Spleen Stiffness Measurements Predict the Risk of Hepatic Decompensation after Direct-Acting Antivirals in HCV Cirrhotic Patients

"Spleen stiffness measurements predict the risk of hepatic decompensation after direct-acting antivirals in HCV-cirrhotics"

Short title: SSM predicts decompensation after DAAs

Authors' names: Elton Dajti[1*], Federico Ravaioli[1*], Antonio Colecchia[2], Giovanni Marasco[1], Maria Letizia Bacchi-Reggiani[3], Agostino Colli[4], Luigina Vanessa Alemanni[1], Mariarosa Tamè[1], Pietro Andreone[1], Stefano Brillanti[5], Francesco Azzaroli[1], Giuseppe Mazzella[1], Davide Festi[1]

Authors' institutions: [1]Department of Medical and Surgical Sciences (DIMEC), University of Bologna; Via Massarenti 9, 40138, Bologna, Italy; [2]Unit of Gastroenterology, Borgo Trento University Hospital of Verona; P.le Aristide Stefani 1, 37126, Verona, Italy; [3]Department of Experimental, diagnostic and specialty Medicine (DIMES), University of Bologna; Via Massarenti 9, 40138, Bologna, Italy; [4] Department of Internal Medicine, General Hospital, Lecco; Via dell'Eremo 9/11, 23900, Lecco, Italy;[5] Department of Medicine, Surgery and Neuroscience, University of Siena; Viale Mario Bracci 16, 53100, Siena, Italy.

Corresponding author: Antonio Colecchia, Unit of Gastroenterology, Borgo Trento University Hospital, Verona, Italy; e-mail: antonio.colecchia@aovr.veneto.it

Financial Support: No grants or other financial support.

Conflict of interest statement: The authors declare that they have no conflict of interest.

Keywords: interferon-free regimen; sustained virologic response; portal hypertension; ascites; prognosis; spleen stiffness measurement; liver stiffness measurement; transient elastography; propensity score modelling; time-dependent analysis

Authors' contributions to manuscript: AC is the guarantor of the article. ED, FR, LVA, GM and AC collected the data, analysed the data, wrote the manuscript, and approved the final manuscript. ED, AC, FA, GM, SB, PA, MT and MLBR analysed the data and contributed to the drafting and final approval of the manuscript. AC and DF provided overall oversight of the study, analysed the data, and contributed to the drafting and final approval of the manuscript.

*** Elton Dajti and Federico Ravaioli contributed to this manuscript equally.**

List of Abbreviations: ACLD: compensated advanced chronic liver disease; AIC: Akaike information criterion; ALBI: Albumin-Bilirubin Grade; APRI: AST to Platelet Ratio Index; BIC: Bayesian information criterion; BL: baseline; cACLD: compensated advanced chronic liver disease; CSPH: clinically significant portal hypertension; CTP: Child-Turcotte-Pugh; DAA: direct-acting antivirals; EFSUMB: European Federation of Societies for Ultrasound in Medicine and Biology; EGD: esophagogastroduodenoscopy; EOT: end of treatment; EV: esophageal varices; FIB-4: Fibrosis-4; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; HD: hepatic decompensation; HE: hepatic encephalopathy; HR: hazard ratio; HRV: high-risk varices; HVPG: hepatic venous pressure gradient; IC: interval of confidence; INR: international normalized ratio; IPTW: inverse probability of treatment weights; IQR: interquartile range; IRB: Institutional Review Board; kPa: kilopascals; LR: Likelihood Ratio; LSM: liver stiffness measurement; MELD: Model for End-Stage Liver Disease; NITs: non-invasive tests; OLT: orthotopic liver transplantation; PCR: polymerase chain reaction; PH: portal hypertension; PLT: platelet count; PS: propensity score; PVT: portal vein thrombosis; PY: person-year; SSM: spleen stiffness measurement; SVR: sustained virologic response; TE, transient elastography; TIPS: transjugular intrahepatic portosystemic shunt; US: ultrasound.

Introduction

Direct-acting antivirals (DAAs) have markedly increased the rate of sustained virologic response (SVR) among patients with compensated advanced chronic liver disease (cACLD).(1) The SVR has been associated with improvement in liver function,(2) and portal hypertension (PH)(3) at six months from viral elimination with DAAs(4) whereas the data regarding hepatocellular carcinoma (HCC) after DAA therapy are still controversial.(5–8)

Furthermore, the long-term impact of SVR in terms of PH-driven complications is still under investigation.(9) The rates of hepatic decompensation (HD) have been reported only marginally in a few studies.(6,10) To date, predictors of such PH-driven complications are still lacking.(9)

Non-invasive tests (NITs), such as liver (LSM) and spleen (SSM) stiffness measurements, have been widely validated as accurate surrogates of PH,(11,12) capable of predicting the presence of clinically significant PH (CSPH)(13) and its complications.(14–17) It has been shown that an SSM cut-off of 54 kPa accurately stratified the risk of HD development in an active HCV cohort. In patients treated with DAAs, several studies have shown that LSM and SSM significantly decrease after DAA therapy,(18,19) but no evidence is yet available regarding the prognostic role of baseline values and their changes after therapy.

The aim of the present study was to assess the risk of HD development and the prognostic role of non-invasive tests of PH in the prediction of HD after DAAs treatment.

Materials and Methods

Study design and population

For the present study, two cohorts of HCV patients who had been included in two previous studies(16,20) were evaluated. The "DAA cohort" was represented by HCV-related cACLD patients treated in our department between January 2015 and September 2017.(20) In particular, patients with valid measurements of LSM and SSM using transient elastography (TE) at baseline (BL) and at 6 months (SVR24) after the end of DAA treatment (EOT) were selected; the patients were then prospectively followed up. The "active HCV cohort" was a historical cohort of untreated HCV-related compensated cirrhotics; the patients were consecutively enrolled at our centre from September 2010 and subsequently followed up for two years.(16) The "active HCV cohort" was used as a control group to assess the effect of DAA treatment on HD development, through propensity score (PS) modelling.(21)

In the DAA cohort, cACLD was defined by values of LSM >10 kPa at BL;(12) SVR was defined as undetectable HCV-RNA, using a real-time polymerase chain reaction (PCR) with a detection limit of 15 IU/mL at a 12-week post-treatment follow-up visit. Laboratory values, Model for End-Stage Liver Disease (MELD) and Child-Turcotte Pugh (CTP) scores, were reported for each patient at BL and at SVR24. A recent esophagogastroduodenoscopy (EGD), defined as within six months pre-DAAs, was reported when available. The presence of previous HD and history of HCC were also reported.

All patients underwent a standard follow-up in agreement with international recommendations.(22) In the DAA cohort, complications of PH, such as ascites, variceal bleeding, hepatic encephalopathy (HE), spontaneous bacterial peritonitis and hepato-renal syndrome, were recorded. Other ACLD-related events, such as high-risk-varices (HRV) treatment, portal vein thrombosis (PVT), HCC, orthotopic liver transplantation (OLT) and death, were also reported. The 1st of February 2020 was considered to be the end of the follow-up; patients who did not develop the event during the follow-up were censored at the time of death, OLT or the last visit to the study centre. Data were reported

according to STROBE guidelines.

Non-invasive tests for evaluation of liver disease severity

LSM and SSM were assessed by TE, using FibroScan® (Echosens, Paris, France) after an overnight fasting and a complete abdominal ultrasound (US) examination. LSM values were obtained according to the recommendations of the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) (23). For each patient, LSM values were considered adequate if the success rate (SR) was >60%, and the interquartile range (IQR) was <30% of the median value. The LSM cut-off ≥21 kPa was used to rule-in CSPH.(24)

SSM values were obtained using the same probe used to perform LS, with the patient in a supine position with maximal abduction of the left arm; the probe was positioned in an intercostal space where the spleen was correctly visualized by US. Moreover, patients with a splenic parenchymal thickness of <4 cm under the probe were excluded. (15) The same reliability criteria as for the measurement of LS were applied (i.e., SR >60%, IQR <30%). SSM cut-off of 54 kPa was applied to predict HD development.

Among the serum biomarkers for non-invasive evaluation of ACLD, MELD, CTP, AST to Platelet Ratio Index (APRI), Fibrosis-4 (FIB-4) Score and ALBI Albumin-Bilirubin (ALBI) score were calculated for each patient.

Statistical analysis

Categorical data were expressed as numbers (percentages), and continuous variables as medians (and values of the 25% and the 75% percentiles, IQR or range). For group comparisons of categorical and continuous variables, the chi-square test or Mann-Whitney test, and the Mc-Nemar test were used, as appropriate.

The primary outcome was the development of decompensation. **Suppl. Material 1** provides complete details of the weighted-PS score (inverse probability of treatment weights, IPTW) applied. The

clinical, biochemical and elastometric variables were evaluated using univariate and multivariate competing risk regression models to assess the factors associated with the primary outcome; death or OLT were considered as competing events. The index of the time-to-event analysis for the DAA cohort was considered to be the EOT. Since a recenteEGD was available in only a subgroup of patients (n=67), the presence of esophageal varices (EV) was not included in the predictive models. After evaluation of the multicollinearity, multivariable competing risk regression analyses were carried out on variables which reached $p<0.1$ at univariate analysis. The final multivariate regression model was built from the set of candidate variables by removing the predictors based on p values, in a stepwise manner. The estimated subhazard ratio (SHR) with the 95%-CI, and the Wald-chi2 tests were reported. Cumulative incidence function (CIF) curves were used to estimate the HD development during the follow-up.

Moreover, in patients who achieved SVR, time-dependent competing risk regression models were built; NITsconsidered as time-dependent covariates, assuming different values at baseline and SVR24. The Akaike information criterion (AIC) and the Bayesian information criterion (BIC) were reported for each predictive model . All p values referred to two-tailed tests of significance. $P<0.05$ was considered significant. The statistical analysis was carried out using Stata/SE (Version 14.0; Stata Corp,Texas,U.S.A.).

Ethics:

This study was conducted in compliance with the Declaration of Helsinki. The DAA treatment protocol was approved by the National Institutional Review Board (IRB) of the Medicines Agency committee. Local IRB approval for subsequent anonymous analysis was authorised.

Results

Patient characteristics

In the DAA cohort, 183 ACLD patients were initially enrolled. Of them, 37 patients were excluded because the SSM at six months from the end of the therapy was not available (n=22) or not feasible (n=15). In the final analysis, 146 cACLD patients with paired TE assessment were included in the study and were prospectively followed up. Of the patients included, 140 (95.9%) achieved SVR status. The median age was 63 (55-73) years; the majority of patients were CTP-A (85.6%); 31 (21.2%) and 16 (11%) had a history of HD and HCC with complete remission, respectively.

Table 1 reports the main characteristics of the patients in both the study and the control group.

Incidence of HD by cohort

The median follow-up in the DAA cohort was 41.5 (32-49) months. During this period, a total of 20 (13.7%) patients developed at least one episode of HD; the incidence rate was 7.07 (4.56-10.96) per-100-PYs. The first decompensating event was ascites in the majority (17/20, 85%) of patients; the others being variceal bleeding and hepatic encephalopathy in 2 (10%) and 1 (5%) patients, respectively. Three (50%) out of the six patients who did not achieve SVR developed HD.

In the active HCV cohort, 30 (32.6%) out of the 92 patients developed HD during the 2-year follow-up period; the first HD event was ascites and variceal bleeding in 26 (86.7%) and 4 (13.3%) patients, respectively. The HD incidence in this group was 19.75 (13.81-28.25) per 100 PYs, higher (p=0.0003) than in the DAA cohort.

Impact of SVR by DAA treatment on HD development

Fifty out of the 238 patients included in both cohorts developed an episode of HD during follow-up. **Supplemental Material 2** shows the results of the unweighted univariate and multivariate competing-risk analysis. Two-year-CIFs of HD development in the treated and untreated cohort are drawn in **Fig. 1a**.

We then applied an IPTW approach to account for the different characteristics between the two cohorts. **Suppl. Material 3** shows an adequate balance between the two groups for the variables included in the PS. The PS-weighted competing-risk analysis confirmed the findings of the unweighted model and demonstrated that SVR by DAA treatment was associated with a reduced risk of HD development (weighted SHR: 0.071, 95% CI: 0.015-0.332) (**Suppl. Material 2)**. **Fig. 1b** shows the CIF curves of HD after the PS-score stabilised IPTW method; the active HCV group showed a significantly incidence of HD ($p< 0.0001$).

Predictive role of NITs for HD development in SVR patients after DAA treatment

Of the 140 patients who achieved SVR status in the DAA cohort, 17 (12.1%) still developed an episode of HD; the incidence rate in this group of patients was 4.12 (2.56-6.63)per 100 PYs. Only 5 (4.5%) patients developed HD for the first time after DAA therapy with an incidence of 1.47 (0.61-3.53) per 100 PYs. **Suppl. Material 4** summarises the cumulative inicidence of clinical events during follow-up.

Predictive role of pre-treatment characteristics

When considering only pre-treatment variables and NITs values, the history of HD and HCC were found as independent predictors of HD development despite SVR achievement **(Suppl. Material 5)**. Baseline SSM ≥54 kPa alone was not associated with a significantly higher risk of HD during the follow-up, but a slight tendency was noted (**Suppl. Material 6)**.

Predictive role of baseline and SVR24 NITs in a time-dependent analysis

Suppl. Material 7 shows the improvement of the evaluated NITs at SVR24. In order to take into account the changes of NITs, we conducted a time-dependent competing risk regression analysis (**Tab. 2)**. At the multivariate analysis, previous HD (SHR: 7.756, 95% CI: 2.611-23.037) and SSM, both as continuous values (SHR: 1.037, 95% CI: 1.011-1.064) and dichotomized according to the 54 kPa cut-off (SHR: 4.169, 95% CI: 1.050-16.559), were independently associated with a higher risk of

HD development after DAA treatment. Noteworthy, FIB4-Index was the only of the evaluated serum biomarkers significantly associated with HD development at univariate analysis, but this was not confirmed in the multivariate analysis. In **Fig. 2** are shown the different CIF curves of the HD according to the two newly identified predictors.

Fig. 3 represents a pragmatic flowchart depicting the incidence of HD according to the SSM cut-off of 54 kPa, both in the first six months from EOT and after the visit at SVR24; patients with and without previous HD were analysed separately.

Predictive role of NITs and their changes at SVR24

In order to investigate the role of the values of NITs at SVR24 in the prediction of HD development, we performed a subgroup analysis only in the patients still at risk for the primary event at SVR24 (n=125) (Tab. 3). Changes in SSM (<10%), but not in LSM, were associated with an increased risk of decompensation, alongside with a higher MELD score at SVR24.

Baseline predictors of de novo HCC in our cohort

Baseline predictors of de novo HCC development in a subgroup of patients (n=125) were investigated and summarized in **Suppl. Material 8**. In the final multivariate model, presence of CSPH at baseline and higher MELD values significantly increased the risk of HCC development after SVR.

Discussion

Paired evaluations of SSM before and after DAA treatment can accurately and non-invasively assess the amelioration of portal hypertension after therapy and identify the patients still at risk of decompensation (HD) despite viral elimination.

The introduction of DAA-based treatment has revolutionised the natural history of patients with HCV infection. Several initial studies have shown that PH(3) improves immediately after the achievement of SVR. However, the real effect of DAA regimens on robust long-term clinical outcomes, especially HD, has yet to be determined.(9)

In the present study, it was demonstrated that treatment with DAA-based regimens reduced the risk of decompensation in ACLD patients. The SVR status achieved by DAA treatment was found to be an independent protective factor for HD development, also when a propensity-based (IPTW) method was applied to the competing risk analysis (**Fig. 1**).(21) This result is relevant since HD represents an essential point of reference beyond which there is increased liver-related morbidity, health costs and overall mortality in ACLD patients.(10) Noteworthy, a recent review(9) concluded that the evidence regarding the risk of PH-related complication, such as HD, after SVR by DAAs is lacking(25) and . the most extensive study to date on this matter failed to demonstrate the benefit of SVR on this clinical outcome.(26)

Considering that some ACLD patients still develop HD despite viral elimination, the identification of HD predictors in this context would be very important for the clinician in order to select patients at risk and, ideally, to offer an individualised follow-up strategy for each patient.

To the best of the Authors' knowledge, this is the first study which investigated the presence of non-invasive prognostic parameters associated with decompensation after successful DAA therapy. Applying a time-dependent regression analysis to account for changes in NITs values after therapy, it was found that a history of decompensation before DAA treatment and SSM, both as continuous

and dichotomized values (54 kPa),(16) were independently associated with HD development in SVR patients who underwent DAA treatment **(Tab. and Fig. 2)**, these patients should therefore be closely monitored.

In the present study, SSM values ≥54 kPa at baseline and SVR24 were independently associated with a higher risk of HD after DAA treatment, confirming SSM as a helpful tool to predict PH-related complications also in the post-SVR context. Indeed, several studies have shown that both LSM and SSM decrease after SVR;(19,27); however, until now, the prognostic significance of these changes had not been investigated. Our preliminary hypothesis(20) was confirmed in the present paper, as the models including SSM were more accurate than those considering LSM or other NITs.in predicting HD development after SVR **(Tab. 3)**. This better predictive role of SSM was, however, not surprising since SSM has been more accurate than LSM also in other contexts.(13–15)

Regarding the timing of the TE measurement, the sole baseline values of NITs were unable to independently predict HD **(Suppl.Material 5&6)**. However, when including both baseline and SVR24 measurement in a time-dependent model, this way taking into account the effect of DAA treatment on the PH degree in each patient, SSM emerged as the only NIT able to correctly predict HD development.

A graphical representation of HD incidence according to the dynamic changes of SSM and a history of decompensation is presented in **Fig. 3**. For instance, among patients with compensated cirrhosis, only patients with SSM ≥54 kPa developed an episode of decompensation during the first 6 months. For the patients still at risk at SVR24, SSM was re-evaluated, and once again, the events of first decompensation were observed only in patients in whom SSM remained, or increased, above the threshold of 54 kPa.

Another take home message from our paper is that SSM reduction <10% is also a valid method to identify patients at risk of decompensation despite SVR achievement (**Tab. 3**). These results are completely in line with the recent paper of Mandorfer et al.,(28) which evaluated the prognostic role

of changes in HVPG values after DAA therapy, and showed that areduction >10% reduced the risk of decompensation. However, it should be mentioned that this model predicts the risk of decompensation after SVR24, and therefore it does not provide a thorough risk stratification for all patients undergoing DAA treatment (i.e. the risk of developing the event in between the two TE evaluations is not considered), unlike the time-dependent model discussed above.

In summary, with our study, paired evaluations of SSM were confirmed as an accurate and non-invasive surrogate to identify patients at risk of complications even after therapies that improve portal hypertension, similary to what Kim et al. recently reported for non-invasive prediction of response to non-selective beta-blockers.(29)

The present study has some limitations. First, it was a single-centre observational study, and the non-randomized assignation of DAA therapy could have introduced selection bias between the two cohorts;(21) for this purpose a weighted IPTW analysis was carried out to overcome the differences. Second, the selection of patients included in the DAA cohort was retrospectively carried out (patients with two available SSM measurements); however, this was the largest cohort to date with paired non-invasive evaluations in which the patients were prospectively followed for a long time. Moreover, the number of HD events in the DAA cohort was relatively small, limiting the possibility of identifying more predictors of HD without overfitting the model. Finally, the use of SSM involves some previously discussed limits,(15,20) such as the ceiling effect and the technical unfeasibility in 5-15% of the cases;(15) however, these limits are expected to be overcome by a new SSM-dedicated device.(30)

In conclusion, the risk of hepatic decompensation in HCV patients with ACLD was significantly reduced but was not completely eliminated, after treatment with interferon-free regimens. Among the studied non-invasive tests, only the evaluation of SSM before and after DAA treatment could identify the patients still at risk of decompensation despite viral elimination. Ultimately, paired SSMs may

represent a novel and promising non-invasive tool to assess the response to etiological or specific treatments that improve portal hypertension.

References

1. Ioannou GN, Beste LA, Chang MF, Green PK, Lowy E, Tsui JI, et al. Effectiveness of Sofosbuvir, Ledipasvir/Sofosbuvir, or Paritaprevir/Ritonavir/Ombitasvir and Dasabuvir Regimens for Treatment of Patients With Hepatitis C in the Veterans Affairs National Health Care System. Gastroenterology 2016 Sep;151(3):457-471.e5.

2. Flisiak R, Janczewska E, Łucejko M, Karpińska E, Zarębska-Michaluk D, Nazzal K, et al. Durability of virologic response, risk of de novo hepatocellular carcinoma, liver function and stiffness 2 years after treatment with ombitasvir/paritaprevir/ritonavir±dasabuvir±ribavirin in the AMBER, real-world experience study. J Viral Hepat 2018 Jul 3;

3. Lens S, Alvarado E, Mariño Z, Londoño M-C, LLop E, Martinez J, et al. Effects of All-oral Anti-viral Therapy on HVPG and Systemic Hemodynamics in Patients With Hepatitis C Virus-associated Cirrhosis. Gastroenterology 2017 Jul 20;

4. Pawlotsky J-M, Negro F, Aghemo A, Berenguer M, Dalgard O, Dusheiko G, et al. EASL Recommendations on Treatment of Hepatitis C 2018. J Hepatol 2018 Aug;69(2):461–511.

5. Conti F, Buonfiglioli F, Scuteri A, Crespi C, Bolondi L, Caraceni P, et al. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. J Hepatol 2016 Oct;65(4):727–33.

6. Nahon P, Layese R, Bourcier V, Cagnot C, Marcellin P, Guyader D, et al. Incidence of Hepatocellular Carcinoma After Direct Antiviral Therapy for HCV in Patients With Cirrhosis Included in Surveillance Programs. Gastroenterology 2018 Jul 18;

7. Ioannou GN, Green PK, Beste LA, Mun EJ, Kerr KF, Berry K. Development of Models Estimating the Risk of Hepatocellular Carcinoma After Antiviral Treatment for Hepatitis C. J Hepatol 2018 Aug 20;

8. Kanwal F, Kramer J, Asch SM, Chayanupatkul M, Cao Y, El-Serag HB. Risk of Hepatocellular Cancer in HCV Patients Treated With Direct-Acting Antiviral Agents. Gastroenterology 2017 Oct;153(4):996-1005.e1.

9. Ioannou GN, Feld JJ. What are the Benefits of a Sustained Virologic Response to Direct-acting Antiviral Therapy for HCV Infection? Gastroenterology 2018 Oct 24;

10. Park H, Wang W, Henry L, Nelson DR. Impact of all-oral direct-acting antivirals on clinical and economic outcomes in chronic hepatitis C patients in the U.S. Hepatology 2018 Oct 5;

11. Berzigotti A. Non invasive evaluation of portal hypertension using ultrasound elastography. J Hepatol. 2017 Feb;

12. de Franchis R, Baveno VI Faculty. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. J Hepatol 2015 Sep; 63(3):743–52.

13. Song J, Ma Z, Huang J, Liu S, Luo Y, Lu Q, et al. Comparison of three cut-offs to diagnose clinically significant portal hypertension by liver stiffness in chronic viral liver diseases: a meta-analysis. Eur Radiol 2018 Jun 1;

14. Manatsathit W, Samant H, Kapur S, Ingviya T, Esmadi M, Wijarnpreecha K, et al. Accuracy of liver stiffness, spleen stiffness, and LS-spleen diameter to platelet ratio score in detection of esophageal varices: Systemic review and meta-analysis. J Gastroenterol Hepatol 2018 May 30;

15. Colecchia A, Ravaioli F, Marasco G et al. A combined model based on spleen stiffness measurement and BavenoVIcriteria to rule out high-risk varices in advanced chronic liver disease. J Hepatol 2018; 69 (2): 308 317.

16. Spleen stiffness measurement can predict clinical complications in compensated HCV-related cirrhosis: A prospective study. J Hepatol 2014; 60: 1158–1164.

17. Singh S, Fujii LL, Murad MH, Wang Z, Asrani SK, Ehman RL, et al. Liver stiffness is associated with risk of decompensation, liver cancer, and death in patients with chronic liver diseases: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2013 Dec; 11(12):1573-84.e1-2; quiz e88-9.

18. Pons M, Santos B, Simón-Talero M, Ventura-Cots M, Riveiro-Barciela M, Esteban R, et al. Rapid liver and spleen stiffness improvement in compensated advanced chronic liver disease patients treated with oral antivirals. Therap Adv Gastroenterol. 2017 Aug;10(8):619–29. 8

19. Knop V, Hoppe D, Welzel T, Vermehren J, Herrmann E, Vermehren A, et al. Regression of fibrosis and portal hypertension in HCV-associated cirrhosis and sustained virologic response after interferon-free antiviral therapy. J Viral Hepat. 2016 Aug;

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

21. Austin PC. The use of propensity score methods with survival or time-to-event outcomes:

reporting measures of effect similar to those used in randomized experiments. Stat Med. 2014 Mar 30;33(7):1242–58. World J Hepatol 2018; 10: 731–742

22. Angeli P, Bernardi M, Villanueva C, Francoz C, Mookerjee RP, Trebicka J, et al. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol 2018 Aug;69(2):406–60.

23. Dietrich CF, Bamber J, Berzigotti A, Bota S, Cantisani V, Castera L, et al. EFSUMB Guidelines and Recommendations on the Clinical Use of Liver Ultrasound Elastography, Update 2017 (Long Version). Vol. 38, Ultraschall in der Medizin. 2017. p. e16–47.

24. Llop E, Berzigotti A, Reig M, Erice E, Reverter E, Seijo S, et al. Assessment of portal hypertension by transient elastography in patients with compensated cirrhosis and potentially resectable liver tumors. J Hepatol. 2012 Jan;56(1):103–8.

25. Dajti E, Ravaioli F, Festi D et al. Clinical outcomes after treatment with direct-acting antivirals: not all concern hepatocellular carcinoma risk. Hepatobiliary Surg Nutr 2019; epub ahead of print

26. Carrat F, Fontaine H, Dorival C, Simony M, Diallo A, Hezode C, et al. Clinical outcomes in patients with chronic hepatitis C after direct-acting antiviral treatment: a prospective cohort study. Lancet 2019 Apr 6 ;393(10179):1453–64.

27. Mauro E, Crespo G, Montironi C, Londoño M-C, Hernández-Gea V, Ruiz P, et al. Portal pressure and liver stiffness measurements in the prediction of fibrosis regression after SVR in recurrent hepatitis C. Hepatology. 2017 Sep;

28. Mandorfer M, Kozbial K, Schwabl P, Chromy D, Semmler G, Stättermayer AF, et al. Changes in HVPG predict hepatic decompensation in patients who achieved SVR to IFN - free therapy. Hepatology 2019 Jul 31;hep.30885.

29. Kim HY, So YH, Kim W, Ahn D-W, Jin Jung Y, Woo H, et al. Noninvasive Response Prediction in Prophylactic Carvedilol Therapy for Cirrhotic Patients with Esophageal Varices. J Hepatol 2018 Oct 30;

30. Bastard C, Miette V, Calès P, Stefanescu H, Festi D, Sandrin L. A Novel FibroScan Examination Dedicated to Spleen Stiffness Measurement. Ultrasound Med Biol. 2018 Aug;44(8):1616–26.