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Original article

Assessment of Liver Fibrosis after Direct-Acting Antiviral Therapy in Compensated and Decompensated HCV-related Liver Diseases

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Abstract

Background and Aim: Successful HCV eradication was associated with significant improvement in liver histology. Direct-acting antiviral (DAAs) therapies are associated with significantly higher rates of sustained virologic response (SVR) compared to interferon-based therapies. Several non-invasive methods have been developed and validated with robust reliability and clinical applicability in evaluating hepatic fibrosis prior to HCV therapy. However, the use of these measures in monitoring fibrosis regression after HCV eradication with DAAs is currently limited. So, the aim was to assess the impact of DAAs on fibrosis regression in chronic HCV Egyptian patients with either compensated or decompensated liver diseases. ***Patients and Methods:*** A total of 228 Egyptian chronic HCV patients eligible for treatment with DAAs were enrolled in this prospective study. All subjects selected from outpatient's Hepatology clinic of Mansoura university hospital received DAAs with different regimens after consent. The endpoint was a sustained virologic response at 12 (SVR12) weeks post-treatment. All participants were evaluated non-invasively by fibrosis-4 index (FIB-4), Aspartate Aminotransferase-to-Platelet Ratio Index (APRI) score, and liver stiffness measurement (LSM) by FibroScan before DAAs treatment, at end of treatment (EOT), 6- and 12-months post-treatment. ***Results:*** SVR achieved by DAAs therapy was associated with significant improvement ($p < 0.05$) of non-invasive fibrosis markers (FIB-4, APRI score, and LSM by FibroScan) from baseline compared to EOT, 6-and 12-months post-treatment among HCV patients with significant (F2) and advanced liver fibrosis (≥F3). ***Conclusions:*** fibrosis regressed significantly after DAAs therapy regardless of its baseline grade. Also, baseline LSM by FibroScan predicted fibrosis regression.

Keywords: *Direct-acting antiviral agents; HCV; Hepatic fibrosis; APRI score; FIB-4 index*

Introduction

Hepatitis C virus (HCV) infection promotes liver fibrogenesis by direct and indirect mechanisms through chronic inflammation. There are tremendous changes in the management of chronic HCV infection over the past several decades. Direct-acting antiviral (DAA) agents have a virologic cure with a significantly higher rate of sustained virologic response (SVR) over 90% compared to interferon-based therapies even in patients with decompensated cirrhosis.[1]

Measurement of hepatic fibrosis noninvasively enables the identification of at-high risk patient without the need for liver biopsy. The application of the noninvasive techniques produced a simplified approach in the management of patients with chronic HCV infection. The achievement of SVR after treatment had been evidenced to have a reduced risk of hepatocellular carcinoma (HCC) and liver cell failure.[2] This is probably attributed to the fibrosis regression after viral eradication.[3] Unfortunately, patients who have advanced fibrosis or cirrhosis remain at a higher risk of complications even after SVR achievements.[4] Associated co-morbidities, such as metabolic syndrome, alcoholic or nonalcoholic

steatohepatitis (NASH), may also contribute to such liver-related complications.[5,6]

In this era of highly effective DAA agents leading to enormous cure rates, identifying and monitoring patients who remain at a high complication risk after achieving SVR continue to be a critical issue. Several validated methods for noninvasive measurement of liver fibrosis can be used in the management of HCV infection. Several noninvasive serologic markers have been developed to determine the degree of liver fibrosis. The Aspartate Aminotransferase (AST)-to-Platelet Ratio Index (APRI) score, which was originally proposed in 2003 by Wai and colleagues is a validated measure.[7] The Fibrosis-4 (FIB-4) index is another validated noninvasive serologic measure of fibrosis.[8] These scores were able to reliably determine moderate to advanced fibrosis (Metavir score F2-F4 on liver biopsy).[9]

The advent of liver stiffness measurement (LSM) has led to the development of sophisticated methods for noninvasively detecting fibrosis. Technologies such as vibration-controlled transient elastography (VCTE) or magnetic resonance elastography (MRE) have revolutionized the monitoring of patients with liver disease in clinical settings. These technologies provide reliable ways to measure fibrosis without a liver biopsy.

Vibration-Controlled Transient Elastography (VCTE), often referred to as FibroScan, is approved for use by the US Food and Drug Administration and now serves as the standard of care in many health centers. FibroScan outperforms serologic tests for the diagnosis of cirrhosis, in addition, it has a short procedure time, provides immediate results, and is easily operated at the bedside.[10] The limitations of FibroScan include the presence of increased necroinflammatory activity and edema within the liver, manifested as aminotransferase elevations. These pathologic changes can falsely elevate the score and overestimate the degree of fibrosis.[11] Despite these limitations, VCTE is still a useful tool that allows for a more streamlined approach to monitoring fibrosis in patients during the management of HCV and other liver diseases.[12] VCTE also allows for a simpler way to monitor patients after HCV eradication who have baseline pretreatment advanced fibrosis or cirrhosis.

The combination of individual tests is earning publicity and is commonly done in a clinical practice scenario in order to better predict fibrosis and avert liver biopsy.[13] However, the utility of these noninvasive modalities in detecting fibrosis regression and predicting complication risk after achieving SVR is not well defined. To address this gap in knowledge, this article assesses the impact of DAAs on fibrosis regression in patients with either compensated or decompensated liver disease using the current available noninvasive modalities (APRI score, FIB-4 index, and LSM by FibroScan) and discusses their applicability in the management of individuals after successful HCV eradication.

Patients and Methods

Inclusion Criteria: A total of 228 Egyptian outpatients with a confirmed diagnosis of chronic HCV, the age range of 18-70 years and eligible for receiving DAAs were enrolled in this prospective study from July 2016 through 2018. All subjects were selected from the outpatient's clinic of Hepatology department of Mansoura university hospital. A written informed conscious consent was obtained from all participants before their participation. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by the Institutional Review Board of Mansoura Faculty of Medicine (MFM-IRB; R.18.02.42).

Exclusion Criteria: Patients who have hypersensitivity to the drugs used, pregnancy, breastfeeding, poorly controlled diabetics (Glycated hemoglobin: HbA1C >8) and hepatocellular carcinoma were excluded. Patients with renal disease [serum Creatinine >2.5 mg/dl or glomerular filtration rate (GFR) <30 ml/min/1.73m^2] were also excluded.

Methods: Initially, all patients completed a detailed questionnaire regarding diet and habits, submitted to thorough history taking with detailed physical examinations performed at fasting in the morning. The diagnosis of chronic HCV was done by Quantitative HCV-PCR using the COBAS AmpliPrep/COBAS TaqMan (CAP/CTM, v2.0) assay performed according to the manufacturer's instructions. At the day of study inclusion, height and weight were measured. BMI was calculated as weight in kilograms divided by height squared in meters (kg m^{-2}). Venous blood samples were obtained from each subject after a minimum of 10 hours of fasting. Serum tubes were centrifuged at 1500 g for 10 min at 4°C, followed by a second centrifugation at 2000 g for 3 min at 4°C, aliquoted and stored at −80°C until assayed. Liver biochemical profile was done including total and direct bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), serum albumin (ALB) and international normalized ratio (INR). Also, complete blood count (CBC), HBsAg, HCV-Ab, HCV PCR quantitative, serum creatinine, alpha-fetoprotein (AFP), fasting blood sugar (FBS), and HbA1c (if diabetic), and pregnancy test (for female patients in the childbearing period) were done. Levels of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), were also determined in all participants.

LSM by FibroScan and Abdominal ultrasonography were done for all participants to detect the echopattern of the liver (ultrasonographic features of cirrhosis), the degree of fibrosis, presence of signs of portal hypertension, maximum spleen bipolar diameter, and to exclude hepatocellular carcinoma. **FIB-4 index** was calculated to all patients using the following formula:$[Age\ (years) \times AST(U/L)] \div [platelets\ (10^9/\mathrm{L}) \times \sqrt{ALT(U/L)}]$. **APRI score** was calculated too using this equation:$[AST(U/L) \div AST(upper\ limit\ of\ normal\ (U/L))] \div platelets\ (10^9/\mathrm{L}) \times 100$.[14,15]

Liver Stiffness Measurement (LSM): Liver stiffness was measured for all included patients using a standard M probe or an XL probe (for obese patients)[16] of the FibroScan device (Echosens, Paris) before treatment (baseline), at EOT, at 6-and 12-months post-treatment. Measurements were performed through the intercostal spaces on fasting patient lying in the dorsal decubitus position with the right arm maximally abducted. The tip of the probe was applied in contact with the intercostal skin through a coupling gel in the 9th to 11th intercostal space at the level where a liver biopsy would be performed. The operator locates a liver portion at least 6 cm thick and free of large vascular structures then the operator presses the probe button to start shots. Measurement depth was between 25 mm and 65 mm below the skin surface. The software determined whether each measurement was successful or not. The examination was considered reliable if ≥10 valid measurements were acquired, the success rate (the number of valid acquisitions divided by the number of attempts) was >60%, and the ratio of the interquartile range to the median of 10 measurements (IQR/M) was ≤0.3. The used cutoff values for defining each stage

of hepatic fibrosis were 8.8-9.5 kPa for significant fibrosis group (F2), >9.5 kPa for advanced fibrosis group (≥F3) and Liver stiffness (LS) score more than 14.5 kPa indicated LS-defined cirrhosis. Clinically significant portal hypertension was present if LSM≥ 21 kPa, and absent if LSM <13.6 kPa.[17] Any decrease in LSM by FibroScan more than 30% was considered a clinically significant improvement.[18]

All patients had HCV RNA positivity, they were either naïve to HCV treatment or had a previous treatment experience whether interferon-based or Sofosbuvir-based and no restrictions were put on either BMI or fibrosis stage. All patients received DAAs with different regimens (Sofosbuvir 400mg plus either Daclatasvir 60mg or Ledipasvir 90mg with or without Ribavirin 400-800mg; oral administration). The primary endpoint of treatment was sustained virologic response at 12weeks (SVR12) post-treatment with DAAs and the secondary endpoint was adverse outcomes (worsening in model for end-stage liver disease (MELD) score or serious adverse event) within 3 months. Revisions of the efficacy, toxicity and potential drug-drug interactions of concurrent drugs given for associated co-morbidities were performed prior to initiation of therapy. All participants were followed up and evaluated by HCV RNA quantitation, FIB-4 index, APRI score, and LSM by FibroScan before DAAs treatment (baseline), at EOT, 6- and 12-months post-treatment.

Efficacy of Treatment was monitored by the COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test; v2.0 (CAP/CTM, v2.0) performed according to the manufacturer's instructions. HCV RNA was extracted from 850 µl according to the manufacturer's instructions. Specimens' preparation and processing were automated using the COBAS AmpliPrep Instrument with automated amplification and detection using the COBAS TaqMan 96 Analyzer. The dynamic range of quantification was 15 to 100,000,000 IU/ml (1.2- 8.0 Log_{10} IU/ml), with the claimed lower limit of detection equal to the lower limit of quantification (15 IU/ml, i.e., 1.2 Log_{10} IU/ml). HCV RNA quantitation was performed at baseline, at EOT, 6- and 12-months post-treatment. HCV RNA values less than the lower limit of detection at EOT were considered a virologic response. Sustained virologic response (SVR) was defined when HCV RNA less than lower limit of detection at 12 weeks after EOT. Treatment discontinuation due to adverse events was considered as treatment failure.

Statistical Analyses were carried out using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp).[19] Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution. Quantitative data were described using mean ± standard deviation if normally distributed and median and interquartile range (IQR) if not. Statistical significance was accepted at a level of $P < 0.05$. Chi-square test was used for categorical variables, to compare between different groups. Monte Carlo correction for chi-square when more than 20% of the cells have expected count less than five. Student t-test and Mann Whitney test were used to compare between two studied groups for normally and abnormally distributed quantitative variables respectively. Paired samples were analyzed using the Wilcoxon matched pair-signed-rank test. Mixed-effect models for analyzing repeated-measures technique were constructed to compare the change in FIB- 4, APRI and LSM by Fibroscan among both patient groups along the follow-up time points. Univariate logistic regression analyses were performed to identify factors associated with lack of improvement of LSM by FibroScan at 12-months post-treatment compared to its baseline value.

Results

The present study cohort included 228 Egyptian patients who were eligible for DAAs for their chronic HCV infection. Thirteen patients escape follow-up and treatment discontinuation in fifteen patients due to adverse events. The remaining 200 patients were predominantly males (136; 68%), treatment naïve (150; 75%) with a mean age of 54.12 years. The mean duration of HCV infection was 12 years. Liver stiffness measurement (LSM) by FibroScan was significant fibrosis (F2: 8.8-9.5kPa) in 122; 61% patients and advanced fibrosis (≥F3: >9.5kPa) in 78; 39% patients. Table 1 compared between significant and advanced fibrosis as regard baseline clinical and laboratory data, DAAs regimens and non-invasive fibrosis markers. No significant differences were noted between the significant and advanced fibrosis (p> 0.05) except in LSM by FibroScan, albumin and AFP levels (P <0.05).

Table 1: Baseline clinical and laboratory characteristics of all studied patients

	Overall	Significant fibrosis (F2)	Advanced fibrosis (≥F3)	P-value
Number	200	122 (61%)	78 (39%)	
Age (yrs): mean±SD	54.12±7.8	53.89±8.1	54.31±7.9	0.561
Gender (M/F)	136/64	85/37	51/27	0.784
BMI (kg/m^2)	26.23±4.12	25.98±3.07	26.71±3.21	0.156
Diabetes (yes) n (%)	118 (59%)	70 (59.3%)	48 (40.7%)	0.672
Hypertension (yes) n (%)	78 (39%)	44 (56.4%)	34 (43.6%)	0.057
Treatment-experienced/Naïve	50/150	28/86	22/64	0.871
Duration of HCV (yrs): mean ± SD)	12±2.6	11±3.4	13±4.5	0.094
DAAs regimen: (n)				0.625
• SOF/DAC	45	25	20	
• SOF/DAC/RIB	60	33	27	
• SOF/LED	50	27	23	
• SOF/LED/RIB	45	23	22	
WBCs (10^3mm^3)	5.6±2.14	5.9±2.4	5.2±2.9	0.347
Hemoglobin (g/dl)	12.99±2.66	13.21±2.45	12.55±2. 78	0.289
Platelets (10^3mm^3)	144.3±55.4	142.2±62.3	148±49.6	0.146
ALT (IU/L)	89.53±22.3	88.53±31.5	87.98±27.2	0.098
AST (IU/L)	79±33.5	75.5±32.2	77.1±31.4	0.167
ALP (IU/L)	132.9±41.9	133.8±42.6	132.3±41.2	0.712

Bilirubin (mg/dL)	0.68±0.25	0.99±0.38	1.03±0.75	0.098
Albumin (g/dl)	4.01±0.25	3.42±0.19	3.03±0.15	**0.001**
AFP (IU/mL): median (IQR)	5.3(3.1-6.7)	5.1 (3.2-6.5)	7.3 (4.9-7.9)	**0.014**
INR	1.09±0.19	1.12±0.15	1.17±0.11	0.098
Log_{10} HCV PCR (IU)	6.18±0.81	6.14±0.79	6.17±0.80	0.754
Fasting blood sugar (mg/dl)	128±32.4	126±34.2	131±28.3	0.298
Glycated hemoglobin (HA1C %)	6.71±1.35	6.62±1.42	6.65±1.74	0.335
Creatinine (mg/dL)	1.1±0.29	1.01±0.39	1.09±0.18	0.191
FIB-4 index	3.13±1.97	3.05±2.87	3.28±1.47	0.452
APRI score	1.22±1.03	1.18±1.11	1.26±1.05	0.712
LSM by Fibroscan (kPa)	15.98±9.95	9.18±0.76	18.3±3.32	**<0.001**

Data are presented as mean ± SD or median (IQR), SD, standard deviation; IQR, inter-quartile range; SD, standard deviation; IQR, inter-quartile range, n, number; %, percentage. AFP, alpha-fetoprotein; ALP, alkaline phosphatase; yrs: years; ALT, alanine transaminase; APRI, Aspartate Aminotransferase Platelet Ratio Index; AST, aspartate transaminase; BMI, body mass index; FIB-4, fibrosis-4 score; INR, international normalized ratio; kPa, kilopascals; LSM, liver stiffness measurement; WBC, white blood cell count; F2, significant fibrosis; F3, advanced fibrosis; Significance at p-value ≤ 0.05.

Pair-wise changes in hematological parameters, liver biochemical necroinflammatory profile and non-invasive fibrosis markers from baseline compared to end of treatment (EOT), 6- and 12-months post-treatment among patients with significant and advanced fibrosis were shown in Table 2 and Table 3 respectively. In the significant fibrosis group (F2), there were significant improvements ($p<0.05$) in necroinflammatory profile (AST, ALT), platelets and non-invasive fibrosis markers (FIB-4 index and APRI score) at EOT, 6-and 12-months post-treatment. The improvement in LSM by fibroscan started to be significant at 6-and 12-months post-treatment ($P=0.001$ and $p<0.001$ respectively)**.** Moreover, WBCs, hemoglobin, ALP, albumin, and bilirubin levels were improved significantly only at 12-months post-treatment ($p<0.05$, Table 2).

In the advanced fibrosis group (≥F3), the improvements in non-invasive fibrosis markers (FIB-4 index, APRI score and LSM by fibroscan) were not significant except at 6- and 12-months post-treatment ($p<0.01$). Additionally, platelets were non-significantly increased along the different follow-up points in this group ($p>0.05$). WBCs, hemoglobin, and albumin levels were not significant except at 12-months post-treatment ($p<0.05$), Table 3. Interestingly, the reduction in LSM by fibroscan from 6- to 12-months post-treatment was significant in advanced fibrosis (≥F3, Table 3) group (*P4=0.019*) but not in the significant fibrosis (F2, Table 2) group (*P4=0.061*). The hematological parameters, liver biochemical profile and other fibrosis markers (FIB-4 index and APRI score) did not change significantly from 6- to 12-months post-treatment neither in F2 nor in advanced fibrosis (≥F3) [P4 >0.05, Table 2, 3].

Table 2: Changes in hematological parameters, liver biochemical profile and fibrosis markers from baseline compared to end of treatment (EOT), and 6- and 12-months post-treatment among patients with significant fibrosis (F2), n=122.

	Baseline (F2)	**End of Treatment**	**6-months post-treatment**	**12-months post- treatment**	***P1***	***P2***	***P3***	***P4***
WBCs (10^3mm^3)	5.9±2.4	6.03±2.5	6.28±2.9	7.28±2.9	0.347	0.403	**0.01**	0.420
Hemoglobin(g/dl)	13.21±2.45	13.42±2.35	13.87±2.55	15.87±2.55	0.289	0.08	**0.014**	0.126
Platelets(10^3mm^3)	142.2±62.3	151.8±67.3	164.8±47.3	172.71±67.3	**0.01**	**0.001**	**0.001**	0.142
ALT (IU/L)	88.53±31.5	72.64±30.1	67.14±34.2	52.22±32.1	**0.01**	**0.004**	**0.001**	0.09
AST (IU/L)	75.2±32.2	55.01±31.9	49±33.9	41.01±33.7	**0.01**	**0.004**	**<0.001**	0.312
ALP (IU/L)	133.8±42.6	131.8±39.8	129.8±45.8	105.7±45.9	0.465	0.125	**0.023**	0.545
Albumin (g/dl)	3.42±0.19	3.54±0.29	3.71±0.45	4.38±0.39	0.291	0.087	**0.031**	0.491
Bilirubin (mg/dL)	0.99±0.38	0.78±0.55	0.81±0.49	0.54±0.67	0.621	0.127	**0.048**	0.64
AFP (IU/mL): median (IQR)	5.1 (3.2-6.5)	4.9 (3.2-6.2)	4.7 (3.1-5.9)	4.2 (2.9-5.2)	0.523	0.481	0.614	0.563
INR	1.12±0.15	1.01±0.12	1±0.03	0.9±0.23	0.098	0.08	0.131	0.178
FIB-4 index	3.03±2.87	2.29±1.87	1.26±1.12	1.07±091.	**0.046**	**0.01**	**0.001**	0.052
APRI score	1.18±1.31	0.81±0.38	0.69±0.27	0.53±0.14	**0.032**	**0.01**	**0.008**	0.271
LSM by Fibroscan (kPa)	9.18±0.76	9.12±0.52	7.55±1.32	6.12±0.87	0.310	**0.001**	**<0.001**	0.061

Data are presented as mean ± SD or median (IQR), SD, standard deviation; IQR, interquartile range, n, number; %, percentage. AFP, alpha-fetoprotein; ALP, alkaline phosphatase; ALT, alanine transaminase; APRI, Aspartate Aminotransferase Platelet Ratio score; AST, aspartate transaminase; BMI, body mass index; FIB-4, fibrosis-4 index; INR, international normalized ratio; kPa, kilopascals; LSM, liver stiffness measurement; WBC, white blood cell count; F2, significant fibrosis; P1, compared baseline *vs* EOT; P2, compared baseline *vs* 6-months post-treatment; P3, compared baseline *vs* 12-months post-treatment; *P4*, compared 6- *vs* 12-months post-treatment; Significance at p-value ≤ 0.05.

Table 3: Changes in hematological parameters, liver biochemical profile and fibrosis markers from baseline compared to end of treatment (EOT), and 6- and 12-months post-treatment among patients with advanced fibrosis (≥F3), n=78.

	Baseline (≥F3)	**End Of Treatment**	**6-months post-treatment**	**12-months post- treatment**	***P1***	***P2***	***P3***	***P4***
WBCs (10^3mm^3)	5.2±2.9	5.18±2.5	5.68±2.9	6.12±2.3	0.447	0.063	**0.012**	0.420
Hemoglobin (g/dl)	12.55±2. 8	11.98±2.12	12.87±2.67	14.19±1.99	0.089	0.071	**0.041**	0.106
Platelets(10^3mm^3)	136±49.6	151.9±63.2	154.8±55.3	159.8±79.3	0.460	0.164	0.081	0.634

ALT (IU/L)	87.98±27.2	79.64±41.1	68.14±29.2	54.22±32.1	**0.047**	**0.012**	**0.004**	0.087
AST (IU/L)	77.1±31.4	61.2±15.9	49.2±13.9	42.4±22.7	**0.031**	**0.001**	**0.001**	0.372
ALP (IU/L)	132.3±41.2	131.8±37.8	129.8±47.8	122.7±44.9	0.455	0.565	0.487	0.560
Albumin (g/dl)	3.03±0.15	3.24±0.19	3.41±0.55	4.07±0.36	0.331	0.0124	**0.009**	0.491
Bilirubin(mg/dL)	1.03±0.75	0.85±0.56	0.84±0.59	0.66±0.47	0.338	0.289	0.191	0.64
AFP (IU/mL): median (IQR)	7.3 (4.9-7.9)	6.9 (3.2-6.2)	6.7 (3.1-5.9)	5.9 (2.9-5.2)	0.616	0.512	0.236	0.563
INR	1.17±0.11	1.01±0.12	1±0.07	0.9±0.19	0.198	0.059	0.191	0.178
FIB-4 index	3.28±1.47	2.85±1.87	1.59±2.12	1.26±1.57	0.107	**0.004**	**0.001**	0.061
APRI score	1.26±1.01	0.98±0.78	0.71±0.58	0.69±0.29	0.131	**0.009**	**0.001**	0.413
LSM by Fibroscan (kPa)	18.3±3.32	15.2±0.52	11.9±1.32	9.6±0.87	0.054	**0.004**	**<0.001**	**0.019**

SD, standard deviation; IQR, interquartile range, n, number; %, percentage; AFP, alpha-fetoprotein; ALP, alkaline phosphatase; ALT, alanine transaminase; APRI, Aspartate Aminotransferase Platelet Ratio score; AST, aspartate transaminase; BMI, body mass index; FIB-4, fibrosis-4 index; INR, international normalized ratio; kPa, kilopascals; LSM, liver stiffness measurement; WBC, white blood cell count; F3, advanced fibrosis; P1, compared baseline *vs* EOT; P2, compared baseline *vs* 6-months post-treatment; P3, compared baseline *vs* 12-months post-treatment; *P4*, compared 6- *vs* 12-months post-treatment; Significance at p-value ≤ 0.05.

The change in liver fibrosis indices (FIB-4 index, APRI score, LSM by FibroScan) at different time points from the baseline to 12-months post-treatment in patients with significant fibrosis (F2) and advanced fibrosis (F3) were shown in Figure 1 (A, B, C). There were significant improvements from the baseline values to 6- and 12-months post-treatment values in both groups (P<0.05). However, FIB-4 index and APRI score were improved significantly from the baseline to EOT only in the significant fibrosis (F2). Also, the improvement in LSM by FibroScan from 6- to 12-months post-treatment was significant only in advanced fibrosis (≥F3).

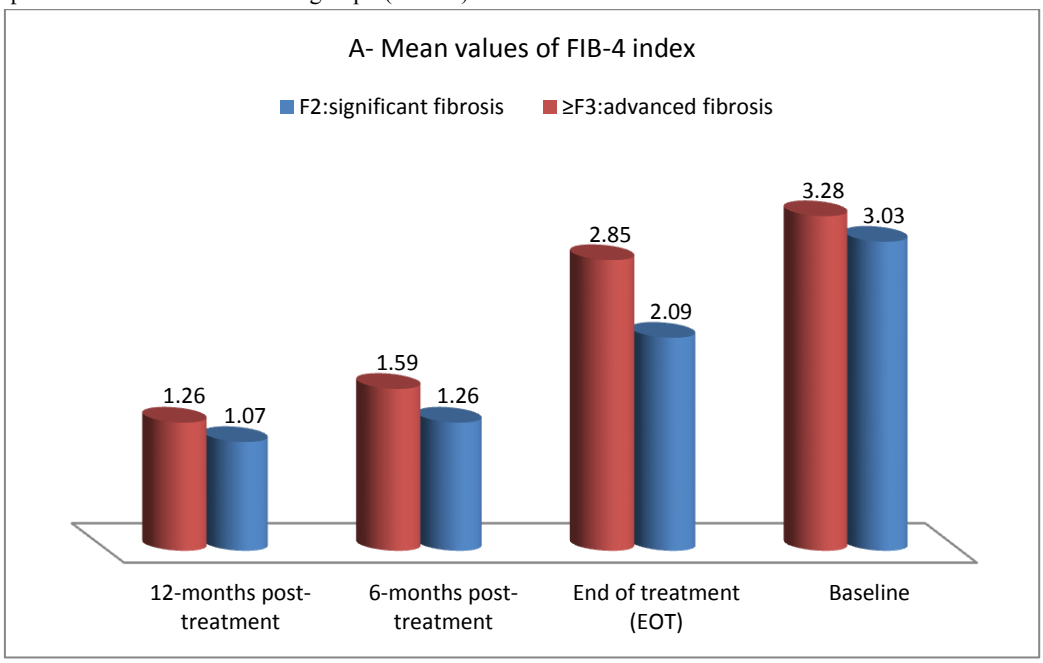

Figure 1 (A): Change in FIB-4 index at different time points from the baseline to 12-months post- treatment in patients with significant fibrosis (F2) and advanced fibrosis (≥F3)

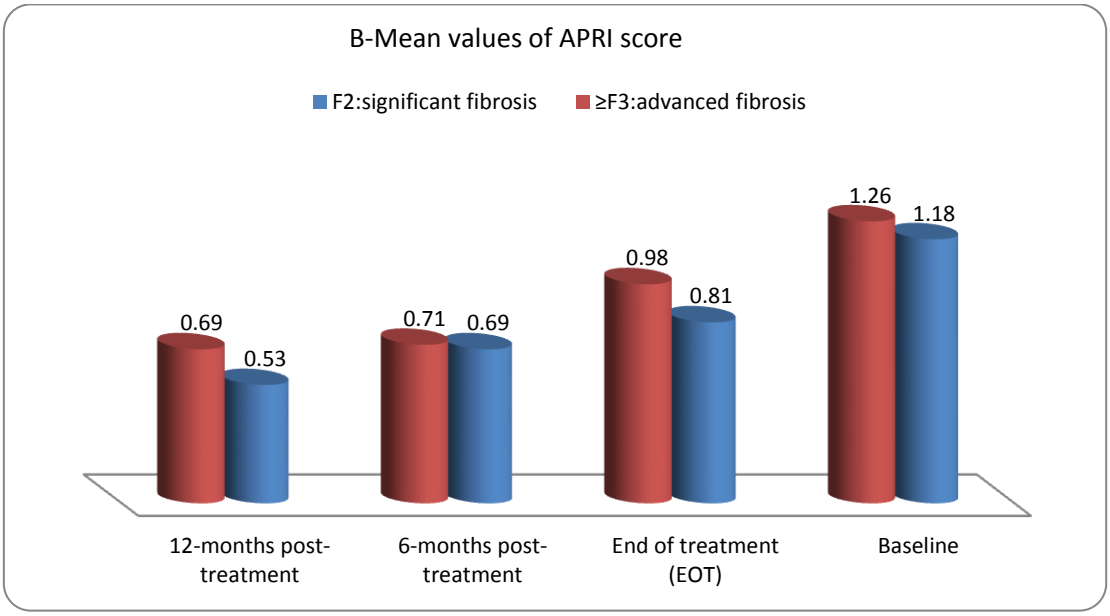

Figure 1 (B): Change in APRI score at different time points from the baseline to 12-months post- treatment in patients with significant fibrosis (F2) and advanced fibrosis (≥F3)

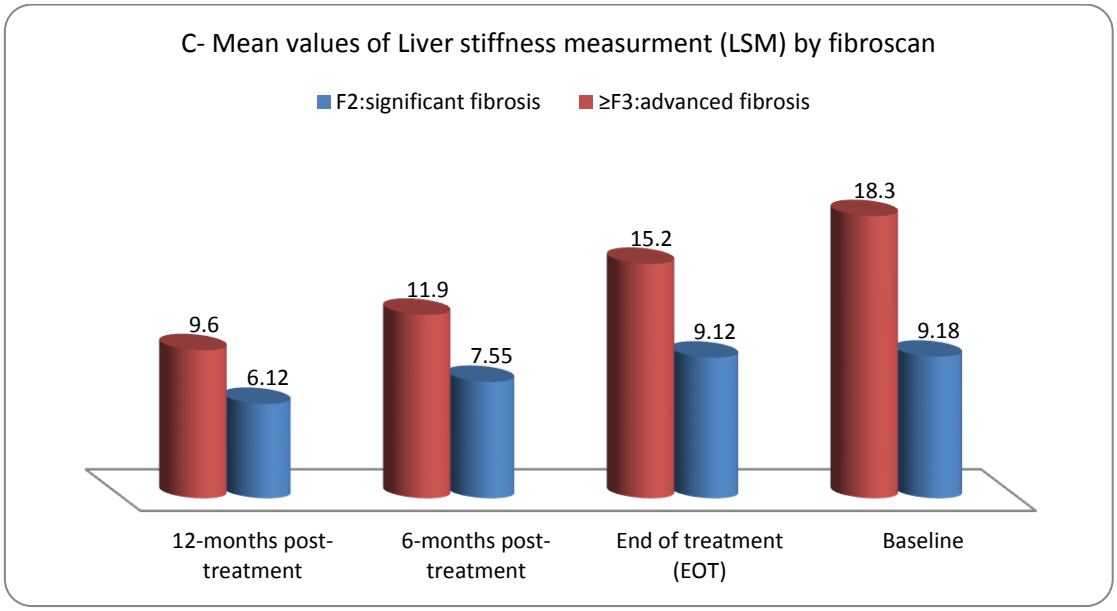

Figure 1 (C): Change in LSM by fibroscan at different time points from the baseline to 12-months post- treatment in patients with significant fibrosis (F2) and advanced fibrosis (≥F3)

Discussion

This study assessed the impact of DAAs on fibrosis regression in chronic HCV patients with either compensated (F2) or decompensated liver disease (≥F3). The results demonstrated significant serial improvements of FIB-4 index, APRI score and LSM by FibroScan along the follow-up periods (EOT, 6-months and 12-months post-treatment) in chronic HCV patients with SVR12 after DAAs treatments. Interestingly, these non-invasive fibrosis markers improved significantly regardless of the patient's baseline fibrosis grade. Moreover, the significant decline of the hepatic necroinflammation was evident by significant improvement of baseline necroinflammatory markers along the follow-up periods (EOT, 6- and 12-months post-treatment) regardless of the patient's baseline fibrosis grade. Tada et al. demonstrated a significant improvement of liver stiffness in patients with chronic HCV infection achieving SVR12 after treatment by DAAs.[20]

Several recent studies reported a remarkable decrease in hepatic enzymes and improvement of the biochemical profile after DAAs therapy.[21] Zhang et al. reported a favorable improvement of hematological parameters (especially the platelets) after sustained virologic response.[22] Similarly, in this study, a significant improvement in baseline platelets throughout the follow-up period was demonstrated in patients with significant hepatic fibrosis (F2). However, such improvements in hematological parameters reached significance only later in follow-up time points in patients with advanced fibrosis (≥F3). These liver enzymes' and platelets' improvements throughout the follow-up period mirrored the changes and consequent improvements in fibrosis markers (Fib-4 and APRI score). Consistent with these results, Crissien and colleagues reported that HCV eradication could lead to regression of advanced hepatic fibrosis (≥F3) over a long period with a median time of 2.5 years and even 3 years for those with cirrhosis.[23]

A recent study in Georgia demonstrated reversal of transient elastography (TE) scores in 304 patients with advanced fibrosis or cirrhosis following SVR at a similar rate to that reported by Crissien et al.[24] Nevertheless, considering these fibrosis indices as a reflection for fibrosis regression may be misleading as it could reflect resolution of necroinflammation rather than a true regression of fibrosis. Moreover, there is a paucity of DAAs-era literature correlating fibrosis regression assessed by FibroScan (LSM) and histology. Previous evidence has shown a very slow fibrosis regression following interferon-based regimens.[25] Consequently, the degree of fibrosis regression following DAAs therapy might be overestimated by FibroScan compared to liver biopsy, the gold standard, reliable and practical approach for liver fibrosis staging after achieving SVR.

In this study, liver stiffness measurement (LSM) by FibroScan significantly reduced from baseline along the follow-up periods (EOT, 6-months and 12-months post-treatment) in chronic HCV patients with SVR12 after DAAs treatments. This observation occurred in either compensated (F2) or decompensated liver disease (≥F3). Regardless of SVR achievement and fibrosis stage, liver damage still persisted in a significant portion of patients. Despite the significant reduction in baseline LSM among decompensated cirrhotic patients, ≥50% of the LS-defined cirrhotic patients remained cirrhotic at 6-months post-treatment. In this work, a trivial number of patients had no LSM improvements after DAAs therapy. The majority of patients in either group had significant improvement in FIB-4 index (reduction above 60% from baseline values), APRI score (reduction above 35% from baseline values) and LSM by FibroScan (reduction above 46% from baseline values) at 12-months post-treatment.

The results in this study matched those obtained by Bruno and colleagues despite including a smaller portion of compensated and decompensated cirrhotic patients but longer follow-up period compared to our study.[26] In addition, patients with higher baseline LSM by FibroScan as in advanced fibrosis (≥F3) showed a delayed fibrosis regression after HCV eradication by DAAs therapy as shown in Figure 1C. This result could imply that higher baseline LSM by FibroScan may be considered as a valuable predictor of lack of or delayed improvement in hepatic fibrosis after HCV eradication by DAAs therapy. It is unclear for how long cirrhotic patients should be monitored after SVR achievement by DAAs therapy. Certainly, the early DAAs therapy of HCV infected subjects can significantly prevent residual hepatic damage. In concordance with these results, Omar et al. reported that baseline LSM by FibroScan could predict fibrosis regression after DAAs therapy.[27]

It is concluded that SVR achievement after DAAs therapy is associated with significant fibrosis regression estimated by the reliable non-invasive markers (FIB-4 index, APRI score, and LSM by FibroScan) regardless of the baseline fibrosis stage in both compensated and decompensated liver disease. Higher baseline LSM by FibroScan could be beneficial in predicting lack of or delayed fibrosis regression after DAAs therapy. Unfortunately, the initial improvements in FIB-4 index, APRI score, and liver stiffness may merely reflect necroinflammatory resolution rather than true fibrosis regression. This might lead to overestimation of fibrosis regression. It is suspected that the improvement in liver biology, portal hypertension, and liver architecture might develop with longer follow-up periods. Therefore, it is recommended that a correlation between fibrosis regression by LSM (FibroScan) and histology (liver biopsy) should be evaluated in the DAAs-era. Also, other studies with longer follow-up periods (median of 3 years) should be performed.

Conflict of Interest

The authors declared no conflicts of interest

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