascular anatomy (inferior vena cava, left and right portal veins, right and middle hepatic veins) and ligaments (falciform and venosum) were marked independently by two experienced radiologists. Thereafter, the software provided automatic calculation of the total liver volume and volumes of Couinaud segments, excluding the inferior vena cava and gallbladder [Figure 1C]. Radiologists were blinded to clinical data when viewing the patients. For analysis, the liver was divided into four lobes according to the Goldsmith and Woodburne system [19]: left lateral and medial lobes (segments II and III and segment IV, respectively), right lobe (segment V-VIII) and

caudate lobe (segment I). Left lateral liver lobe volume (LLV), left medial liver lobe volume (LMV), right liver lobe volume (RV), and caudate lobe volume (CV) were obtained by means of the sum of the corresponding segments. The following parameters for each participant were then calculated: total liver volume (TLV), CV, LLV, LMV, RV and (spleen) SV, as well as the ratios of CV to SV (CV/SV), RV to SV (RV/SV), LLV to SV (LLV/SV), LMV to SV (LMV/SV), and TLV to SV (TLV/SV).

STATISTICAL ANALYSIS

Data were expressed as mean ± standard deviation. Kruskal-Wallis test and Spearman's rank correlation analysis were performed to assess the correlations between volumetric parameters and the stage of liver fibrosis. Multiple pairwise comparisons for post-hoc analysis were conducted with the Bonferroni correction. Receiver operating characteristic (ROC) curve analysis was used to assess the utility of TLV, RV, LLV, LMV, CV, SV, as well as the ratios of CV/SV, RV/SV, LLV/SV, LMV/SV, and TLV/SV, as predictors of early and advanced liver fibrosis. Intra- and inter-observer agreement of volumetric measurements was indicated by calculating the intra-class correlation coefficient (ICC) with a 95% confidence interval (95%CI). The analysis was performed with SPSS version 21.0 (SPSS, IBM, USA). $P < 0.05$ was considered statistically significant.

RESULTS

CORRELATION OF VOLUMETRIC PARAMETERS AND LIVER FIBROSIS STAGE

Baseline characteristics, including volumetric parameters, for each group are shown in Table 1. The intra- and inter-observer agreement showed ICC values of 0.93 (95%CI 0.90–0.96) and 0.89 (95%CI 0.83–0.95), respectively. There was a statistically significant increase in SV and CV and a decrease in RV, TLV/SV, LMV/SV and RV/SV with an increase in the severity of liver fibrosis stage (all $P < 0.05$) [Table 1]. No such correlation was noted for the volumetric parameters TLV, LLV, LMV, CV/SV and LLV/SV. However, SV, CV, RV, TLV/SV, LLV/SV, LMV/SV and RV/SV discriminated significantly between advanced and severe liver fibrosis, whereas RV/SV was the only volumetric parameter to discriminate between non-advanced and advanced fibrosis [Table 1].

UTILITY OF VOLUMETRIC PARAMETERS FOR PREDICTING LIVER FIBROSIS STAGE

The area under the ROC curves (AUC), threshold values, sensitivity and specificity of CV, LLV, LMV, RV, TLV and SV, and the ratio of CV, LLV, LMV, RV and TLV to SV for differentiating between patients with non-advanced and advanced liver fibrosis and between patients with advanced and severe liver are shown in Tables 2 and 3, respectively. RV/SV was found to be the only volumetric parameter to discriminate significantly between non-advanced and advanced HCV patients [Table 3]. RV/SV ≤ 3.6 was identified as the cutoff value for discrimination between non-advanced and advanced fibrosis with sensitivity of 72.2% and specificity of 72.7% ($P = 0.001$, AUC = 0.797).

SV, CV, RV and the ratios TLV/SV, LMV/SV and RV/SV significantly discriminated between patients with advanced

Table 1. Baseline characteristics of hepatitis C virus patients

	Non-advanced fibrosis group (n=29)	Advanced fibrosis group (n=19)	Severe fibrosis group (n=16)	*P* value	Spearman's Rho value
Gender (M/F)	15/14	9/10	10/6	0.440	–
Age	52.6 ± 18	54.8 ± 12.9	57.8 ± 13.0	0.192	–
SV (cm^3)	243.71 ± 93.78†	332.72 ± 188.52†	535.24 ± 211.03	‹ 0.001	0.57
TLV (cm^3)	1739.99 ± 523.29	1671.33 ± 552.67	1566.81 ± 500.63	0.192	-0.15
CV (cm^3)	25.75 ± 6.98†	33.03 ± 16.33†	54.52 ± 29.22	0.002	0.48
LLV (cm^3)	265.86 ± 86.26	289.11 ± 108.53	390.21 ± 136.82	0.215	0.15
LMV (cm^3)	249.93 ± 161.13	266.13 ± 145.92	265.22 ± 200.63	0.716	0.06
RV (cm^3)	1199.11 ± 171.1†	1083.12 ± 317.6†	857.93 ± 277.33	0.001	-0.57
TLV/SV	6.65 ± 3.19†	5.95 ± 2.76†	3.34 ± 1.37	‹ 0.001	-0.58
CV/SV	0.12 ± 0.08	0.12 ± 0.09	0.11 ± 0.06	0.574	-0.11
LLV/SV	1.08 ± 1.17†	0.93 ± 0.49†	0.85 ± 0.31	0.102	-0.14
LMV/SV	0.95 ± 1.14†	0.81 ± 0.51†	0.53 ± 0.36	0.026	-0.53
RV/SV	5.05 ± 1.87†Δ	3.41 ± 1.32†	1.94 ± 1.18	‹ 0.001	-0.61

ΔDifferent from advanced fibrosis group

†Different from severe fibrosis group

All comparisons denote significance after Bonferroni correction ($P < 0.05$)

SV = spleen volume, TLV = total liver volume, CV = caudate volume, LLV = left lateral segment volume, LMV = left medial segment volume, RV = right lobe volume, TLV/SV = ratio of TLV to SV, CV/SV = ratio of CV to SV, LLV/SV = ratio of LLV to SV, LMV/SV = ratio of LMV to SV, RV/SV = ratio of RV to SV

Table 2. Receiver operating curve analysis of the volumetric variables for the prediction of advanced liver fibrosis

	Threshold value	AUC	95%CI	Sensitivity (%)	Specificity (%)	*P* value
SV (cm^3)	≥ 292.35	0.641	0.467–0.816	44.4	72.7	0.128
TLV (cm^3)	≤ 1728.75	0.596	0.388–0.804	61.1	63.6	0.302
CV (cm^3)	≥ 29.15	0.649	0.461–0.837	61.1	67.3	0.109
LLV (cm^3)	≥ 306.90	0.534	0.351–0.717	27.8	50.0	0.714
LMV (cm^3)	≥ 151.40	0.556	0.375–0.736	88.9	27.3	0.550
RV (cm^3)	≤ 1114.60	0.675	0.501–0.849	61.1	77.3	0.064
TLV/SV	≤ 6.34	0.640	0.463–0.815	66.7	63.6	0.112
CV/SV (%)	≤ 0.10	0.581	0.395–0.767	33.3	41.9	0.384
LLV/SV (%)	≤ 1.03	0.404	0.426–0.781	45.6	68.2	0.265
LMV/SV (%)	≤ 0.87	0.578	0.396–0.761	83.3	50	0.399
RV/SV	≤ 3.58	0.797	0.660–0.933	72.2	72.7	0.001

SV = spleen volume, TLV = total liver volume, CV = caudate volume, LLV = left lateral segment volume, LMV = left medial segment volume, RV = right lobe volume, TLV/SV = ratio of TLV to SV, CV/SV = ratio of CV to SV, LLV/SV = ratio of LLV to SV, LMV/SV = ratio of LMV to SV, RV/SV = ratio of RV to SV, AUC = area under the receiver operating curve, CI = confidence interval

Table 3. Receiver operating curve analysis of the volumetric variables for the prediction of severe liver fibrosis

	Threshold value	AUC	95%CI	Sensitivity (%)	Specificity (%)	*P* value
SV (cm^3)	≥ 376.30	0.819	0.655–0.966	91.7	72.2	0.005
TLV (cm^3)	≤ 1632.65	0.551	0.340–0.762	66.7	44.4	0.641
CV (cm^3)	≥ 38.55	0.694	0.525–0.905	66.7	72.2	0.049
LLV (cm^3)	≥ 444.95	0.722	0.428–0.877	50.0	94.4	0.162
LMV (cm^3)	≥ 182.30	0.556	0.369–0.817	33.3	11.1	0.397
RV (cm^3)	≤ 1019.10	0.741	0.558–0.924	75.0	61.1	0.028
TLV/SV	≤ 4.24	0.833	0.689–0.998	83.3	66.7	0.002
CV/SV (%)	≤ 0.07	0.542	0.340–0.781	58.3	16.7	0.582
LLV/SV (%)	≤ 0.83	0.694	0.493–0.887	66.7	72.2	0.090
LMV/SV (%)	≤ 0.58	0.806	0.618–0.954	66.7	88.9	0.031
RV/SV	≤ 2.87	0.847	0.696–0.998	92.7	77.8	0.001

SV = spleen volume, TLV = total liver volume, CV = caudate volume, LLV = left lateral segment volume, LMV = left medial segment volume, RV = right lobe volume, TLV/SV = ratio of TLV to SV, CV/SV = ratio of CV to SV, LLV/SV = ratio of LLV to SV, LMV/SV = ratio of LMV to SV, RV/SV = ratio of RV to SV, AUC = area under the receiver operating curve, CI = confidence interval

and severe liver fibrosis [Table 3]; of these parameters, RV/SV was the most significant ($P = 0.001$, AUC = 0.847). SV ≥ 376.3 cm^3, CV ≥ 38.6 cm^3, RV ≤ 1019 cm^3, TLV/SV ≤ 4.2, LMV/SV ≤ 0.58 and RV/SV ≤ 2.9 were identified as the cutoff values for discrimination between advanced and severe, with sensitivities of 91.7%, 66.7%, 75%, 83.3%, 66.7% and 92.7%, and specificities of 72.2%, 72.2%, 61.1%, 66.7%, 88.9% and 77.8%, respectively ($P < 0.05$).

DISCUSSION

Identifying patients with advanced or severe fibrosis is of particular importance since the post-treatment prognosis depends on the stage of fibrosis [2]. In our study we investigated whether volumetric parameters of liver and spleen could be used for quantitatively monitoring and staging liver fibrosis in patients with HCV. To the best of our knowledge, no studies involving liver and spleen volumetry in patients with HCV for evaluating the stage of liver fibrosis have been reported to date.

We divided our patient population into three groups according to the severity of liver fibrosis. The differentiation of advanced (F2) and severe (F3–F4) fibrosis is particularly relevant in HCV, because according to the latest clinical practice guidelines of the European Association for the Study of the Liver (EASL) [2], antiviral treatment should be prioritized for the latter patient group due to its high cost and disparate availability. As shown in our study, there was a significant decrease in RV and increase in CV and SV as the stage of fibrosis advanced [Table 1]. The decrease in RV may be explained by the reduced blood perfusion through the portal vein [20]. Hepatic fibrosis causes attenuation of the intrahepatic portal and hepatic venous branches, and the hepatic vascular bed is reduced. Impaired drainage of blood from the liver, caused by compression of hepatic venous tributaries by regenerating nodules or fibrosis, also increases the resistance to portal flow [20]. However, the venous drainage of the caudate lobe is preserved, probably because it is supplied by the posterior branch of the right portal vein, which has a shorter intrahepatic course, preventing this region of the liver from atrophying significantly [21]. The spleen is normally enlarged with increasing hepatic fibrosis, based on hemodynamic considerations. In hepatic fibrosis, distinct alterations of the hepatic microvasculature including rarefaction of sinusoids and structural changes of sinusoidal endothelia result in diminished nutritive blood supply, increased total hepatic vascular resistance, and hence, portal hypertension and portosystemic collateralization [22]. Due to portal hypertension, spleen enlargement is thought to first appear at the stage of bridging fibrosis as a result of liver central vein occlusion, prior to the onset of cirrhosis [23]. In our study we found that the performance of the RV/SV ratio was superior to other volumetric parameters, including either RV or SV, for identifying the severity of liver fibrosis. RV/SV discriminated better between patients for all the groups, including those with non-advanced to advanced liver fibrosis and those with advanced to severe liver fibrosis (AUC = 0.797, 0.847, with 95%CI 0.660–0.993 and 0.696–0.998, respectively). The volumetric ratio RV/SV was recently shown to be clinically valuable in patients with cirrhosis due to chronic HBV infection [23]. Chen and colleagues [24] found that RV/SV, detected by MRI, was the most accurate parameter to indicate the severity of liver cirrhosis and to discriminate it between different Child-Pugh classes. We also detected decreasing RV/SV with the progression to severe liver fibrosis ($P = 0.001$); therefore, the use of RV/SV as a reference index to evaluate severity of liver fibrosis may be valuable for both hepatic fibrosis and cirrhosis.

Similar to RV/SV, the ratio TLV/SV was found to discriminate significantly between patients with advanced and severe liver fibrosis [Table 3]. Liu et al. [13] and Goshima et al. [25] also demonstrated with CT and MRI, respectively, that the TLV/SV ratio has significant clinical value in the diagnosis of advanced liver fibrosis in patients with hepatic fibrosis. TLV/SV was gradually decreased with the aggravation of hepatic fibrosis, similar to our results. However, RV/SV may be a better indicator of fibrosis than TLV/SV because of the contribution of both CV and LLV which, in fact, increase significantly with fibrosis, as shown in Table 1.

Changes in LLV and LMV proved not to be predictive of the degree of fibrosis. This may reflect the influences of competing factors, such as anatomic variations in hepatic venous drainage, compensatory hypertrophy of the left lobe, or other unknown factors. Our study showed that LMV/SV decreased with the increase in the severity of liver fibrosis and cirrhosis. We suspect that the reduction of this ratio is linked to the

increased SV with the progression of fibrosis since there is no statistically significant difference in LMV between the groups. Other than RV/SV, there were no significant differences in the volumetric parameters that were studied between patients with non-advanced and advanced liver fibrosis, probably because of the early stage of the fibrotic changes [Table 2].

Our results suggest that CT volumetric measurements, a reliable and reproducible non-invasive method, may be helpful to clinicians and radiologists in evaluating and monitoring liver fibrosis stage in HCV patients. Automatic or semi-automatic volumetric measurements are accurate, rapid and efficient [15], and the physiological significance of these measurements may be of prognostic value [16]. As a non-invasive modality, CT has an advantage over elastography techniques, either in ultrasound or MRI, where all equipment is expensive and not commonly available. CT can provide accurate and reliable three-dimensional reconstruction images with fine anatomic images of each liver segment or spleen and can reveal additional abdominal pathologies, accounting for its widespread application in clinical practice.

There are several limitations to our study. First, we used SWE as our reference standard to establish fibrosis stages, and no patient underwent a biopsy, still considered the gold standard for evaluating liver fibrosis. In order to include more subjects in our study, we decided to use SWE as the reference method instead of liver biopsy, also because fewer and fewer patients accept this invasive method for liver injury assessment. However, SWE is a recognized technique for the non-invasive evaluation of liver fibrosis, included in the EASL guidelines [2]. According to a recent prospective study [11], it can be used as a non-invasive test to differentiate intermediate degrees of liver fibrosis in HCV patients. Second, the time-consuming post-processing required for obtaining the liver segmental volumes and SV may be a barrier to the potential widespread use of CT volumetry. Third, our study population is still limited to patients with HCV and there is no comparison with patients who do not have liver disease. Further prospective studies involving a larger number of HCV patients and healthy controls, and correlation with other reference methods for liver fibrosis staging are needed to evaluate the liver and spleen volumetric parameters as a new tool for staging hepatic fibrosis.

In conclusion, RV/SV may be the best volumetric parameter for the staging of hepatic fibrosis in patients with HCV infection, considering SWE as the reference method. Semi-automated CT volumetry may be utilized by radiologists and clinicians as a non-invasive tool for the assessment and monitoring of liver fibrosis stage prior to the administration of antiviral therapy and prior to performing selective hepatic resection or living-donor liver transplantation.

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