Evaluating the effect of direct-acting agents on liver fibrosis, by real-time elastography, Fibroscan and FIB4 score in chronic HCV patients

Raed H. Mansour[a], Samy Zaky[a], Mohamed El Kassas[b], Haitham Mamdouh[c], Gamal Esmat[d]

Background One of the most important questions is what happens with liver fibrosis following a sustained virological response (SVR), although the current anti-HCV therapies were not designed to be antifibrotic. Liver biopsy was replaced by multiple noninvasive means, which were validated in chronic HCV patients, such as Fibroscan, seromarkers such as aminotransferase-to-platelet ratio index (APRI) and FIB4 scores, and new nonvalidated means such as real-time elastography (RTE). The aim of the study was to evaluate the early changes of liver fibrosis after direct-acting agents (DAAs) using these noninvasive means.

Materials and methods This was a prospective study that included 200 chronic HCV-naive patients during the period spanning from December 2014 to January 2016. All patients received sofosbuvir – based treatment regimen (with or without pegylated interferon). They were evaluated using Fibroscan, RTE, APRI and FIB4 scores at the baseline and SVR24.

Results All the studied patients showed a statistically significant decline in ALT, AST, liver stiffness (by Fibroscan), elasticity index (RTE), FIB4 score and APRI score, regardless of the response to DAAs. Moreover, there was a significant increase in platelet count from baseline to SVR24. The average improvement of the liver stiffness in different fibrosis stages was 22%. There was a positive correlation between stiffness score and all other fibrosis markers before and after treatment.

Conclusion There was a significant improvement of liver stiffness after 12 weeks of end of treatment, regardless of the DAA regimen used, and regardless of the treatment outcome (response), as evidenced by Fibroscan, RTE, FIB4 and APRI scores.

Sci J Al-Azhar Med Fac, Girls 2019 3:237–245

The Scientific Journal of Al-Azhar Medical Faculty, Girls
2019 3:237–245

Keywords: chronic hepatitis C, elastography, liver fibrosis, sofosbuvir

[a]Department of Tropical Medicine, Al-Azhar University, [b]Department of Endemic Medicine, Helwan University, [c]Department of Hepatology, National Hepatology and Tropical Medicine Research Institute, Cairo, [d]Department of Hepatology and Endemic Medicine, Cairo University, Giza, Egypt

Correspondence to Haitham M. Ibrahim, MSc in Tropical medicine, Ain Shams university, National hepatology and Tropical Medicine Research Institute IRB 10 (A) Kasr El- Eini st. Cairo, Egypt. Tel: +20 223 642 494; fax: +20 223 683 723;
e-mail: haitham.mamdouh@gmail.com

Received 10 February 2019 **Accepted** 10 March 2019

Introduction

For ~20 years, the only treatment of HCV chronic infection was interferon based, first with standard interferon and later with pegylated interferon in combination with ribavirin. In the last few years, new treatments for HCV infection were developed, the so-called direct-acting agents (DAAs) or interferon-free treatment. The advantages of such drugs are the high success rates (>90%), the short duration of the treatment (12 or 24 weeks), and the few side effects [1].

The current anti-HCV therapies were not designed to be antifibrotic, but focused on virus eradication, as HCV is a composite indicator of liver fibrosis and a causative agent of liver injury and inflammation [2]. In spite of that, one of the most important questions is what happens with liver fibrosis following a sustained virological response (SVR). Many published studies have shown partial reversibility of fibrosis during treatment or after SVR in HCV chronic infection [3–7].

Post-treatment evaluation of liver fibrosis was performed only by liver biopsy for a long time, as it was always considered as the gold standard for assessing liver fibrosis. This is the reason why few longitudinal studies evaluated this aspect. Only two or rarely three liver biopsies have been performed after treatment, because few patients accept serial liver biopsies, because of its invasiveness and possibility of complications, even if it is low, especially when the viral infection is successfully treated. Therefore, assessment of liver fibrosis by liver biopsy is gradually replaced by noninvasive and safe methods, and they are currently being used in clinical practice [8–10].

Transient elastography (TE) is the most widely used and validated technique that measures liver stiffness. It was the first ultrasound-based elastography technique used in clinical practice, and is currently recommended

by international guidelines for the evaluation of patients with chronic liver diseases, and it was also approved by the Egyptian National Committee for Control of Viral Hepatitis (NCCVH) to replace liver biopsy in evaluating liver stiffness in chronic HCV patients [11]. Real-time elastography (RTE) is another noninvasive radiology means to evaluate liver stiffness, which is technically different from Fibroscan, but not as widely used as Fibroscan, with less evidence and fewer studies having been carried out in CHC patients [12,13]. Several noninvasive seromarkers such as FIB4 and aminotransferase-to-platelet ratio index (APRI) have been demonstrated to be accurate in estimating hepatic fibrosis before antiviral treatment [14–16]. Moreover, they have been used to follow-up patients with chronic hepatitis C and to assess the effect of antiviral treatment [6].

Materials and methods

This prospective study included 200 chronic HCV-naive patients who were candidates for antiviral therapy according to the HCV treatment protocol issued by the NCCVH during the period spanning from December 2014 to January 2016. Patients were recruited from the HCV treatment-specialized clinic at the National Hepatology and Tropical Medicine Research Institute (NHTMRI), Cairo. The selection and stratification of the patients were based on sample size calculation and the competence of the availability of the data.

On December 2014, the first available HCV antiviral regimens in treatment centers affiliated to NCCVH were either PegIFN/SOF/RBV for 12 weeks for interferon-eligible patients or of SOF/RBV for 24 weeks that was given to interferon-ineligible patients. Thereafter, in May 2015, NCCVH ceased the pegylated interferon-containing regimen completely, and all regimens became 'IFN-free regimens'. Treatment protocol at this time included two new regimens: SOF/DAC, with or without RBV for 12 weeks. During the initial phase of patients' recruitment, we included two groups of patients: group I received PegIFN/SOF/RBV regimen for 12 weeks, and group II received SOF/RBV regimen for 24 weeks. This continued until the change of these regimens in NCCVH protocols in May 2015, wherein SOF/DAC±RBV replaced the previous two regimens [17]. Accordingly, we included another two groups of patients: group III, which received SOF/DAC for 12 weeks, and group IV, which received SOF/DAC/RBV for 12 weeks.

The inclusion and exclusion criteria for our patients were defined by the issued protocol by NCCVH. We included all patients of at least 18 years of age, with positive serology for HCV Ab (by ELISA), and detected HCV viremia, who agreed to sign the study's informed consent form. The following groups of patients were excluded: those with a history of ascites (as evidenced by abdominal ultrasound), or hepatic encephalopathy, pregnant or nursing females, those with other coexisting chronic liver disease, those with a history of hepatocellular carcinoma or other extrahepatic malignancies, those who were under chronic use of a systematically immunosuppressive agent, those with a history of solid organ transplantation, those with a reported hypersensitivity to recommended therapy, and those with a comorbid condition such as poorly controlled diabetes (HbA1c≥9%).

The study was approved by the Ethical Committee of NHTMRI. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Patients were subjected at the pre-enrollment phase (week 0) and at week 24 to thorough history taking, and clinical examination. The performed laboratory work-up included complete liver profile tests (AST, ALT, total bilirubin, serum albumin, prothrombin concentration, INR), serum creatinine, CBC, HBs Ag, HCV RNA viral load by quantitative PCR, and α-fetoprotein. All patients were subjected to abdominal ultrasound at weeks 0 and 24, in addition to noninvasive means for fibrosis assessment (TE, RTE, APRI score and FIB4 score). Aspartate APRI and FIB4 score were calculated at baseline and 12 weeks after treatment cessation according to the following equations: aspartate aminotransferase-to-platelet ratio index score was calculated using Wai's formula: (AST/upper limit of normal)/platelet count (expressed as platelets $\times 10^9$/l)×100 [18]. FIB4 score was calculated using Sterling's formula: Age (years)×AST (IU/l)/platelet count ($\times 10^9$/l)×$\sqrt{}$ALT (IU/l)) [19].

APRI cut-off greater than 1.0 predicts cirrhosis, while a cut-off greater than 0.7 predicts significant hepatic fibrosis, and FIB4 cut-off more than 3.25 had a positive predictive value of 65% for advanced fibrosis, and cut-off less than 1.45 had a negative predictive value of 90% for advanced fibrosis and cirrhosis.

Liver stiffness (LS) measurements were performed for all patients with Fibroscan 502 machine (Echosens, Paris, France). At least 10 valid measurements were

performed, and median of LS expressed in kilopascals (kPa) was reported. Only examinations with a success rate more than 60% and interquartile range less than 30% were considered. TE results were correlated to different stages of liver fibrosis according to the histological staging system of METAVIR. The used cut-off values were as follows:

(1) Less than 7.1 kPa, nonsignificant fibrosis (<F2).
(2) From at least 7.1 kPa to less than 9.5 kPa, significant fibrosis (≥F2).
(3) At least 9.5 kPa for advanced fibrosis (≥F3) and at least 12.5 kPa for cirrhosis (F4) [20].

Another method for fibrosis assessment was used, which is the RTE (Hitachi (Tokyo, Japan), Hi vision Avius, Linear probe EUP – L52). The tissue elasticity was calculated by the strain and stress of the examined tissue. In the first step, the amount of displacement of the reflected ultrasound echoes before and under compression was measured (stress field). In the second step, a strain field was reconstructed from the measured displacements (strain image). High elasticity areas (i.e. soft tissue) were shown as places of high strain and low elasticity areas (i.e. hard tissue) were shown as places of low strain. Ten valid measurements were performed in each subject and recorded as color-coded images [21].

Statistical analysis

Analysis of data was performed using the statistical package for the scientific studies [SPSS 17 (IBM, Armonk, New York, United States)] for Windows. Description of variables was presented as follows: description of quantitative variables in the form of mean, SD, minimum and maximum, and description of qualitative variables in the form of numbers and percent. Data were explored for normality using Kolmogorov–Smirnov test of normality. The results of the Kolmogorov–Smirnov test indicated that most of the data were normally distributed (parametric data); thus, parametric tests were used for the comparisons. Comparison between quantitative variables was carried out by the Student *t*-test of two independent samples. The repeated measures of analysis of variance test was used instead of the *t*-test when comparing between four groups of independent variables. The results were expressed in the form of *P*-values. Comparison between qualitative variables was carried out by the χ^2-test. The Fisher exact test was used instead of the χ^2-test when one expected cell or more were up to 5. A value of *P* less than 0.05 was considered as statistically significant.

Results

The studied groups included 73 patients in group I, 27 patients in group II, 64 patients in group III, and 36 patients in group IV. The mean age of the studied patients was 50.9±5.7 years with a male predominance (58%), as shown in Table 1. The table illustrates that there was no statistical difference between the different groups with regard to the demographic data (sex and age). The response rate was 91% at week 24 after treatment (SVR24) for all included regimens of treatment (Table 1).

Table 1 shows that the mean age was 50.9±5.7, and the studied groups of patients comprised 116 male and 58 female patients The table illustrates that there was no statistical difference between the different groups with regard to the demographic data (sex and age). Moreover, the table showed that 91% of the studied cases achieved SVR. The least response percentage was in group II of patients (88.8%), and the highest was in group I (91.8%).

All patients were treatment naive, with 85.5% with advanced fibrosis (F3 and F4) by LS measurement. A total of 29 patients were diagnosed as F2, 43 patients as F3, and 128 patients were staged as F4. The mean value of LS before treatment was 19.1±10.1. The mean value of the RTE was 3.43±0.58. The mean value of FIB4 score was 3.4±1.4, while the mean value of APRI was 1.4±0.8.

All the studied patients showed a statistically significant decline in ALT, AST, LS [by Fibroscan (Echosense, Paris, France)], elasticity index (by RTE), FIB4 score and APRI score. Furthermore, there was a

Table 1 Demographic features and baseline characteristics of the studied patients

Items	*N*	Age (mean±SD) (years)	Sex		Responders [*n* (%)]	Relapsers [*n* (%)]
			Male [*n* (%)]	Female [*n* (%)]		
Group I	73	50.0±6.0	43 (58.9)	30 (41.1)	67 (91.8)	6 (8.2)
Group II	27	53.0±4.8	13 (48.1)	14 (51.9)	24 (88.8)	3 (11.2)
Group III	64	50.7±6.1	39 (60.9)	25 (39.1)	58 (90.6)	6 (9.4)
Group IV	36	51.3±4.8	21 (58.3)	15 (41.7)	33 (91.7)	3 (8.3)
Total	**200**	**50.9±5.7**	**116 (58)**	**84 (42)**	**182 (91)**	**18 (9)**
P		0.128	0.722			

Table 2 Changes in the CBC values, liver tests and noninvasive measures before and after treatment

Items	Before (mean±SD)	After (sustained virological response) (mean±SD)	Change (mean±SD)	*P* value
Hb (g/dl)	13.4±0.9	11.2±0.7	−2.2±0.3	<0.001
WBC (×10^3/ml)	6.2±1.5	3.9±0.6	−2.2±1.0	<0.001
Platelets (×10^3/ml)	143.9±38.0	190.4±41.9	46.5±15.8	<0.001
Albumin (g/dl)	4.1±0.4	4.2±0.3	0.1±0.4	<0.001
INR	1.3±0.1	1.1±0.1	−0.2±0.2	<0.001
AST (IU/l)	74.7±33.1	38.3±9.9	−36.4±29.2	<0.001
ALT (IU/l)	70.5±35.9	55.6±17.3	−14.9±26.4	<0.001
Total bilirubin (g/dl)	0.8±0.3	0.6±0.4	−0.2±0.1	<0.001
Stiffness score (Fibroscan)	19.1±10.1	17.4±10.5	−1.8±1.3	<0.001
Elasticity index (RTE)	3.43±0.58	2.84±0.59	−0.60±0.11	<0.001
FIB4 score	3.4±1.4	1.5±0.7	−1.9±1.2	<0.001
APRI score	1.4±0.8	0.5±0.2	−0.9±0.7	<0.001

APRI, aminotransferase-to-platelet ratio index; RTE, real-time elastography.

Table 3 Noninvasive measures before and after treatment among the studied cases

Items	Fibrosis grades	Before (number of patients)	After (number of patients)	*P*
Stiffness score	F2	29	62	<0.001
	F3	43	21	
	F4	128	117	
FIB4 score	No fibrosis	0	120	<0.001
	Grey zone	119	72	
	Fibrosis	81	8	
APRI score	No fibrosis	24	172	<0.001
	Early fibrosis	60	18	
	Cirrhosis	116	10	
Elasticity index	Fibrosis	0	16	<0.001
	Significant fibrosis	121	159	
	Cirrhosis	79	25	

APRI, aminotransferase-to-platelet ratio index.

significant increase in platelet count from baseline to SVR12 (Table 2).

Table 2 shows that hemoglobin and WBC were significantly decreased after treatment, platelets significantly increased after treatment, ALT and AST significantly decreased after treatment, and the stiffness score, FIB4 score, APRI score and elasticity index were also 'significantly' decreased after treatment.

The improvement of the LS in different fibrosis stages was in F2 (14.5% before, and 31% after), F3 (21.5% before, and 10.5% after), F4 (64% before, and 58.5 after) with an average improvement of 22% (Table 3). There was no significant difference with regard to improvement of all noninvasive measures in the different studied groups.

Table 3 shows that stiffness score, FIB4 score, APRI score, and elasticity index were significantly decreased after treatment.

There was a positive correlation between stiffness score and all other fibrosis markers (elasticity index, APRI score and FIB4) before and after treatment. In addition, Also, there is a positive correlation between Alanine Aminotransferase (ALT), Aspartate transaminase (AST), stiffness score and elasticity index before and after treatment. There was a positive correlation between albumin and APRI and FIB4 scores before and after treatment. There was a positive correlation between total bilirubin and stiffness score before and after treatment. A positive correlation was found between INR and only FIB4 score before treatment, while, after treatment, there was a positive correlation between INR and all fibrosis markers (stiffness, elasticity index, APRI score and FIB4). There was a negative correlation between platelets and all fibrosis markers (stiffness, elasticity index, APRI score and FIB4) before and after treatment. Further, there was a negative correlation between hemoglobin and FIB4 score before and after treatment (Table 4).

Table 4 shows that there were positive correlations between stiffness score and all other fibrosis markers (elasticity index, APRI score and FIB4) before and after treatment, between albumin and APRI and FIB4

Table 4 Correlations between the noninvasive means and each other, and other laboratory values, before and after treatment

Items	Stiffness				FIB4				APRI				Elasticity index			
	Before		After		Before		After		Before		After		Before		After	
	r	*P*	*R*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Platelets	−0.367	<0.001	−0.459	<0.001	−0.669	<0.001	−0.657	<0.001	−0.577	<0.001	−0.711	<0.001	−0.306	<0.001	−0.372	<0.001
INR	0.109	0.124	0.482	<0.001	0.211	0.003	0.718	<0.001	0.181	0.010	0.852	<0.001	0.024	0.740	0.437	<0.001
AST	0.356	<0.001	0.230	0.001	0.603	<0.001	−0.128	0.070	0.812	<0.001	0.272	<0.001	0.403	<0.001	0.388	<0.001
ALT	0.261	<0.001	0.195	0.006	0.403	<0.001	0.026	0.720	0.759	<0.001	0.098	0.167	0.358	<0.001	0.321	<0.001
Total bilirubin	0.201	0.004	0.487	<0.001	0.168	0.017	0.885	<0.001	0.214	0.002	0.110	0.122	0.082	0.250	0.084	0.235
FIB4	0.511	<0.001	0.562	<0.001	–	–	–	–	–	–	–	–	–	–	–	–
APRI	0.424	<0.001	0.128	0.071	0.852	<0.001	0.270	<0.001	–	–	–	–	–	–	–	–
Elasticity index	0.570	<0.001	0.608	<0.001	0.417	<0.001	0.278	<0.001	0.409	<0.001	0.410	<0.001	–	–	–	–

APRI, aminotransferase-to-platelet ratio index.

scores before and after treatment, between total bilirubin and stiffness score before and after treatment, and between ALT and AST and stiffness score and elasticity index before and after treatment. There were negative correlations between platelets and all fibrosis markers (stiffness, elasticity index, APRI score and FIB4) before and after treatment, and between hemoglobin and FIB4 score before and after treatment.

Discussion

This study was carried out on 116 male and 84 female patients. This male predominance came close to what was mentioned by the Demographic Health Survey 2015 in Egypt [22], which reported a higher prevalence of chronic hepatitis C among male individuals: 27.8% of male individuals and 17.6% of female individuals were positive in the age group of 50–55 years [22].

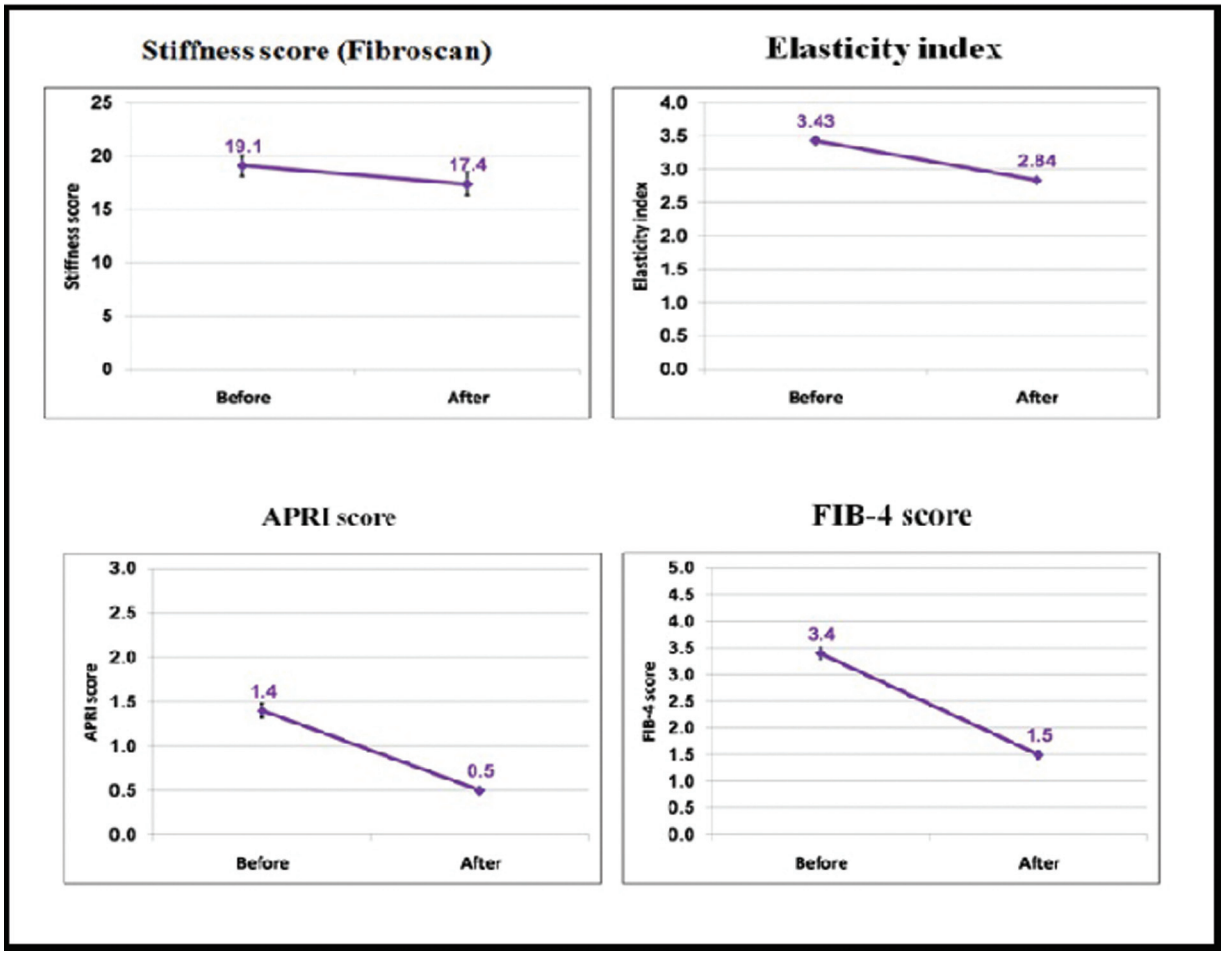
The mean age of the studied sample was 50.9±5.7. This relatively late age of diagnosis come in agreement with the ″Demographic Health Survey - Egypt 2015″ [22], as it reported that the majority of the Egyptian patients present at an older age with higher grades of liver fibrosis, as most of them are not health insured, and not aware of the risk of the disease.

The response rate to treatment in this study was 91%, regardless of the treatment regimen used, and regardless of the sex and age of the studied sample. This is quite similar to the results of two large Egyptian real-world studies. The Omar *et al.* [23] study included 18 378 patients who received daclatasvir plus sofosbuvir, with or without ribavirin, with an overall response rate of 95.1%. El Kassas *et al.* [24] studied 7042 chronic hepatitis C patients who received seven different DAAs regimens, with an overall response rate of 95.5% regardless of the regimen used.

With the previously used pegylated interferon and ribavirin treatment regimen, several studies reported factors associated with a decline in liver stiffness after therapy, such as baseline fibrosis stage, response to treatment, age, and viral load [25]. With the recent use of DAAs, it seems that these factors will no longer have a role, as evidenced also in this study, with a similar conclusion in the study by Elsharkawy *et al.* [26].

All patients in this study, whether cirrhotic or not, showed a statistically significant decline in ALT, AST, liver stiffness measurement, elasticity index (measured by RTE), FIB4 score and APRI score, with significant improvement in platelet count in cirrhotic patients

Figure 1



Noninvasive tools (stiffness score, elasticity index, FIB4 and APRI scores) before and after treatment among the studied cases. APRI, aminotransferase-to-platelet ratio index.

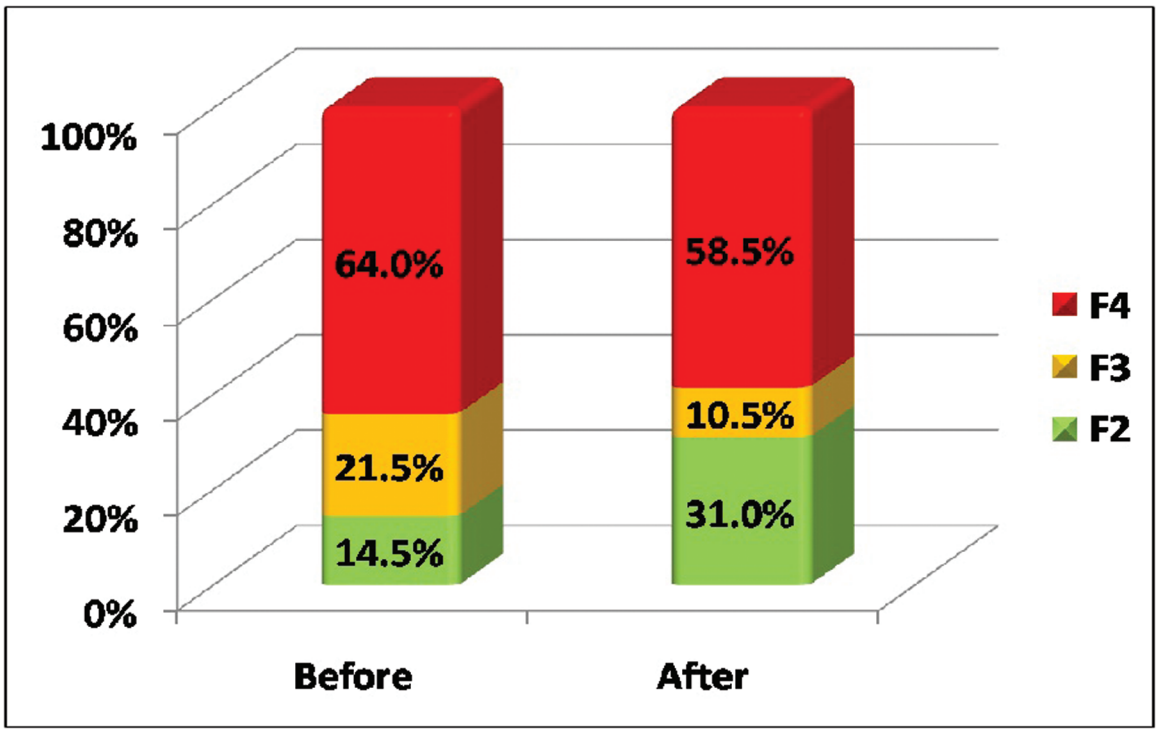
from baseline to SVR12. The same conclusion was also reported by El Kassas *et al*. [24], as they described an improvement of the liver function tests in chronic HCV patients after receiving DAAs.

There was a statistically significant improvement in the fibrosis stages after 12 weeks of EOT (early improvement), as evidenced by 'all' noninvasive means' scores used in this study. This is quite similar to Bachofner *et al.* [3] who reported a significant decline of LS measurements and other validated fibrosis scores such as FIB4 and APRI after the end of treatment by 12 weeks, as in this study, regardless of the treatment outcome. These scores are affected by the reduction of AST, ALT, and platelets levels, denoting significant improvement of liver fibrosis (platelets), and necroinflammation (AST and ALT) following treatment with DAAs. The same results were also reported by Elsharkawy *et al.* [26]. The reported improvement among the different noninvasive means was unproportionate. The improvement rate in LS was 22% in different fibrosis stages, and it was 35% in elasticity index, while it was 81.5 and 93% in FIB4 and APRI scores respectively.

Figure 1 shows unproportionate improvement of the noninvasive means used in the study.

A previous study that assessed TE considering liver biopsy as a reference method demonstrated that LS is a sum of fibrosis and inflammation, and that it also might be influenced by liver steatosis [27]. Some studies suggested that LS increased with the increasing necroinflammatory activity of the liver [28], and the resolution of this necroinflammatory activity is correlated with transaminases, which normalize following antiviral therapy, while other studies reported that inflammatory activity did not influence LS [20]. Thus, the post-treatment LS decrease can be the result of the attenuated inflammation, and/or of a decrease in fibrosis severity. Hence, this may explain the marked improvement of the APRI and FIB4 scores, which were impacted by the marked improvement of the ALT and AST after EOT, with the mild (but significant)

Figure 2



The change in the fibrosis stages before and after treatment using the stiffness score by Fibroscan.

improvement of the TE and RTE, which were impacted mainly by the improvement of liver fibrosis.

The question arises whether LS should be evaluated very early (12 weeks after EOT), or later after treatment, and how much later. The aim of this study was to assess the dynamics of LS by means of TE in patients with post-HCV liver cirrhosis, before and at week 12 after EOT. As the follow-up period was short, most probably not only fibrosis regression was responsible for LS decrease, but also improvement of inflammation. Therefore, the elastographic follow-up of cirrhotic patients who achieved SVR should start, as we suggested, from the values measured at EOT or 12 weeks after EOT (when SVR is evidenced), so that we can find out how much fibrosis has decreased in the advanced liver disease.

Moreover, this study showed a significant improvement in stiffness score of Fibroscan in patients with advanced fibrosis (F3 and F4 patients) who represented 85.5% of the whole studied sample; the percentage of these patients was changed from 85.5% before treatment to 79.5% after treatment.

Figure 2 shows that most of the patients with cirrhosis (F4) remain after treatment in the same grade with mild changes (64% before treatment to 58.5% after treatment).

They continue to have advanced fibrosis, but with lower LS values than pretreatment values. Similarly, Chekuri *et al.* [2] reported a significant reduction in LS values among cirrhotic patients, but 60% who were cirrhotic before treatment remained cirrhotic at SVR [2]. Cirrhosis almost persists in patients who achieved SVR, as reported also in the studies by D'Ambrosio *et al.* [6] and Balart *et al.* [29], which justify the continuation of surveillance program of these patients even after achieving SVR, as cirrhosis remains as an independent risk factor for HCC.

In this study, there was a positive correlation between the stiffness score by Fibroscan and elasticity index, FIB4 and APRI scores before and after the treatment. This is quite similar to the conclusion of Ragazzo *et al.* [30] with regard to Fibroscan, APRI score and FIB4 score. Another study by Bonnard *et al.* [16], in which they studied Fibroscan, APRI score, FIB4 and Fibrotest, reported that the most useful to use scores were Fibroscan and FIB4 score. With regard to the RTE, there are fewer studies comparing the accuracy of the RTE with other noninvasive means. In two studies, Tatsumi *et al.* [21] and Meng *et al.* [31] reported that it is an effective method for assessing liver fibrosis, with diagnostic performance quite similar to that of TE. In contrast, Friedrich-Rust *et al.* [32] reported that RTE still cannot replace TE (Fibroscan) for noninvasive assessment of liver fibrosis.

Conclusion

There was a significant improvement of the LS after 12 weeks of the end of HCV antiviral therapy, regardless of the DAA regimen used, and regardless of the treatment outcome (response), as evidenced by Fibroscan, RTE, FIB4 score and APRI score. More longer and serial follow-up studies for changes in the LS are required to fully understand the dynamics of liver fibrosis after achieving SVR, and to clarify the role of inflammation reduction – apart from fibrosis regression – in this improvement in LS.

The persistence of cirrhosis after achieving SVR in most cases supports the concept of valuing early diagnosis and treatment of HCV infection before progression to advanced fibrosis and permanent liver damage occurrence. It also highlights the need to continue HCC surveillance after SVR in this group of patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Elbaz T, El-Kassas M, Esmat G. New era for management of chronic hepatitis C virus using direct antiviral agents: a review. *J Adv Res* 2015; **6**:301–310.

2 Chekuri S, Nickerson J, Bichoupan K, Sefcik R, Doobay K, Chang S, *et al.* Liver stiffness decreases rapidly in response to successful hepatitis C treatment and then plateaus. *PLoS One* 2016; **11**:e0159413.

3 Bachofner JA, Valli PV, Kröger A, Bergamin I, Künzler P, Baserga A, *et al.* Direct antiviral agent treatment of chronic hepatitis C results in rapid regression of transient elastography and fibrosis markers fibrosis-4 score and aspartate aminotransferase-platelet ratio index. *Liver Int* 2017; **37**:369–376.

4 Tada T, Kumada T, Toyoda H, Mizuno K, Sone Y, Kataoka S, *et al.* Improvement of liver stiffness in patients with hepatitis C virus infection who received direct-acting antiviral therapy and achieved sustained virological response. *J Gastroenterol Hepatol* 2017; **32**:1982–1988.

5 George SL, Bacon BR, Brunt EM, Mihindukulasuriya KL, Hoffmann J, Di Bisceglie AM. Clinical, virologic, histologic, and biochemical outcomes after successful HCV therapy: a 5-year follow-up of 150 patients. *Hepatology* 2009; **49**:729–738.

6 D'Ambrosio R, Aghemo A, Fraquelli M, Rumi MG, Donato MF, Paradis V, *et al.* The diagnostic accuracy of Fibroscan for cirrhosis is influenced by liver morphometry in HCV patients with a sustained virological response. *J Hepatol* 2013; **59**:251–256.

7 Singal AG, Volk ML, Jensen D, Di Bisceglie AM, Schoenfeld PS. A sustained viral response is associated with reduced liver-related morbidity and mortality in patients with hepatitis C virus. *Clin Gastroenterol Hepatol* 2010; **8**:280–288.

8 Shiha G, Ibrahim A, Helmy A, Sarin SK, Omata M, Kumar A, *et al.* Asian-Pacific Association for the Study of the Liver (APASL) consensus guidelines on invasive and non-invasive assessment of hepatic fibrosis: a 2016 update. *Hepatol Int* 2017; **11**:1–30.

9 Lackner C, Struber G, Liegl B, Leibl S, Ofner P, Bankuti C, *et al.* Comparison and validation of simple noninvasive tests for prediction of fibrosis in chronic hepatitis C. *Hepatology* 2005; **41**:1376–1382.

10 Madan K. Is liver biopsy still the gold standard for diagnosing liver fibrosis? *Trop Gastroenterol* 2011; **32**:253–255.

11 El-Akel W, El-Sayed MH, El Kassas M, El-Serafy M, Khairy M, Elsaeed K, *et al.* National treatment programme of hepatitis C in Egypt: hepatitis C virus model of care. *J Viral Hepat* 2017; **00**:1–6.

12 Ippolito D, Schiavone V, Talei Franzesi CR, Casiraghi AS, Drago SG, Riva L, *et al.* Real-time elastography: noninvasive diagnostic tool in the evaluation of liver stiffness in patients with chronic viral hepatitis, correlation with histological examination. *Dig Dis* 2018; **36**: 289–297.

13 Mobarak L, Nabeel MM, Hassan E, Omran D, Zakaria Z. Real-time elastography as a noninvasive assessment of liver fibrosis in chronic hepatitis C Egyptian patients: a prospective study. *Ann Gastroenterol* 2016; **29**:358–362.

14 Rosenberg WM, Voelker M, Thiel R, Becka M, Burt A, Schuppan D, *et al.* Serum markers detect the presence of liver fibrosis: a cohort study. *Gastroenterology* 2004; **127**:1704–1713.

15 Yosry A, Fouad R, Alem SA, Elsharkawy A, El-Sayed M, Asem N, *et al.* Fibroscan, APRI, FIB4, and GUCI: role in prediction of fibrosis and response to therapy in Egyptian patients with HCV infection. *Arab J Gastroenterol* 2016; **17**:78–83.

16 Bonnard P, Elsharkawy A, Zalata K, Delarocque-Astagneau E, Biard L, Le Fouler L, *et al.* Comparison of liver biopsy and noninvasive techniques for liver fibrosis assessment in patients infected with HCV-genotype 4 in Egypt. *J Viral Hepat* 2015; **22**: 245–253.

17 El Kassas M, Omran D, Elsaeed K, Alboraie M, Elakel W, El Tahan A, *et al.* Spur-of-the-moment modification in national treatment policies leads to a surprising HCV viral suppression in all treated patients: real-life egyptian experience. *J Interferon Cytokine Res* 2018; **38**:81–85.

18 Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, *et al.* A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology* 2003; **38**:518–526.

19 Martínez SM, Crespo G, Navasa M, Forns X. Noninvasive assessment of liver fibrosis. *Hepatology* 2011; **53**:325–335.

20 Castéra L, Vergniol J, Foucher J, Le Bail B, Chanteloup E, Haaser M, *et al.* Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. *Gastroenterology* 2005; **128**:343–350.

21 Tatsumi C, Kudo M, Ueshima K, Kitai S, Takahashi S, Inoue T, *et al.* Noninvasive evaluation of hepatic fibrosis using serum fibrotic markers, transient elastography (Fibroscan) and real-time tissue Elastography. *Inter Virol* 2008; **51**(Suppl 1):27–33.

22 El-Zanaty and Associates. *DHS final report. Egypt special 2015*. Available at: https://dhsprogram.com/publications/publication-fr313-dhs-final-reports.cfm. Accessed on [2017 June 15]

23 Omar H, El Akel W, Elbaz T, El Kassas M, Elsaeed K, El Shazly H, *et al.* Generic daclatasvir plus sofosbuvir, with or without ribavirin, in treatment of chronic hepatitis C: real-world results from 18378 patients in Egypt. *Aliment Pharmacol Ther* 2018; **47**:421–431.

24 El Kassas M, Alboraie M, Omran D, Salaheldin M, Wifi MN, ElBadry M, *et al.* An account of the real-life hepatitis C management in a single specialized viral hepatitis treatment centre in Egypt: results of treating 7042 patients with 7 different direct acting antiviral regimens. *Expert Rev Gastroenterol Hepatol* 2018; **24**:1–8.

25 Wang JH, Changchien CS, Hung CH, Tung WC, Kee KM, Chen CH, *et al.* Liver stiffness decrease after effective antiviral therapy in patients with chronic hepatitis C: longitudinal study using Fibroscan. *J Gastroenterol Hepatol* 2010; **25**:964–969.

26 Elsharkawy A, Alem SA, Fouad R, El Raziky M, El Akel W, Abdo M, *et al.* Changes in liver stiffness measurements and fibrosis scores following sofosbuvir based treatment regimens without interferon. *J Gastroenterol Hepatol* 2017; **32**:1624–1630.

27 Lupşor M, Badea R, Stefănescu H, Grigorescu M, Sparchez Z, Serban A, *et al.* Analysis of histopathological changes that influence liver stiffness in chronic hepatitis C. Results from a cohort of 324 patients. *J Gastrointestin Liver Dis* 2008; **17**:155–163.

28 Ogawa E, Furusyo N, Toyoda K, Takeoka H, Maeda S, Hayashi J. The longitudinal quantitative assessment by transient elastography of chronic hepatitis C patients treated with pegylated interferon alpha-2b and ribavirin. *Antiviral Res* 2009; **83**:127–134.

29 Balart LA, Lisker-Melman M, Hamzeh FM, Kwok A, Lentz E, Rodriguez-Torres M; LATINO Study Investigators. Peg interferon α-2a plus ribavirin in latino and

non-latino Whites with HCV genotype 1: histologic outcomes and tolerability from the LATINO study. *Am J Gastroenterol* 2010; **105**:2177–2185.

30 Ragazzo TG, Paranagua-Vezozzo D, Lima FR, de Campos Mazo DF, Pessoa MG, Oliveira CP, *et al.* Accuracy of transient elastography-Fibroscan®, acoustic radiation force impulse (ARFI) imaging, the enhanced liver fibrosis (ELF) test, APRI, and the FIB-4 index compared with liver biopsy in patients with chronic hepatitis C. *Clinics (Sao Paulo)* 2017; **72**:516–525.

31 Meng F, Zheng Y, Zhang Q, Mu X, Xu X, Zhang H, *et al.* Noninvasive evaluation of liver fibrosis using real-time tissue elastography and transient elastography (Fibroscan). *J Ultrasound Med* 2015; **34**:403–410.

32 Friedrich-Rust M, Schwarz A, Ong M, Dries V, Schirmacher P, Herrmann E, *et al.* Real-time tissue elastography versus Fibroscan for noninvasive assessment of liver fibrosis in chronic liver disease. *Ultraschall Med* 2009; **30**:478–484.