**Name of Journal***:* ***World Journal of Hepatology***

**Manuscript NO: 40647**

**Manuscript Type: Original Article**

***Retrospective Cohort Study***

**Spleen stiffness mirrors changes in portal hypertension after successful interferon-free therapy in chronic-hepatitis C virus patients**

Ravaioli F *et al.* Spleen stiffness measurement and PH after DAAs

Federico Ravaioli, Antonio Colecchia, Elton Dajti, Giovanni Marasco, Luigina Vanessa Alemanni, Maria Rosa Tamè, Francesco Azzaroli, Stefano Brillanti, Giuseppe Mazzella, Davide Festi

**Federico Ravaioli, Antonio Colecchia, Elton Dajti, Giovanni Marasco, Luigina Vanessa Alemanni, Maria Rosa Tamè, Francesco Azzaroli, Stefano Brillanti, Giuseppe Mazzella, Davide Festi,** Gastroenterology Unit, Sant’Orsola-Malpighi University Hospital, Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Bologna 40138, Italy

**Antonio Colecchia,** Unit of Gastroenterology, Borgo Trento University Hospital, Verona 37100, Italy

**ORCID number:** Federico Ravaioli (0000-0002-1142-8585); Antonio Colecchia (0000-0002-8384-801X); Elton Dajti (0000-0003-2905-1146); Giovanni Marasco (0000-0001-7167-8773); Luigina Vanessa Alemanni (0000-0003-3013-7772); Maria Rosa Tamè (0000-0002-6299-216X); Francesco Azzaroli (0000-0003-3675-8545); Stefano Brillanti (0000-0003-4181-795X); Giuseppe Mazzella (0000-0001-8656-8112); Davide Festi (0000-0001-9534-1745).

**Authors contributions:** Ravaioli F, Dajti E, Marasco G and Alemanni V collected data, analysed data, wrote the manuscript, approved the final manuscript; Tamè MR, Azzaroli F, Brillanti S and Mazzella G analysed data and contributed to the drafting and final approval of the manuscript; Colecchia A, Mazzella G and Festi D provided overall oversight of the study, analysed data and contributed to the drafting and final approval of the manuscript.

**Institutional review board statement:** This study was approved by the National Institutional Review Board of the Italian Medicines Agency committee. Local IRB [Institutional Ethics Committee of Sant’Orsola-Malpighi University Hospital (Bologna, Italy)] approval was authorized.

**Informed consent statement:** Patients were not required to give informed consent to the study because the analysis used anonymous data that were obtained after each patient agreed to treatment by written consent.

**Conflict of interest statement:** The authors disclose no conflicts.

**STROBE statement:** The guidelines of the STROBE statement have been adopted and a fulfilled version of the checklist has been attached with the submission of the manuscript**.**

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**Manuscript source:** Invited manuscript

**Correspondence to: Antonio Colecchia, MD, Assistant Professor, Chief Doctor,** Unit of Gastroenterology, Borgo Trento University Hospital, Verona 37100, Italy**.** antonio.colecchia@aovr.veneto.it

**Telephone:** +39-335-5876834

**Fax:** +39-51-2144111

**Received:** July 3, 2018

**Peer-review started:** July 3, 2018

**First decision:** July 24, 2018

**Revised:** July 27, 2018

**Accepted:** August 12, 2018

**Article in press:**

**Published online:**

**Abstract**

***Aim***

to investigate changes in spleen stiffness measurements (SSMs) and other non-invasive tests (NITs) after treatment with direct-acting-antivirals (DAAs) and identify predictors of SSM change after sustained virological response (SVR).

***Methods***

We retrospectively analysed 146 advanced-chronic-liver-disease (ACLD) patients treated with DAA with available paired SSM at baseline (BL) and SVR24. Liver stiffness (LSM), spleen diameter (SD), platelet count (PLT) and liver stiffness-spleen diameter-to-platelet count ratio score (LSPS) were also investigated. LSM ≥ 21 kPa was used as a cut-off to rule-in clinically significant portal hypertension (CSPH). SSM reduction > 20% from BL was defined as significant.

***Results***

SSM significantly decreased at SVR24, in both patients with and without CSPH; in 44.8% of cases SSM reduction was > 20%. LSPS significantly improved in entire cohort at SVR24; SD and PLT changed significantly only in patients without CSPH. LSM significantly decreased in 65.7% of patients; also in 2/3 patients in whom SSM did not decrease. The independent predictor of SSM decrease was median relative change of LSM. CSPH persisted in 54.4% patients after SVR. Delta LSM and baseline SSM were independent factors associated with CSPH persistence.

***Conclusion***

SSM and other NITs significantly decrease after SVR, although differently according to the patient's clinical condition. SSM faithfully reflects changes in portal hypertension and could represent a useful NIT for the follow-up of these patients.

**Key words:** Spleen stiffness measurement; Advanced chronic liver disease; clinically significant portal hypertension; non-invasive test; Portal hypertension, Direct-acting-antivirals; Hepatitis C

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**Core tip**: Liver stiffness measurement (LSM) and spleen stiffness measurement (SSM) are widely validated surrogates of portal hypertension (PH) and its complications. Their role in the assessment of therapy response, such as treatment with direct-acting antivirals (DAAs) of HCV patients, is still under investigation. We demonstrated in a large cohort that not only LSM, but also SSM, is reduced six months after successful DAA therapy. As opposed to LSM, SSM directly reflects PH and is less influenced by the immediate reduction of liver necro-inflammation. We believe that SSM could represent a helpful tool for the clinician in the follow-up of these patients.

Ravaioli F, Colecchia A, Dajti E, Marasco G, Alemanni LV, Tamè MR, Azzaroli F, Brillanti S, Mazzella G, Festi D. Spleen stiffness mirrors changes in portal hypertension after successful interferon-free therapy in chronic-hepatitis C virus patients. *World J Hepatol* 2018;In press

# **INTRODUCTION**

Chronic hepatitis C virus (HCV) infection represents one of the major causes of liver disease and is a leading cause of liver transplantation[1,2]. Recently, the introduction of the highly effective interferon-free direct-acting antivirals (DAAs) has enormously increased the number of patients who have achieved sustained viral response (SVR), even in patients with liver cirrhosis[3–5].

Although studies mostly from the interferon era have shown that achieving SVR improves liver function[6,7], liver histology[8] and overall clinical outcomes[9], the real impact of SVR in the DAA-era in terms of changes in portal hypertension (PH), risk of decompensation on immediate follow-up, is not completely known, especially in patients with advance chronic liver diseases (ACLD). PH is a progressive condition that represents a key point in the natural history of liver diseases[10]; therefore its assessment by hepatic venous pressure gradient (HVPG) measurement is fundamental in ACLD patients[11–14]. Indeed, the development of clinically significant portal hypertension (CSPH) in patients with compensated ACLD (cACLD)[11] is highly associated with the risk of clinical decompensation events (ascites, variceal bleeding, jaundice and hepatic encephalopathy)[10].

To date, several studies have demonstrated a significant reduction in HVPG (> 10%-20%) after achieving SVR, both after interferon-based[15–17] and DAA-based regimen[18–21]. Although HVPG measurement is the gold standard to assess PH[11], it remains an invasive method[22] and its use is still limited only to highly specialized centres[12]; thus its repeated measurements during the follow-up would ~~be~~ result hardly applicable.

Consequently, in the last decade, a lot of non-invasive tests (NITs), including liver and spleen stiffness measurement (LSM and SSM), as well as liver stiffness to spleen/platelet score (LSPS) have been developed and validated to accurately assess PH degree and its complications[11,22–29]. In fact, recently~~,~~ the Baveno VI Consensus recommended LSM values of 10 kPa to rule out cACLD patients, and values of 20-25 kPa to accurately identify patients with CSPH in patients with chronic viral hepatitis[11]. However, to date, few studies have evaluated the role of NITs in PH assessment in SVR patients after DAA treatment and their role in the follow-up. Even if, most studies agree on the fact that LSM rapidly decreases after virus eradication[18,19,30–32], controversial data have emerged regarding the changes of SSM after SVR[30–32].

**MATERIALS AND METHODS**

***Aims of the study***

We aimed to: (1) investigate the possible effect of HCV-DAA treatment on PH evaluated by spleen stiffness changes as mirror of PH; (2) as well as those of other NITs, after HCV-DAA treatment; moreover, we aimed to (3) identify the presence of predictors of the SSM changes in SVR patients after DAA therapy.

***Study design and population***

This is a retrospective analysis of prospectively collected data of HCV-related cACLD patients treated with DAAs between January 2015 and September 2017 at our department, with valid measurement of LSM and SSM by transient elastography (TE) at baseline (BL) and at 6 mo after end of DAA treatment (SVR24).

According to the Baveno VI Criteria[11], values of LSM > 10 kPa at TE were considered suggestive of having cACLD and whom with LSM ≥ 21 kPa were defined to rule-in CSPH as previously described[33,34]. At baseline, laboratory values, Model for End-Stage Liver Disease (MELD) and Child-Turcotte Pugh (CTP) scores were also reported for each patient.

We excluded patients who (1) had incomplete response to surgical resection or loco-regional ablation of previous HCC; (2) developed HCC during antiviral treatment; (3) developed variceal bleeding and/or endoscopic ~~EV~~ banding legation (EBL) during study period; and (4) initiated or changed dosage of non-selective beta-blockers (NSBB) or had portal vein thrombosis, transjugular intrahepatic portosystemic shunt (TIPS) and non-cirrhotic PH. A subgroup of the patients who did not achieve SVR were separately investigated.

***Antiviral treatment***

Eligibility for treatment of HCV patients with DAAs was assessed following the priority criteria established in the protocol approved by the Italian Medicines Agency committee (AIFA). The choice of DAA and treatment duration (12 or 24 wk) was based on viral genotype and stage of disease, according to the guidelines available at the time of enrolment[35]. SVR was defined as undetectable HCV-RNA, using real-time PCR, with detection limit of 15 IU/mL, at 12-wk post-treatment follow-up visit.

***NITs for PH assessments***

LSM values were assessed by expert operators, using the FibroScan® apparatus with “M” probe (Echosens®, Paris, France) after overnight fasting and after a complete abdominal US examination. LSM values were obtained as previously reported[16] and the reliability criteria considered were according to the last EFSUMB Guidelines and Recommendations on the Clinical Use of Ultrasound[36]. SSM was assessed on the same day as LSM assessment, with the same probe utilized to perform LSM using the FibroScan® apparatus, as previously described[24]. Since no specific literature is present, translating data from HVPG experience[11], we defined significant a SSM reduction > 20% from BL. LSPS was calculated as liver stiffness × (spleen diameter/platelet count)[37]. Spleen diameter (SD) was considered as bipolar diameter of the spleen assessed by ultrasound.

***Statistical analysis***

Categorical data are expressed as numbers (percentages) and continuous variables as medians (IQR or range). For group comparison, the Mann-Whitney *U* test was used for continuous variables and the chi2 test for categorical variables. Group comparisons among NITs at BL and SVR24 were evaluated with Friedman’s non-parametric test, and Bonferroni-corrected alphas were used for post hoc pairwise comparison. Demographic, clinical, functional and elastometric variables were evaluated with univariate and multivariate Logistic Regression models in order to assess the predictive factors associated with PH improvement assessed by SSM. After evaluation of multicollinearity, variables with a *p*-value < 0.10 at univariate analysis were included in several multivariate Logistic Regression models with stepwise backward procedures. Prevalence of esophageal varices (EV) was not included in the multivariate analysis due to the limited number of patients with available (within 6 mo from TE assessment) EGD data. The estimated hazard ratios (HRs) with their 95% confidence intervals (CIs), LR chi2 and Area under ROC Curve (AUROC) were presented. For each multivariable logistic regression, the model discrimination and calibration were reported together with AIC (Akaike information criterion) and BIC (Bayesian information criterion) measures for comparing maximum likelihood models. Only *P*-values less than 0.05 were considered statistically significant. The statistical analysis was conducted using Stata/SE (Version 14.0; Stata Corp, Texas, United States).

***Ethics***

The DAAs-treatment protocol was approved by the National Institutional Review Board (IRB) of the Italian Medicines Agency committee. Local IRB [Institutional Ethics Committee of Sant’Orsola-Malpighi University Hospital (Bologna, Italy)] approval was authorized.

**RESULTS**

***Patients characteristics***

One hundred-ninety-seven cACLD patients treated with DAAs and with available valid baseline LS and SS measurements were evaluated. The following patients were excluded: 2 (1%) had HCC occurrence and 3 (1.5%) presented active HCC, 1 (0.5%) underwent EBL during study period, 4 (2%) had previous EBL, 2 (1%) patients presented complete portal vein thrombosis, 1 (0.5%) required increase of NSBB dosage and 1 (0.5%) previous TIPS placement. Additional 37 (18.8%) patients were excluded: 22 (out of 197, 11.2%) due to lacked follow-up and 15 (out of 197, 7.6%) due to unfeasible SSM at follow-up. Accordingly, a total of 134 patients with paired LSM and SSM at BL and SVR24 was included in the final analysis; 12 (6%) patients who did not achieve SVR were separately analysed (Figure 1).

Table 1depicts baseline characteristics of the study cohort. Regarding main NITs, the median values at BL were LSM 19.3 kPa (14.1-27 kPa) and SSM 58.8 kPa (42.2-75 kPa). In a sub-analysis, patients with CSPH (LSM ≥ 21 kPa) differed significantly for MELD score, platelet count, total serum bilirubin, INR, SSM, LSM, SSM and LSPS.

**Changes in SSM and LSM after SVR**

In the patients who achieved SVR, the median of SSM significantly decreased from 58.8 kPa to 38.2 kPa (*p* = 0.001), with a median delta change in SSM of – 12.3%. The decrease in SSM was statistically significant in both groups, CSPH and not (Figure 2a); the median delta SSM was higher in patients without CSPH at baseline if compared to patients with CSPH (-20.4% *vs* -4.7%), although this difference did not reach statistical significance. Decrease in SSM values was found in 92 (68.7%) patients, of whom the majority had a decrease of > 10% and of > 20%, respectively 73 (54.5%) and 60 (44.8%) (Table 2 and Figure 3a). LSM values also decreased after SVR, with respective median values of 19.3 kPa and 13.8 kPa at BL and SVR24 (*p* < 0.0001). The median delta LSM was -30%, with similar changes in both groups LSM decreased in 114 (85.1%) patients, of whom 88 (65.7%) had a decrease of > 20% (Table 2 and Figure 3a).

A LSM decrease was found in almost all patients in whom SSM decrease (95.3%). On the other hand, LSM significantly decreased (*p* = 0.022) in 2/3 of the patients in whom SSM did not decrease, with a median delta LSM of -28.3%. (Figure 3b).

***Changes in other NITs after SVR***

The median spleen diameter (SD) at BL and SVR24 were respectively 14 cm and 13.2 cm. Although the reduction was not statistically significant in the overall population, it reached significance in the subgroup of patients without CSPH. The increase of PLT (from 110 109/L to 130 109/L) did not reach statistical significance in the entire cohort too, but only in patients without CSPH (Figure 2b). Moreover, median LSPS differed significantly between BL (2.78) and SVR (1.34); also in both subgroups.

***Non-SVR patients***

Twelve patients did not achieve SVR in our cohort. Baseline characteristics did not statistically differ from the patients included in the final analysis. In particularly, in non-SVR patients a LSM decrease (23.2 kPa at BL *vs* 21.6 kPa at FU24), a SSM increase (45.6 kPa at BL *vs* 57.8 kPa at FU24) and a PLT decrease (128 × 109/L at BL *vs* 100 × 109/L at FU24) were observed; none of these changes reached statistical significance (Supplementary Table 1).

***Predictors of significant SSM Decrease (> 20%)***

Table 3 shows the differences observed between patients who had a SSM decrease of > 20% and those who did not. In the entire cohort, patients with significant SSM reduction differed in prevalence of EV, MELD score, albumin levels as well as BL SSM, LSPS values and LSM-related variables. At multivariate analysis, relative LSM change remained as the only independent predictor of SSM decrease > 20%. Furthermore, predictors of SSM decrease > 20% (Supplementary Table 2) were investigated among patients with CSPH at BL. Once again, higher prevalence of EV, higher creatinine levels, lower LSM values at SVR24 and higher delta LSM were observed among patients with SSM decrease > 20%. At multivariate analysis, higher serum creatinine levels and delta LSM > 20% were the predictors of significant SSM decrease.

***Changes of CSPH-state after SVR***

Figure 4showed that 60 (44.8%) patients presented with CSPH at BL, defined as LSM ≥ 21 kPa. After 6 mo of follow-up, none of the 74 patients without CSPH at BL progressed to CSPH. In patients with CSPH, 46.7% of them reduced LSM under the CSPH threshold after treatment. Supplementary Table 3 shows the predictors of CSPH persistence after DAA treatment.

# **DISCUSSION**

The main aim of our study was to evaluate PH changes assessed by non- invasive methods after successful viral eradication in patients treated with DAAs. Our data shows that SSM and LSM significantly decrease after SVR, according to the baseline clinical patient condition.

The IFN-free regimens are highly effective, allowing to treat and achieve SVR also in patients with ACLD[4,38]. However, the individual clinical benefit in these patients is still under debate, especially in terms of changes in PH and CSPH-driven complications[39–41]. While results from the interferon era might not necessarily be translatable to DAA regimens[21], also recent studies have unanimously demonstrated that HVPG significantly decreases after SVR in all its degree[18–21]. Although many studies have shown that LSM rapidly decreases after DAA treatment[42,43], not much is known about the changes of PH surrogate NITs, such as SSM and LSPS, after viral eradication. In fact, NITs have yet to be validated in SVR patients and their role in the clinical follow-up is still to be determined.

The main finding of this study is that SSM significantly changes after 24 wk of SVR in patients with cACLD, with a median relative change of -12.3%(Table 2). To our knowledge, only two complete papers[30,32] and one letter to editor[39] have investigated the changes in SSM after SVR, with opposite results. In fact, only in the study by Pons *et al*[32] SSM was found to rapidly decrease at only 4 wk after therapy initiation in 41 patients, with no ulterior significant changes until 48 wk of follow-up; the other studies concluded that SSM did not significantly decrease at SVR24[30,32].

In our study that analyzed a large cohort of cACLD patients, we demonstrated that SSM significantly decreased after DAA-treatment. These results confirm previous studies in which PH was assessed by paired HVPG measurements[18–21]. Moreover, our study is the first to assess and demonstrate the improvement of LSPS, another accurate surrogate of PH, after SVR24. Moreover, in the 8 patients who did not achieve SVR, SSM and other NITs did not significantly differ during follow-up measurements (Supplementary Table 1).

We classified patients with and without CSPH according to LSM cut-off 21 kPa[33,34]. Interestingly, the relative changes in SSM and LSM performed differently in patients with and without CSPH. In fact, while the median delta LSM in patients with and without CSPH was very similar (-28.3% *vs* -30.8%), the reduction of SSM was much more evident in patients without CSPH (-20.4% *vs* -4.7%). This last result is coherent with the HVPG relative changes described by Mandorfer *et al*[18]. Moreover, the other surrogates of PH as platelets and spleen diametersignificantly changed only when split by CSPH presence. Regarding the different changes of NITs in patients with and without CSPH, we could speculate that this behaviour can reflect the different stage of underlying PHpathogenetic mechanisms. Indeed, determinants of portal pressure affecting SSM, such as intrahepatic resistance and liver necro-inflammation[44] improve in both subgroups. However, in CSPH, other major actors of PH, such as extra-hepatic hemodynamic factors[34] and spleen structural changes[45], might not ameliorate in the short-term follow-up (6 mo after SVR). This hypothesis could explain why we found a less prominent SSM decrease (-4.7% *vs* -20.4%) even if liver necro-inflammation reduction, assessed by delta LSM (-28.3% vs -30.8%), is the same.

SSM reduction was present in 68.7% of patients after 6 mo of follow-up. We found that the only independent predictor of a significant PH improvement, as reflected by SSM decrease > 20% was the relative change in LSM (Table 3), confirming previous studies with HVPG[18,21]. However, when we assessed PH improvement, reflected by SSM in our study, as PH surrogate, and by HVPG in the study by Lens *et al*[21], we noticed similar portions of patients with a significant response (> 20%) only comparing SSM and HVPG (38.3% vs 39.8%, respectively), and not LSM and HVPG (66.7% *vs* 39.8%, respectively) (Figure 3a). Even if a correlation between HVPG and SSM changes after DAA-treatment has not been demonstrated yet, our data may suggest that a SSM reduction > 20% could be a more accurate non-invasive predictor of a significant HVPG reduction[11].

A statement of the Baveno VI consensus was that the main target in patients with mild PH (6-9 mmHg) is to prevent CSPH development[11]. In our cohort, none of the patients who achieved SVR progressed to CSPH. More challenging instead, due to its clinical implications, is the concept of assessment of CSPH presence/absence after SVR, because there is not sufficient evidence showing that the cut-offs after DAAs are the same as the ones used in the pre-treatment phase[23,46]. However, promising data documented that LSM 20-25 kPa could be an accurate cut-off to rule-in CSPH after DAA therapy[21]. Accordingly, we also investigated CSPH persistence after SVR (Figure 4). Using these cut-offs, we found that 53% of the patients with CSPH at baseline presented CSPH at SVR24. At multivariate analysis, higher baseline values of SSM, indicating a more severe PH, and lower LSM relative changes were found to be predictors of CSPH persistence (Supplementary Table 3). These results are in line another study[21], in which higher BL HVPG and relative LSM changes were predictors of CSPH persistence after DAA treatment.

All the above results seem to reflect the different dynamics in LSM and SSM changes after achieving SVR. LSM consensually decreases in almost all patients (95.2%) with SSM reduction, while the opposite was not found true. In fact, LSM significantly decreased, with median delta -28.3%, in 2/3 of the patients in whom no SSM reduction was found. This result emphasizes the fact that, being LSM heavily influenced by the reduction of liver necro-inflammation[44] after SVR, changes in LSM might not be the most adequate predictors of PH changes in this context. On the other hand, SSM decrease > 20% could identify patients who significantly clinically benefit from viral eradication. When looking at the bigger picture, SSM could represent a feasible tool to monitor therapy response and assess its benefit. This is also supported by a recent study by Buechter *et al*[47] that investigated LSM and SSM changes after TIPS placement.

The present study has some limitations: Its retrospective nature, even though SSM and LSM were prospectively collected according to AIFA eligibility criteria for treatment of HCV patients with DAAs, and the absence of a gold-standard reference. However, according to Baveno VI consensus[11], we could considered NITs, as LSM, good surrogates of invasive methods, as liver biopsy and HVPG. The time of follow-up was too short to fully correlate SSM changes after viral eradication, with clinical outcomes, for instance events of decompensation after SVR[48]. As in previous studies including SSM, the upper limit of 75 kPa for SSM affects the possibility to detect changes in patient with severe PH[49,50]; in fact, BL and SVR24 values were both 75 kPa in 7 (5.2%) of them.

In conclusion, SSM could be an accurate and useful NIT for the follow-up of patients after SVR, as it faithfully reflects changes in PH better than other NITs including LSM. Further prospective studies are required in order to confirm the accuracy and usefulness of SSM and other NITs in the follow-up of patients with ACLD and its correlation with clinical outcomes.

**Article Highlights**

***Research background***

The long-term benefits of achieving sustained viral response (SVR) in cirrhotic patients are still to be established. Non-invasive tests (NITs), such as liver (LSM) and especially spleen stiffness (SSM), are widely validated in hepatology as portal hypertension (PH) surrogates. However, the use in SVR patients and their changes after virus eradication is still under discussion.

***Research motivation***

Many studies have reported rapid LSM decrease after achieving SVR. However, only a few have investigated changes in SSM in such patients, with contrasting results. Given that there is a decrease in SSM after therapy, means that SSM could be exploited to assess changes in PH and PH-driven complication after achieving SVR.

***Research objectives***

The main objective of the study was to investigate changes in PH after successful eradication of HCV-infection, as reflected by its non-invasive assessment by SSM and other NITs.

***Research methods***

This is retrospective study of prospectively collected data. Patients with available paired SSM assessment, at baseline (BL) and 6 mo after end-of therapy (SVR24), were included in the study.

***Research results***

Our main result is that a significant SSM decreases at SVR24 was demonstrated in a large cohort of 134 patients. This is the first study that also reveals a decrease in LSPS after SVR. SSM reduction differed according to the patient's clinical condition, especially when divided by presence of clinically significant PH. An LSM decrease of > 20% was evident in the majority of patients, also in patients in whom no SSM reduction was present. This finding probably reflects the reduction in liver necro-inflammation rather than PH improvement.

***Research conclusions***

PH, reflected by NITs, improves after achieving SVR in cirrhotic patients. SSM is a direct surrogate of PH and less influenced by liver necro-inflammation, as opposed to LSM. Its decrease (> 20%) could help the clinician to stratify the risk for PH-related complication after DAA therapy.

***Research perspectives***

Future prospective studies should investigate whether changes in SSM are predictive of clinical decompensation or other complications of cirrhosis after viral eradication. SSM could become a helpful and accurate method to assess therapy response and risk of complications.

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**P-Reviewer:** Ferraioli G, Furuichi Y, Kahraman A **S-Editor:** Gong ZM

**L-Editor:** **E-Editor:**

**Specialty type:** Gastroenterology and hepatology

**Country of origin:** Italy

**Peer-review report classification**

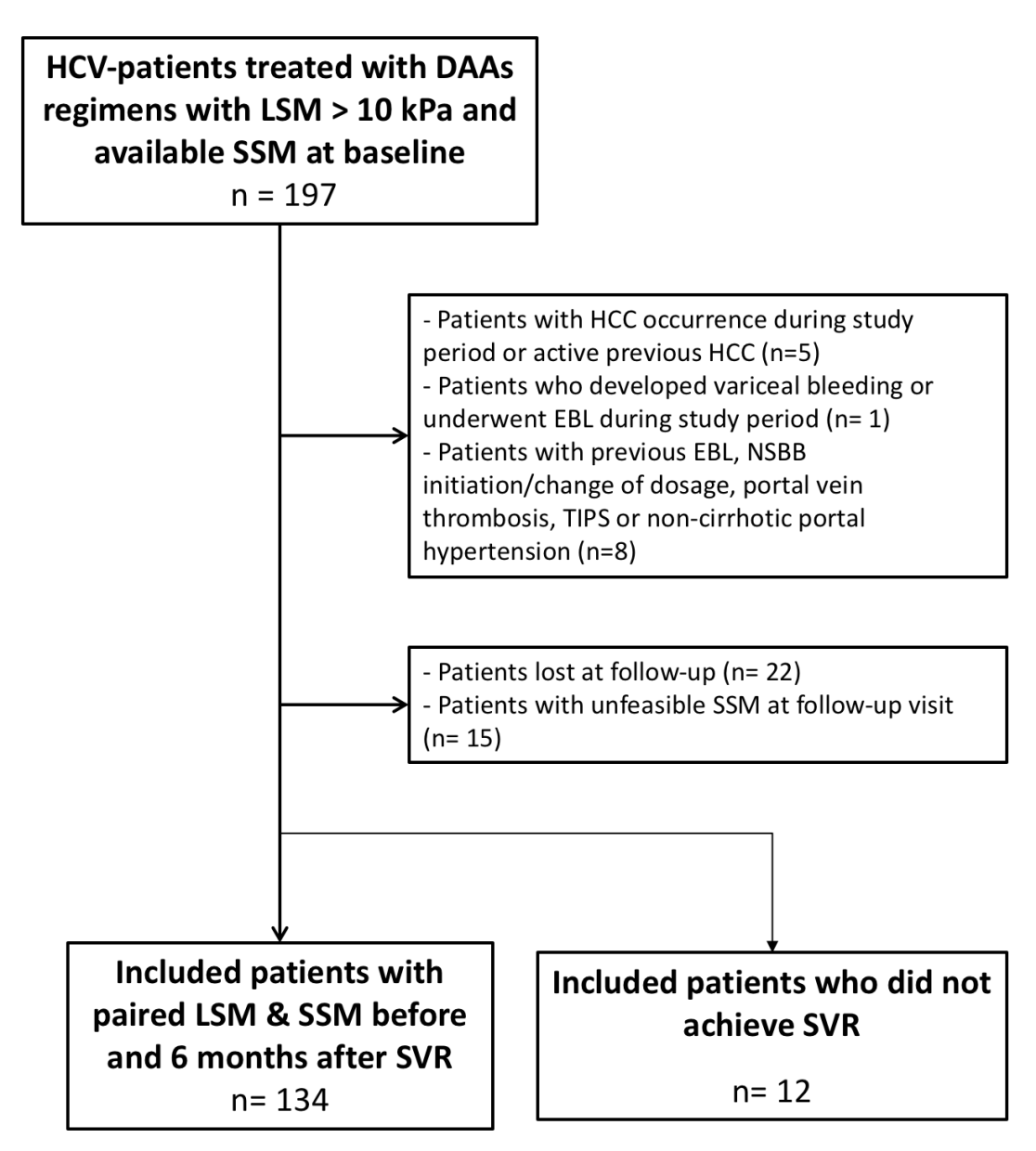
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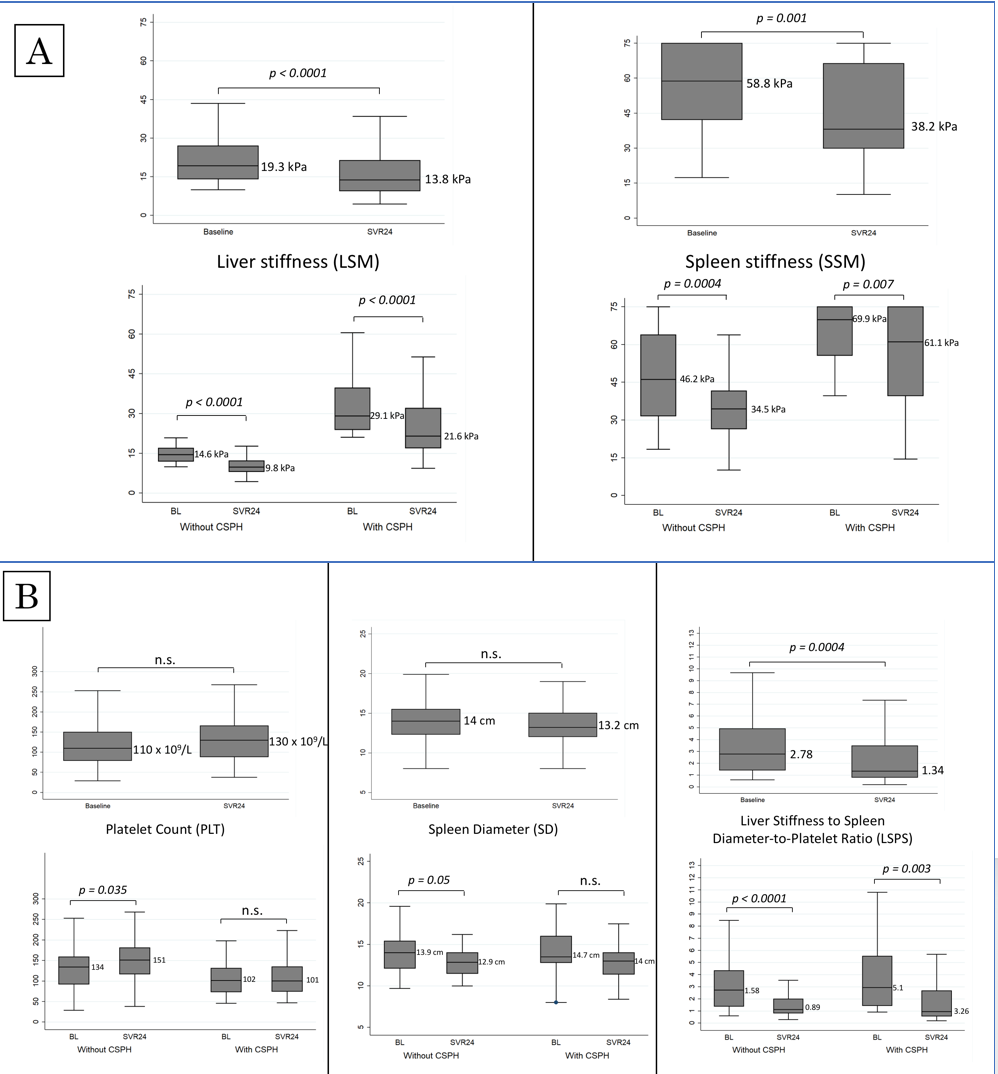
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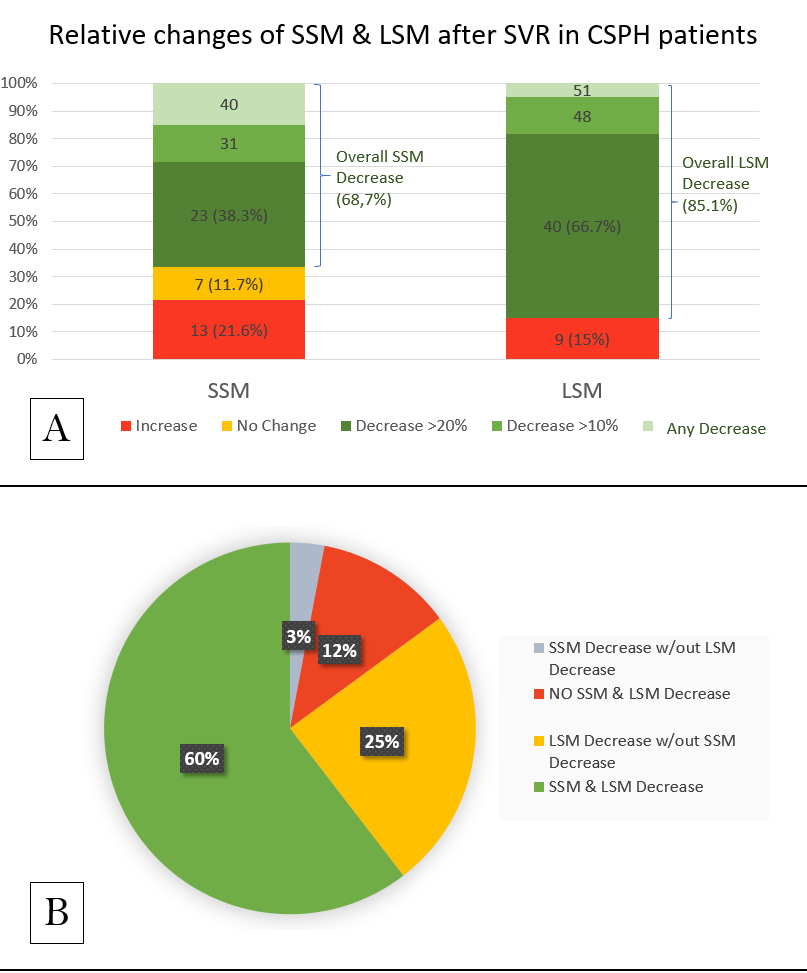
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**Figure 1 Flowchart of study design.** DAA: Direct-acting antiviral; EBL: Endoscopic band ligation; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; LSM: Liver stiffness measurement; NSBB: Non-Selective Beta-Blocker; SSM: Spleen stiffness measurement; SVR: Sustained viral response; TIPS: Transjugular intrahepatic portosystemic shunt.



**Figure 2 Non-invasive tests changes after sustained viral response, by clinically significant portal hypertension presence.** A: LSM and SSM changes; B: PLT, SD, LSPS changes. CSPH: Clinically significant portal hypertension; LSM: Liver stiffness measurement; SSM: Spleen stiffness measurement; PLT: Platelets count; SD: spleen diameter; LSPS: Liver stiffness-spleen diameter-to-platelet count ratio score.



**Figure 3** **Spleen and liver stiffness measurement decrease after sustained viral response (A) and liver stiffness measurement decrease in patients without spleen stiffness measurement improvement (B).** BL: Baseline; CSPH: Clinically significant portal hypertension; LSM: Liver stiffness measurement; SSM: Spleen stiffness measurement; SVR: Sustained viral response.

* ~~~~

**Figure 4 Clinically significant portal hypertension presence, according Baveno VI (liver stiffness measurement ≥ 21 kPa) at baseline and after SVR24.** CSPH: Clinically significant portal hypertension; LSM: Liver stiffness measurement; SSM: Spleen stiffness measurement; SVR: Sustained viral response.

**Table 1 Baseline characteristics of included patients**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Overall (*n* = 134)** | **CSPH (LSM ≥ 21 kPa) (*n* = 60)** | **No CSPH (LSM < 21 kPa) (*n* = 74)** |
| Age (yr) | 60 (51-69) | 57 (50.5-65) | 61.5 (51-70) |
| Male | 92 (68.7) | 42 (70) | 50 (67.6) |
| HCV-genotype |  |  |  |
| 1 | 95 (70.9) | 41 (68.3) | 54 (72.5) |
| 2 | 12 (8.9) | 4 (6.7) | 8 (10.8) |
| 3 | 20 (14.9) | 11 (18.3) | 9 (12.2) |
| 4 | 7 (5.3) | 4 (6.7) | 3 (4.5) |
| Treatment regimen |  |  |  |
| SOF/RBV | 33 (24.6) | 10 (16.7) | 23 (31.1) |
| SOF/SMV | 29 (21.6) | 15 (25) | 14 (18.9) |
| SOF/DCV | 38 (28.4) | 19 (31.6) | 19 (25.6) |
| SOF/LDV | 16 (12) | 7 (11.7) | 9 (12.2) |
| Other | 18 (13.4) | 9 (15) | 9 (12.2) |
| Child Pugh Score |  |  |  |
| A | 115 (85.8) | 52 (86.7) | 63 (85.1) |
| B | 19 (14.2) | 8 (13.3) | 11 (14.9) |
| MELD Score | 8 (7-10) | 9 (8-10) | 8 (7-10) |
| Spleen Diameter (cm) | 14 (12.3-15.5) | 14.7 (12.8-15.8) | 13.9 (12.1-15) |
| Laboratory results |  |  |  |
| Platelets (cells × 109/L) | 110 (79-150) | 102 (74-132) | 134 (92-159) |
| ALT (U/L) | 58 (39-95) | 55 (39-84) | 60 (38-105) |
| Bilirubin (mg/dL) | 0.9 (0.67-1.29) | 1 (0.84-1.52) | 0.8 (0.6-1.1) |
| Albumin (g/dL) | 3.8 (3.6-4.1) | 3.8 (3.5-4.1) | 3.8 (3.6-4.1) |
| Creatinine (mg/dL) | 0.8 (0.7-0.98) | 0.8 (0.70-0.96) | 0.85 (0.71-1.08) |
| INR | 1.1 (1.06-1.2) | 1.17 (1.1-1.21) | 1.08 (1.04-1.13) |
| NITs |  |  |  |
| SSM (kPa) | 58.8 (42.2-75) | 69.9 (55.7-75) | 46.2 (31.6-63.9) |
| LSM (kPa) | 19.3 (14.1-27) | 29.1 (23.9-39.7) | 14.6 (12-17) |
| LSPS | 2.78 (1.4-4.94) | 5.1 (3.05-7.48) | 1.58 (1.09-2.79) |

Qualitative data were expressed as number and perceptual (%); quantitative data were expressed as median (25%-75% quantiles). ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CSPH: Clinical significant portal hypertension; DCV: Daclatasvir; HRV: High risk varices; INR: International normalized ratio; LDV: Ledipasvir; LSM: Liver stiffness measurement; LSPS: Liver stiffness to spleen/platelet score; MELD: Model for End-Stage Liver Disease; NITs: Non-invasive tests; RBV: Ribavirin; SMV: Simeprevir; SOF: Sofosbuvir; SVR: Sustained viral response; SSM: Spleen stiffness measurement.

**Table 2 Liver and Spleen stiffness measurement decrease after sustained viral response**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Overall (*n* = 134)** | **CSPH (LSM ≥ 21 kPa) (*n* = 60)** | **No CSPH (LSM < 21 kPa) (*n* = 74)** |
| Relative SSM decrease (%) | 12.3 (0-36.3) | 4.7 (0-32.5) | 20.4 (0-39.7) |
| Overall SSM decrease | 92 (68.7) | 40 (66.7) | 52 (70.3) |
| > 10% | 73 (54.5) | 31 (51.7) | 42 (56.8) |
| > 20% | 60 (44.8) | 23 (38.3) | 37 (50) |
| Relative LSM decrease (%) | 30 (13.5-42.4) | 28.3 (11.4-41.9) | 30.8 (13.9-42.4) |
| Overall LSM decrease | 114 (85.1) | 51 (85) | 63 (85.1) |
| > 10% | 108 (80.6) | 48 (80) | 60 (81.1) |
| > 20% | 88 (65.7) | 40 (66.7) | 48 (64.9) |
| PLT Increase (%) | 12.4 (-10.1 to 29.6) | 5.5 (-15.6 to 25.9) | 17.4 (-0.67 to 35.6) |

CSPH: Clinical significant portal hypertension; LSM: Liver stiffness measurement; PLT: Platelets count; SSM: Spleen stiffness measurement.

**Table 3 Univariate and multivariate analysis of factors associated with SSM decrease > 20%**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Entire Population (*n* = 134)** | | | | | | |
| **Variable** | **Univariate analysis** | | | | **Multivariate analysis** | |
| **LR Chi-2 = 16.48**  **AUROC = 0.6821** | **AIC = 171.8**  **BIC = 177.6** |
| **SSM Decrease > 20% (*n* = 60)** | **No SSM Decrease > 20% (*n* = 74)** | **OR (95%CI)** | ***p* value** | **OR (95%CI)** | ***p* value** |
| Age (yr) | 62 (52-69) | 56 (50-68) | 1.005 (0.975-1.037) | 0.727 |  |  |
| Sex (male) | 21 (28.4) | 21 (35) | 1.359 (0.653-2.828) | 0.412 |  |  |
| Presence varices (*n* = 67) (yes) | 9 (34.2) | 24 (82.8) | 0.110 (0.031-0.388) | **0.001** |  |  |
| Spleen diameter (cm) | 13.6 (11.65-15.15) | 14.5 (13-16) | 0.800 (0.660-0.970) | **0.023** |  |  |
| Child Pugh Score | 5 (5-6) | 5 (5-6) | 0.885 (0.601-1.303) | 0.535 |  |  |
| Child Pugh Score B (yes) | 8 (13.3) | 11 (14.9) | 0.881 (0.330-2.352) | 0.801 |  |  |
| MELD score | 8 (7-10) | 9 (8-10) | 0.786 (0.648-0.954) | **0.015** |  |  |
| MELD > 10 | 12 (20) | 30 (40.5) | 0.367 (0.167-0.804) | **0.012** |  |  |
| AST (U/L) | 54.5 (38-85) | 56 (35.5-87) | 0.996 (0.987-1.004) | 0.322 |  |  |
| ALT (U/L) | 62 (37 - 105) | 53 (40 - 90) | 1.002 (0.995-1.008) | 0.620 |  |  |
| ALT ≥ 2 × ULN at BL | 59.5 (37.5-101) | 54 (40-91.5) | 1.326 (0.597-2.944) | 0.489 |  |  |
| INR | 1.09 (1.05-1.17) | 1.12 (1.09-1.21) | 0.127 (0.001-0.551) | **0.023** |  |  |
| Bilirubin (mg/dl) | 0.85 (0.65-1.16) | 1.02 (0.71-1.52) | 0.903 (0.535-1.525) | 0.703 |  |  |
| Albumin (g/dl) | 3.8 (3.52-4.12) | 3.78 (3.52-4.12) | 2.096 (0.959-4.581) | **0.063** |  |  |
| Creatinine (mg/d) | 0.8 (0.7-1) | 0.81 (0.69-0.93) | 0.327 (0.674-1.585) | 0.165 |  |  |
| Platelet count (10^9/L) | 118 (92-154) | 91 (74-137) | 1.002 (0.996-1.007) | 0.579 |  |  |
| LSM BL (kPa) | 18 (14.6-25.7) | 21.1 (14-38.5) | 0.988 (0.962-1.015) | 0.391 |  |  |
| LSM SVR24 (kPa) | 12.4 (9.4-18) | 17.5 (10.4-32.4) | 0.944 (0.908-0.981) | **0.004** |  |  |
| SSM BL (kPa) | 60.4 (45.7-70.7) | 53.2 (37.4-75) | 1.012 (0.992-1.032) | 0.225 |  |  |
| LSPS BL | 2.17 (1.33-3.77) | 4.15 (1.65-6.26) | 0.817 (0.684-0.975) | **0.025** |  |  |
| LSM decrease (Delta, %) | 33 (18.1 – 44.6) | 19.4 (0 – 31.3) | 0.0332 (0.005-0.225) | **< 0.0001** | 0.0332 (0.005-0.225) | **< 0.0001** |
| LSM decrease > 10% (yes) | 54 (90) | 54 (73) | 3.333 (1.242-8.946) | **0.017** |  |  |
| LSM decrease > 20% (yes) | 47 (78.3) | 41 (55.4) | 2.910 (1.352-6.262) | **0.006** |  |  |

Qualitative data were expressed as number and perceptual (%); quantitative data were expressed as median (25%-75% quantiles). AIC: Akaike information criterion; ALT: Alanine aminotransferase; AUROC: Area under curve roc; AST: Aspartate aminotransferase; BIC: Bayesian information criterion; CSPH: Clinical significant portal hypertension; DCV: Daclatasvir; HRV: High risk varices; INR: International normalized ratio; LDV: Ledipasvir; LR: Like-hood ratio; LSM: Liver stiffness measurement; LSPS: Liver stiffness to spleen/platelet score; MELD: Model for End-Stage Liver Disease; NITs: Non-invasive tests; RBV: Ribavirin; SMV: Simeprevir; SOF: Sofosbuvir; SVR: Sustained viral response; SSM: Spleen stiffness measurement.