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Portal Hypertension Assessment Spleen using Stiffness Measurements after Successful DAAs Therapy in Chronic-HCV Patients

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ABSTRACT

Background: The emergence of noninvasive tests coupled with oral combined DAAs has shifted the paradigm in HCV management. Up to date, it is still questioned if SVR reverse portal hypertension and liver cirrhosis after being treated with direct antiviral therapy.

Aim of the work: To investigate the applicability of using splenic stiffness measurements as indicators of portal hypertension improvement after SVR in patients treated with DAAs.

Methods: This was a prospective study that included 100 HCV patients from Al-Azhar university hospital who achieved SVR after being treated with DAAs. Liver and spleen stiffness measurements as well as biochemical, virologic and clinical data were assessed at baseline (BL), at end of treatment (EOT), 12 weeks post-treatment, and 24 weeks post-treatment. We used Shear wave elastography (SWE) using ultrasound device Aplio 500 system (Toshiba, japan) to assess splenic stiffness.

Results: In our cohort, Spleen stiffness measurements decrease in 58% of the patients. It significantly improved between BL 30.6 kpa (26.3 - 34.8 kPa) and EOT 30.3 kPa (26.2- 34.6 kPa); (P< 0.001), and between BL and 24 weeks post-treatment 30 (26-34.4) kPa. Regarding platelets count, it also improved between BL 205 × 10^9/L (170- 251 × 10^9/L) and 24 weeks 218 × 10^9/L (187- 265 × 10^9/L); (P< 0.001).

Conclusions: NITs, especially SSM, decrease significantly after SVR in patients treated with DAAs. So that, they can be used as a mirror to reflect changes in portal hypertension status during following-up period instead of other available invasive methods which is well-known for their complications.

Keywords: Chronic hepatitis C, Direct-acting antivirals, Elastography; Spleen stiffness measurements; portal hypertension.

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INTRODUCTION

Chronic hepatitis C virus (HCV)) affects 130-170 million people worldwide, and it is estimated morbidity is 350,000 deaths each year [1], [2]. Moreover, it is a leading cause for liver transplantation in developed countries as it is a major cause of liver cirrhosis as well as hepatocellular carcinoma (HCC) [3], [4]. The management of patient with chronic HCV is slowly but surely evolving. Regarding treatments options, the new combination of oral direct acting antiviral therapies (DAAs) has revolutionized the treatment of chronic HCV patients as it provided a significant increase in sustained virological response (SVR) exceeding 90% [5]–[7].

Also patients with advanced disease have a higher risk for developing life-threatening conditions [8], there are emerging data that both portal hypertension and fibrosis may regress following successful DAAs [9]–[11]. Portal hypertension is a part of the natural history of HCV and leads to many complications that is why it has a great prognostic implication. Till now, it is still questioned if SVR has a real impact on portal hypertension and risk of decompensation after DAAs therapy [8], [9]. So that, the exact role of SVR on portal hypertension must be studied further by ascertaining portal hypertension status after successful DAAs treatment.

Regarding portal hypertension assessment, hepatic venous pressure gradient (HVPG) is considered as the gold standard for assessing portal hypertension. However, HVPG can cause severe complications is hard to be repeated in the follow up period. Recently, the emergence of noninvasive tests (NITs) for assessing portal hypertension reflected by liver and spleen stiffness measurements has streamlined the management much more as they have shown sturdy clinical applicability without having to perform invasive methods like HVPG) [14]–[17]. Those noninvasive measurements can be classified into either morphological or laboratory measures. The laboratory measurements include platelet count, AST, Albumin, and international normalized ration (INR). While morphological measures include transient elastography for assessing liver and splenic stiffness. Concomitantly, combination of both further can improve their accuracy much more [18], [19].

In DAAs efficacy era, few prospective studies have evaluated the value of using splenic stiffness measurements for assessing portal hypertension regression in patients with SVR after DAAs therapy. Therefore, we planned this study to assess whether treatment with DAAs leads to significant improvement in portal hypertension over 24 weeks of treatment as well as the use of NITs mainly SSM as indicators of portal hypertension status in patients who achieved SVR.

MATERIAL AND METHOD

Primary Outcome

The primary outcome of this study was to investigate the direct effect of DAAs therapy on portal hypertension after viral eradication and the applicability of using spleen stiffness measurements as indicator in patients with SVR after DAAs therapy.

Study Design

This was a single-center, observational, prospective study

that included 100 patients who were successfully treated with DAAs and achieved SVR between July 2019 and June 2020 at our department in Al-Azhar university hospital, Damietta, Egypt.

Inclusion and exclusion criteria

We enrolled patients aged more than 18 years old who has successfully achieved SVR after DAAs. Patients with co-infection with either hepatitis B or human immunodeficiency virus (HIV), hepatocellular carcinoma (HCC), active drug abusers, and pregnant women were also excluded. Furthermore, patients with autoimmune condition such as autoimmune hepatitis and primary biliary cirrhosis were also excluded.

Antiviral treatment

Patients' eligibility for receiving DAAs was assessed according to priority criteria established by Egyptian National committee for Control of Viral Hepatitis (NCCVH, 2017). This was observational study were patients were treated with DAAs then followed up if they were eligible to continue the study. They were well informed about the importance of adherence to the prescribed regimens. They were divided into two groups; the first was treated with sofosbuvir (SOF) plus daclatasvir (DCV), while the second group was treated with SOF plus DCV plus ribavirin (RBV). Moreover, we evaluated the response of patients to the antiviral therapy by measuring HCV RNA using PCR at the end of treatment (EOT), after 12 weeks, and after 24 weeks. Patients who did not achieve SVR were excluded from the study. Both noncompliant patients and patients how developed complications were excluded from the study too.

Patients assessment

A complete clinical and laboratory data were collected for each patient at baseline, at EOT, SVR12, and SVR24. SSM by Shear wave elastography (SWE) was obtained from each participant prior to the start of the study, at EOT, SVR12, and SVR24. We used ultrasound device Aplio 500 system (Toshiba, japan) was used to assess spleen stiffness reduction. Child-Turcotte Pugh (CTP) scores were also reported for each patient.

Ethical approval

An informed consent was collected from each patient prior to study. The study was conducted according to the protocol of the Egyptian National Committee for Control of Viral Hepatitis (NCCVH, 2017), and approved by the Medical Research Ethics Committee of Al-Azhar University

Statistical analysis

Regarding categorical data, it was expressed as numbers and percentages, while continuous variables were expressed as median and IQR. Collected data were evaluated using non-parametric tests. Chi-square (χ^2) were used for assessing the difference between categorical data, while Wilcoxon test, friedman's tests were used for continuous variables. Group comparisons among NITs at BL, SVR12 and SVR24 were evaluated with Friedman's non-parametric test. We also performed univariate analysis to test for association between patient factors and achieving the outcome. A two-tailed *P*-value was considered statistically significant at a value of < 0.05 with a 95% CI. Statistical analyses were carried out using Jamovi (Version 1.2) [20]–[22].

RESULTS

Study population

Between July 2019 and June 2020, we included patients with chronic hepatitis C with proved positive viremia. One hundred patients who were successfully treated with DAAs (either who received dual or triple therapy) and achieved SVR were included in our study, while we excluded patients with any co-infection including Hepatitis B, HIV or even HCC patients, patients who developed complications, and patients who did not achieve SVR. Seventy-one patient received dual therapy while the remaining 21 patient received triple therapy. In table 1, we summarized the baseline characteristics of the study participants. The two groups differed significantly in age, gender, WBCs count, AST, and albumin levels. While there was a highly significant difference in platelets count and ALT levels. Regarding the main NITs, the median value of SSM at baseline was 30.5 kpa (26- 35 kpa).

Figure 1.

Decline the flowchart of study participants. DAA: Direct-acting antiviral; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; SSM: Spleen stiffness measurement; SVR: Sustained virological response.

Table 1. Shows the baseline characteristics of the study participants before the start of the DAAs treatment.

Variable	Overall (n=100)	Group 1 (n=79)	Group 2 (n=21)	P-value
Age	53 (45.8-60)	52 (34 - 59)	58 (51 - 61)	0.043*
Female	55 (55%)	47 (59.49%)	8 (38%)	0.025*
Child Pugh score A	100 (100%)	79 (100%)	79 (100%)	- †

Platelets (cells × 10^9/L)	199 (166- 244)	205 (183- 259)	90 (84.0- 97.)	< 0.001*
Hb	12.8 (11.9- 13.3)	12.8 (12- 13.2)	12.0 (11.3 - 14)	0.934
WBCs	6.2 (4.6- 7.82)	6.70 (5.15-8.2)	4.60 (3.90- 6.2)	0.011
ALT (U/L)	37 (27- 42.3)	34 (23.5- 38.5)	54 (40.0- 99)	< 0.001*
AST (U/L)	37 (27 – 45)	36 (26 - 40)	68 (35 - 89)	0.002*
AFP (U/L)	6.5 (4.7 – 8.6)	6.50 (4.8- 8.5)	6.50(4.7- 9.7)	0.433*
Bilirubin (mg/dL)	0.9 (.7- 1.1)	0.9 (0.65- 1.05)	0.9 (0.7- 1.2)	0.038*
Albumin (g/dL)	3.9 (3.77- 4.3)	4.00 (3.80- 4.4)	3.50 (3.40- 3.8)	0.002*
SSM	30.5 (26- 35)	31 (26- 36)	30 (28- 33)	0.888*

* Continuous variables were analyzed using Wilcoxon test. † Categorical variables were analyzed using Chi-square test. Qualitative data are presented in numbers and percentages, while quantitative data were expressed as (25%-75% quartiles). ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; AFP: Alpha-fetoprotein; INR: international normalized ratio; SSM= Spleen stiffness measurement.

changes in patients' characteristic after DAAs

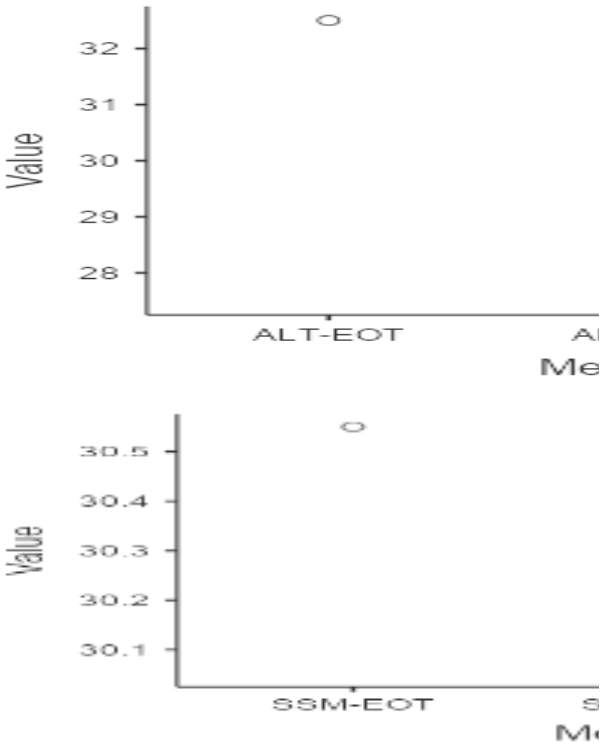
The median value of SSM had significantly decreased after SVR from 30.6 kPa to 30 kPa ($p < 0.001$). Patients with high and low SSM at baseline showed significant decline in the median score of SSM between baseline and end of treatment (Table 2). Moreover, the Improvement in SSM score continues between EOT and 24 weeks Post-treatment ($p<0.001$) (Fig. 2.b). Among all patients in our cohort, the median intra-patient change between EOT and 12 months post-treatment was -0.5 kPa (IQR -2.4, -0.1) (Table 3). We also compared change in platelets count, ALT and AST with change in LSM score between the three time points: (1) baseline—EOT, (2) EOT— 12 weeks post-treatment, and (3) baseline—24 weeks post-treatment. A decrease in ALT median value from 32.5 to 27.5 U/L was also observed ($p < 0.001$). The median AST level significantly decreased from 30 to 22 U/L ($p < 0.001$). Regarding other NITs, platelets count significantly increased after successful DAAs therapy from 205 to 218 (cells × 10^9/L) ($p < 0.001$). (Table 2 and Figure 2).

Table.2 Changes in patients' characteristics at the end of the treatment, after 12 weeks and after 24 weeks.

Variable	Baseline	EOT	12 Weeks	24 Weeks	p-value*
Platelets (cells × 10^9/L)	199 (166- 244)	205 (170- 251)	210 (175- 254)	218 (187- 265)	< .001

Hb	12.8 (11.9- 13.3)	12.8 (11.9 -13.3)	12.6 (12.0- 13.4)	12.6 (12.0- 13.4)	0.917
WBCs	6.2 (4.6- 7.82)	6.20 (4.60- 7.82)	5.30 (4.97- 6)	5.30 (4.9- 6)	< .001
ALT (U/L)	37 (27- 42.3)	32.5 (26.0- 37.0)	27.5 (22.8- 32)	27.5 (22.8- 32)	< .001
AST (U/L)	37 (27 – 45)	30 (24- 40)	22 (19- 28)	22 (19- 28)	< .001
Bilirubin (mg/dL)	0.9 (.7- 1.1)	0.8 (0.7- 1)	0.9 (0.8- 0.9)	0.9 (0.8- 0.9)	-
Albumin (g/dL)	3.9 (3.77- 4.3)	3.90 (3.8- 4.3)	3.90 (3.8- 4.3)	3.90 (3.8- 4.3)	-
SSM	30.5 (26- 35)	30.6 (26.3 – 34.8)	30.3 (26.2- 34.6)	30 (26-34.4)	< .001

* Continuous variables were analyzed using Wilcoxon test. Data were presented as median (25%-75% quartiles). ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; AFP: Alpha-fetoprotein; INR: international normalized ratio**;** SSM= Spleen stiffness measurement.



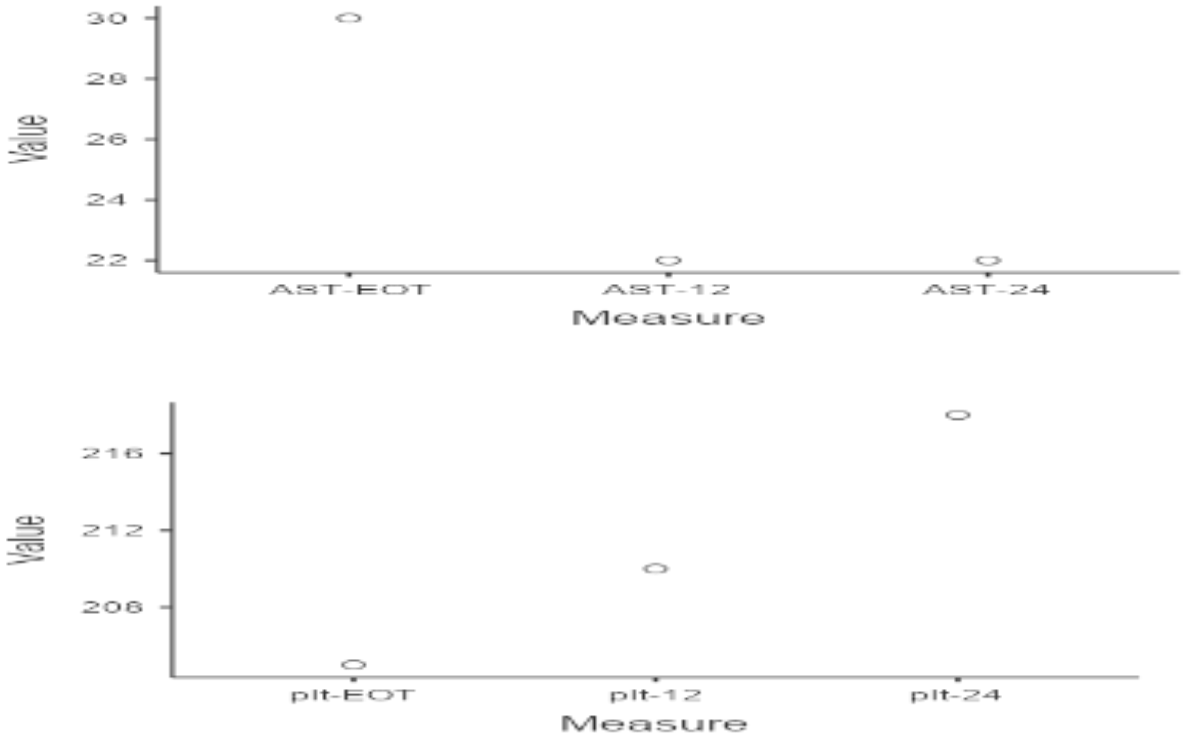


Figure 2. Changes in non-invasive tests after SVR. A: ALT changes; B: SSM change; C: AST change; D: PLT count, SSM: Spleen stiffness measurement; PLT: Platelet count.

DISCUSSION

In treating HCV, the primary goal is to prevent progression of both hepatic and extra-hepatic manifestations in HCV patients. In this study, we aimed to assess the effect of successful DAAs treatment in chronic HCV patients on portal hypertension regression assessed by NITs especially SSM. Also previous literature has shown that interferon therapy leads to long-term improvement in portal hypertension and liver fibrosis when achieving SVR [23]–[25], the log-term improvement with DAAs therapy assessed by NITs, as SSM, after SVR is still to be determined. Our results indicate that patients who successfully achieved SVR after DAAs therapy had long-term improvement in SSM scores over 24 weeks after completion of therapy, suggesting possible early improvement in portal hypertension (Table 2).

After searching previous literature, we found three papers and one litter where they investigated SSM changes following SVR [9], [26]–[28]. Two of them, Pons *et al* and Ravaioli *et al* [26], [28], had similar finding regarding rapid SSM decrease while others had opposing results as they did not find significant change after SVR24 [9]. Moreover, our study results is consistent with previous studies which used HVPG, instead of NITs, where it was significantly decreased after achieving SVR [29]–[31]. In the current literature, there was a lack of prospective studies to observe changes in SSM at standardized time points at baseline before the start of treatment, and after treatment as well as the correlation of SSM with clinical outcomes. Compared to the previous published study in this era [28], we offered a prospective follow-up, with our final SSM score measured at least 24 weeks after end of therapy as following patients after completing therapy reduces the confounding effect of liver inflammation caused by HCV viremia and its effect on stiffness measurements.

The median improvement in LSM between baseline and EOT may be caused by the effect of inflammation resolution following DAAs therapy. Nevertheless, subsequent improvement from EOT to 24 weeks after treatment may represent a combination of continued resolution as well as some improvement in liver fibrosis. Regarding LSM, BL elevation of ALT levels may represent liver inflammation, which mostly resolves at the EOT time point, accounting for some of the regression in LSM score too. However, continued improvement in LSM between the EOT and 24 weeks after treatment suggests the possibility that there is early regression of liver fibrosis as well as resolution of inflammation. Since the majority of ALT and AST improvements occurred between baseline and EOT, it may be attributed to the resolution of live inflammation rather than the treatment. Furthermore, other indicators of PH, including platelet count had significantly changed.

As a summary of our results, the dramatic change in LSM and SSM among patients who successfully achieved SVR indicates that they can be used as noninvasive, feasible tools in monitoring portal hypertension and liver fibrosis status and assessing patients' response to treatment.

Regarding the limitations of this study: (1) we had a relatively small cohort with inadequate statistical power to identify additional patient factors independently associated with significant improvement in portal hypertension. A larger sample size is required in future studies to help in confirming the association between SSM reduction and portal hypertension improvement. (2) We did not have a gold standard reference for assessing portal hypertension. However, according to NITs and LSM can substitute invasive methods including liver biopsy and HVPG. (3) Follow-up was relatively short to sufficiently correlate SSM changes with clinical outcomes after viral eradication.

In conclusion, our study reviled that achieving SVR after DAAs is significantly associated with improvement in portal hypertension and that SSM could provide an accurate method for following-up patients with SVR regarding changes in portal hypertension status. Further studies are required in order to confirm the accuracy of SSM and other NITs in ascertaining portal hypertension in patients with SVR.

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