Original Article

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Impact of long-term eradication of chronic Hepatitis C infection using the direct-acting antiviral treatment on liver fibrosis parameters in Egyptian patients

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Abstract

Background: Hepatitis C virus (HCV) treatment aims to halt the progression of fibrosis and reducing its complications. HCV-treatment has been enhanced by the development of all-oral DAAs with good efficacy and a reasonable side effect. **Aims:** The goal of this study is to see how long-term eradication of HCV affect liver fibrosis following DAAs therapy.

Materials and methods: 500 HCV patients receiving sofosbuvir-based therapy with daclatasvir or ledipasvir (with or without ribavirin). In addition to clinical, laboratory, and radiological examination, FIB-4, APRI, Fibroscan examination, Child and MELD scores were calculated at baseline and one year after end of therapy (EOT). **Results:** Out of 500 participants included in the study, 493 participants complete the study period. 454 (92.1%) patients had sustained virologic response (SVR) during the period of study and 39 patients were non-responders. In patients with SVR, FIB-4 index, APRI score and fibroScan measures showed significant reduction one-year post-EOT versus baseline ($p < 0.001$ for all). Although, Child score in patients had SVR did not demonstrate a significant improvement one year after EOT versus baseline ($p = 0.479$), it showed a significant improvement versus non responder ($p < 0.001$). In addition, MELD score revealed a significant reduction in patients who achieved SVR one-year post-EOT versus baseline ($p = 0.028$). Furthermore, one-year following EOT, there was a significant improvement in MELD score in patients with SVR versus non-responder ($p < 0.001$). **Conclusion:** DAAs therapy in HCV-related liver disease had a good impact on liver fibrosis regression and the improvement of its outcome.

Introduction

HCV infection affects about 185 million people worldwide, with a 2.8 percent increase in the last decade. HCV has been found to be the primary cause of cirrhosis and hepatocellular carcinoma (HCC) worldwide. HCV prevalence estimates vary widely over the world and by area [1], but the most notable preponderance has been documented in China, India, Pakistan, Nigeria, Egypt, and Russia, which together account for more than half of all infections [2].

The World Health Organization (WHO) has released the 'Global Health Sector Strategy on Viral Hepatitis, 2016–2021,'8 which includes service coverage goals to eradicate HCV as a public health issue by 2030 [3].

The target of HCV treatment is to minimize the progression of fibrosis and cirrhosis in addition to lowering the risk of HCC, decompensation events, and thus mortality [4]. Hepatitis C cure results in significant improvements in liver functions, preventing liver disease progression and complications [5]. The development of all-oral, direct-acting antiviral drugs with good efficacy, clear applicability, and a manageable side effect profile stimulated HCV treatment in clinical practice [6].

The discovery of novel DAAs, which have less side effects in compensated liver cirrhosis patients, has prompted clinical trials in decompensated liver cirrhosis patients [5]. For patients with advanced liver cirrhosis, IFN-free DAAs combinations are the best option. Early real-world data show that IFN-free therapy is relatively safe even in patients with advanced liver cirrhosis, however these patients still have a higher risk of hospitalization during treatment, owing to liver disease consequences. Several studies have been carried out on SVR rates in these patients treated with DAAs, and they have shown that cirrhotic patients had lower SVR rates than non-cirrhotic patients [7].

HCV virologic cure has been found to reduce liver inflammation, as indicated by reduced aminotransferase levels and slower advancement of liver fibrosis [8]. Furthermore, HCV eradication has been linked to improvements in extra-hepatic comorbid conditions like cryoglobulinemia, non- Hodgkin's lymphoma, insulin sensitivity, as well as improved cardiac enzymes [9,10].

The main goal of chronic HCV treatment is to prohibit liver-related complications by slowing or even reversing the progression of liver fibrosis. As a result, non-invasive fibrosis testing is crucial in clinical practice. Subsequently, in this study, we aimed to evaluate the impact of long-term

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eradication of chronic hepatitis C infection using the direct acting antiviral treatment on liver fibrosis parameters (including FIB-4, APRI scores and liver stiffness assessed by fibroScan) as well as evaluating changes in liver disease severity (including Child and MELD scores) in Egyptian patients.

Materials and methods

The study was carried out prospectively on 500 patients with confirmed HCV infection. Those patients were recruited from Tropical Medicine Department, Faculty of Medicine, and HCV- treatment clinic in National Liver Institute (NLI), Menoufia University from January 2019 and August 2021. Participants were diagnosed by detecting out the HCV antibodies (HCV Ab) by ELISA that was confirmed by real time PCR.

In this study, patients included were chronic HCV (positive PCR for HCV-RNA) patients aged more than eighteen years, HCV patients with Child–Pugh score less than or equal 8. Furthermore, chronic HCV patients' co-infection with hepatitis B virus or human immunodeficiency virus, those with hepatocellular carcinoma or any extra-hepatic malignancy, renal impairment, as well as pregnant females were derived away from the study.

All patients received a combination therapy of direct acting antiviral drugs (DAAs) sofosbuvir based therapy with either daclatasvir or ledipasvir (with or without ribavirin) for a maximum of 24 weeks' therapy without ribavirin, or 12 weeks with ribavirin. Patients during the course of treatment undergone close follow up by clinical, laboratory and radiological tests at baseline, end of treatment, 3- and 6-months' post treatment, one year after the end of therapy to study the impact on liver fibrosis parameters after long term eradication of chronic HCV using DAAs.

For all participants at zero-point, history was defined with detailed clinical assessment including history of diabetes mellitus and hypertension and their management. Abdominal ultrasound and fibroScan were performed for all participants just before starting DAAs therapy. Laboratory assessment involving, complete blood count, liver function tests [serum albumin, prothrombin time & international normalized ratio (INR), serum total & direct bilirubin, and transaminases ALT & AST], were measured. α-fetoprotein and serum creatinine were estimated. ELISA was used to determine HCV Ab, HBsAg, and HIV Ab. HCV PCR by means of Abbott Real Time HCV RNA Assay, Rungis, France) with a threshold for detection level 10 IU/mL.
Furthermore, we estimated the severity of liver disease by Child-Pugh and MELD (Model for End-stage Liver Disease) scores, besides calculating the APRI (Aspartate aminotransferase-to-platelet ratio index) as well as FIB-4 scores for assessment of liver fibrosis.

MELD score was estimated utilizing the subsequent formula: MELD = 9.57 loge [Creatinine (mg/dL)] + 3.78 loge [Bilirubin (mg/dL)] +11.2 loge [International Normalized Ratio] + 6.43, With subsequent subgroups: $\Delta MELD \leq -2$ (MELD decline), $-2 < \Delta MELD < 2$ (stable MELD), and $\Delta MELD \geq 2$ (MELD increase). According to the previous report, a cut-off of 2 points was decided since it was thought to have a significant impact on the individual's priority on the liver transplantation (LT) waiting list [11].

APRI score was calculated according to the following formula: (AST/upper limit of normal)/platelet count (platelets $\times 10^9$ /L) × 100 [12], with APRI; ≤0.5: indicating absence of cirrhosis, APRI; 0.5-1.5 is inconclusive and APR; ≥1.5: indicating the presence of cirrhosis. FIB-4 score was estimated utilizing; Age (y) × AST (IU/L) /platelet count ($\times 10^9$/L) $\times \sqrt{}$ ALT (IU/L)) formula, with Fib4 < 1.45; indicating absence of cirrhosis, Fib4 of 1.45-3.25 is inconclusive, and Fib4 >3.25 indicates the presence of cirrhosis [13].

Ultrasound of the abdomen:

A 3.5- 5 MHz probe was used to perform abdominal ultrasonography for all of the participants.

FibroScan assessment:

In FibroScan assessment; A mechanical actuator produces a low frequency mechanical push, and the shear wave that results is produced and assessed. Anisotropy, viscosity, and elastic non-linearity characteristics can also be derived using it. All participants were evaluated in the dorsal decubitus while the right arm in maximal abduction using the 5MHz ultrasound transducer probe mounted on the axis of a vibrator of the fibroScan machine (Echosens, Paris, France). By positioning the tip of the transducer in the intercostal space perpendicularly, the measurements were applied on the right lobe of the liver. A cylinder of liver tissue with a diameter of around 1 cm and a length of 2 to 4 cm was chosen, avoiding any significant vascular structures within. This was done using a time-motion ultrasound image. Liver cirrhosis is evident with fibroScan result 14.6 kPa [14].

At end of treatment, 3- and 6-months' post treatment, one year of follow up**,** patients were subjected to clinical evaluation, liver function tests, renal function test, CBC, and HCV PCR. Together with imaging re-evaluation that was carried out for all participants including abdominal ultrasound and fibroScan one-year post treatment.
According to response to DAAs therapy patients were allocated into **responders** who achieved sustained virologic response (SVR-12) or **non-responders** who didn't achieved sustained virologic response or detection of HCV RNA during the period of follow up. SVR12 was determined as undetectable HCV-RNA at 12 weeks after the end of treatment

Ethical approval:

For all participating subjects an elucidation about the research was given. Simultaneously, before enrolling in the study, each participant provided informed consent. The study was carried out after approval from the ethical committee of Faculty of Medicine, Menoufia University, Egypt, and according to the Helsinki Declaration.

Statistical analysis

The IBM SPSS software package version 20.0 was used to examine the data that was supplied into the computer. (IBM Corporation, Armonk, NY). Numbers and percentages were used to represent categorical data. The association between categorical variables was investigated using the Chi-square test. When the expected cell counts were fewer than 5, the Monte Carlo correction test was used instead. The Kolmogorov-Smirnov test was used to check for normality in continuous data. Range (minimum and maximum), mean, standard deviation, and median were used to express distributed data. For normally distributed quantitative variables, the student t-test was used to compare two groups, while the ANOVA with repeated measurements was used to compare more than two periods, with the Post Hoc test (Bonferroni adjusted) used for pairwise comparisons. On the other hand, for not normally distributed quantitative variables Mann Whitney test was utilized to compare two groups, Friedman test was used to compare between more than two periods and followed by Post Hoc test (Dunn's) for pairwise comparisons while for comparison between two periods Wilcoxon signed ranks test was used. Significance of the obtained results was judged at the 5% level

Results

A total of 500 participants with proven HCV infection were enrolled in the study. Seven individuals were eliminated from the study (four patients missed follow-up throughout the study period and three patients died during the study owing to non-hepatic causes). The remaining 493 participants complete the study period, they were, 404 (81.9%) treatment-naïve patients and 89 (18.1%) treatment-experienced patients (either previous interferon-based therapy, pegIFN/RBV, or DAAs therapy). The baseline demographic, clinical and laboratory data are presented in **(table 1).**

Regarding the response for HCV DAAs therapy, 462 (93.7%) patients demonstrated SVR12, among them, 454 (92.1%) patients remained negative one-year post-EOT. Subsequently, patients were allocated into responders (454 patients) who achieve SVR-12 and had negative PCR during the period of follow up or non-responders/ relapsed patients included 39 patients (31 patients who didn't achieve SVR12 and 8 relapsed patients during the period of follow up). Analysis of our data displayed that age and gender did not differ substantially between the two groups ($p = 0.664$ and 0.915, respectively).

Table 2 shows that, patients with SVR showed a significant decrease in serum bilirubin, an increase in serum albumin and decreased INR ($p < 0.001$ for all) one-year post EOT versus baseline. Although both responders and non-responders had non-significant differences in serum bilirubin, albumin, and INR at baseline, patients with SVR had significant improvements in serum bilirubin ($p = 0.001$), albumin ($p = 0.003$), and INR ($p = 0.001$) one year after treatment compared to patients without SVR. In addition, non-responder patients had a significant increase in serum bilirubin ($p = 0.016$) and INR ($p = 0.005$) with a non-significant change in serum albumin ($p = 0.094$).

Figures 1 and 2 show that, there was a significant decrease in liver enzymes (AST and ALT) one year following EOT compared to their baseline values in patients achieving SVR ($p < 0.001$), while, no statistically significant difference was observed in non-responders ($p = 0.308$ and 0.164, respectively).

Table 3 shows that one year after EOT, patients with SVR had a significant decrease in hemoglobin concentration and a significant increase in white blood cell count and platelet count ($p= 0.001$ for all), whereas non-responders had a significant decrease in hemoglobin concentration and platelet count ($p = 0.001$ and 0.028, respectively) compared to their baseline levels. Furthermore, patients with SVR had a significant increase in platelet count ($p = 0.020$) and non-significant changes in hemoglobin concentration and white blood cells one year after EOT compared to patients without SVR.

For assessment of liver fibrosis, we calculated the FIB-4 index and APRI score as well as performed fibroScans for all participants before and one year after EOT. **Table 4 shows** that, compared to baseline there was a significant decrease in FIB-4 index and APRI score one year following EOT in patients achieving SVR ($p < 0.001$for both). While non-responders showed non-significant changes in their FIB-4 index ($p = 0.179$) and APRI score ($p = 0.299$). Furthermore, compared to non-responders, patients with SVR had a significant decrease in FIB-4 index ($p = 0.002$) and APRI score ($p = 0.001$) one year after EOT.

Additionally, FIB-4 showed significant improvements regarding its subgroups, baseline FIB-4 was <1.45, 1.45 – 3.25, and >3.25 in 11.2%, 38.1%, and 50.7% respectively, that was improved to become 15.4%, 49.1%, and 35.5% one-year EOT with p value <0.001**.** Besides, comparable findings were recognized regarding APTI score, the baseline APRI scores were <0.5, 0.5 – 1.5 and >1.5 in 19.4%, 48.7%, and 31.9% respectively which were improved to 37.4%, 51.8%, and 10.8% respectively with a p value of <0.001. Moreover, we noticed that before starting therapy, neither the FIB-4 nor the APRI scores differed significantly between responders and non-responders as demonstrated in **Table 5.**

One year after EOT patients with SVR showed a significant reduction in liver stiffness measured via fibroScan in compression to base line value (20.59 ± 6.16 kPa versus 17.58 ± 5.94 kPa; p = <0.001), however, no significant difference was found in patients fail to achieve or maintain SVR (0.176). Furthermore, a significant reduction in liver stiffness was found in patients with SVR versus non responder one-year post-EOT ($p= 0.002$) **(table 6).**

Coming parallel to the above-mentioned results, we recognized a respectable improvement in liver disease severity (Child Pugh and MELD scores). Although, Child score in patients had SVR did not demonstrate a substantial improvement ($p = 0.479$), it showed a significant improvement versus non responder one year after EOT ($p <0.001$) **(figure 3)**.

Also, in patients without SVR the Child Pugh score was significantly deteriorated compared to baseline score ($p < 0.001$). In addition, MELD score revealed a significant reduction in patients who achieved SVR one-year post-EOT versus baseline (p value = 0.028), however in non-responder a significant deterioration in MELD score was found one-year post-EOT. Furthermore, when compared MELD score in both groups we found a significant improvement in patients with SVR versus non-responder one-year post-EOT ($p < 0.001$) (**table 6**).

Furthermore, when we looked at the change of MELD score (Δ MELD) over a year, we observed remarkable results, where 107 patients (23.6%) showed considerable reduction in their MELD score compared to their baseline scores, 264 patients (58.1%) exhibited a stable MELD score, and only 83 patients (18.3%) displayed a significant increase in their MELD score values. In contrast, those who went awry these results showed different finding regarding Δ MELD, declined, stable, and increased were 5 (12.8%), 12 (30.8%), and 22 (56.4%) respectively.

We found a significant difference between those who achieved SVR and those who did not ($p < 0.001$); the mean of ΔMELD was -0.22 and 1.74, respectively **(table 6).**

Table 1. Bassline demographic, clinical data and laboratory investigations of all patients included in the study (n = 493)

Parameter	Total HCV patients (n = 493)
Sex	
Male	345 (70%)
Female	148 (30%)
Age (years)	
Mean ± SD.	56.5 ± 7.6
Median (Min. – Max.)	57 (27 – 69)
BMI (kg/m^2)	
Mean ± SD.	28.4 ± 2.2
Median (Min. – Max.)	28.7 (22.2 – 33.2)
HB (g/dl)	
Mean ± SD.	12.48 ± 1.95
Median (Min. – Max.)	12.5 (8 – 18.8)
Platelets (×10^3/µl)	
Mean ± SD.	133.9 ± 66.7
Median (Min. – Max.)	120 (43 – 492)
WBCs (×10^3/µl)	
Mean ± SD.	5.55 ± 1.72
Median (Min. – Max.)	5.2 (2.6 – 12.8)
ALT (U/L)	
Mean ± SD.	57.7 ± 33
Median (Min. – Max.)	47 (5 – 244)
AST (U/L)	
Mean ± SD.	56.5 ± 30.8
Median (Min. – Max.)	48 (9 – 210)
Serum creatinine (mg/dl)	
Mean ± SD.	0.74 ± 0.26
Median (Min. – Max.)	0.7 (0.1 – 1.9)
Total bilirubin (mg/dl)	
Mean ± SD.	0.98 ± 0.45
Median (Min. – Max.)	0.9 (0.3 – 2.9)
Serum albumin (gm/dl)	
Mean ± SD.	3.84 ± 0.46
Median (Min. – Max.)	3.9 (2.5 – 5.3)
Blood urea	
Mean ± SD.	25.6 ± 4.2
Median (Min. – Max.)	25 (12 – 55)
INR	
Mean ± SD.	1.13 ± 0.15
Median (Min. – Max.)	1.1 (0.9 – 1.8)

AFP (ng/ml)	
Mean ± SD.	7 ± 8.26
Median (Min. – Max.)	4.65 (0.6 – 34.5)
PCR (×10⁴)	
Mean ± SD.	85.84 ± 98.26
Median (Min. – Max.)	56.0 (11.10 – 120.0)

BMI: body mass index**, HB:** hemoglobin concentration**, WBCs:** white blood cells**, ALT:** Alanine transaminase**, AST:** Aspartate aminotransferase**, PT:** prothrombin time**, INR**: International normalized ratio**, AFP:** alpha fetoprotein

Table 2. Comparison between the different studied periods according to total bilirubin, serum albumin and INR in each group

	Before treatment	End of treatment	After 12 weeks	After 24 weeks	After one year	Fr (p_0)
Total bilirubin (mg/dl)						
Responder	**(n = 454)**	**(n = 454)**	**(n = 454)**	**(n = 454)**	**(n = 454)**	
Mean ± SD.	0.98 ± 0.45	1.22 ± 0.54	1.27 ± 0.59	1.18 ± 0.56	0.97 ± 0.39	252.028*
Median (Min. – Max.)	0.97 (0.3 – 2.9)	1.1# (0.3 – 3.9)	1.2# (0.2 – 4.3)	1.1# (0.3 – 4.1)	0.9# (0.2 – 3.1)	(<0.001*)
Non-Responder	**(n = 39)**	**(n = 39)**	**(n = 39)**	**(n = 39)**	**(n = 39)**	
Mean ± SD.	1.01 ± 0.52	1.35 ± 0.68	1.35 ± 0.7	1.43 ± 1	1.51 ± 1.15	12.230*
Median (Min. – Max.)	0.9 (0.3 – 2.8)	1.3# (0.4 – 3.3)	1.2# (0.4 – 3.5)	1.2# (0.4 – 5.2)	1.1# (0.4 – 7)	(0.016*)
U (p)	8746.5 (0.900)	7930.0 (0.278)	8386.5 (0.584)	8126.5 (0.394)	5862.0(<0.001*)	
Serum albumin (g/dl)						
Responder	**(n = 454)**	**(n = 454)**	**(n = 454)**	**(n = 454)**	**(n = 454)**	
Mean ± SD.	3.85 ± 0.46	3.75# ± 0.43	3.78# ± 0.42	3.77# ± 0.53	3.91# ± 0.47	30.724*
Median (Min. – Max.)	3.9 (2.5 – 5.3)	3.8 (2.9 – 5.4)	3.8 (2.7 – 5.1)	3.8 (2.2 – 5.6)	3.9 (2.9 – 5.7)	(<0.001*)
Non-Responder	**(n = 39)**	**(n = 39)**	**(n = 39)**	**(n = 39)**	**(n = 39)**	
Mean ± SD.	3.73 ± 0.46	3.59 ± 0.42	3.62 ± 0.42	3.58 ± 0.5	3.67 ± 0.42	2.226
Median (Min. – Max.)	3.8 (2.9 – 4.6)	3.6 (2.8 – 4.5)	3.6 (2.8 – 4.5)	3.5 (2.3 – 4.5)	3.8 (2.8 – 4.4)	(0.094)
t (p)	1.494 (0.136)	2.138* (0.033*)	2.383* (0.018*)	2.082* (0.038*)	3.027* (0.003*)	
INR (international normalized ratio)						
Responder	**(n = 454)**	**(n = 454)**	**(n = 454)**	**(n = 454)**	**(n = 454)**	
Mean ± SD.	1.12 ± 0.15	1.18# ± 0.15	1.19# ± 0.15	1.19# ± 0.17	1.01# ± 0.14	42.921
Median (Min. – Max.)	1.1 (0.9 – 1.7)	1.2 (0.9 – 2.1)	1.2 (0.9 – 2)	1.2 (0.5 – 2)	1.1(0.88 – 1.8)	(<0.001*)
Non-Responder	**(n = 39)**	**(n = 39)**	**(n = 39)**	**(n = 39)**	**(n = 39)**	
Mean ± SD.	1.14 ± 0.20	1.20 ± 0.18	1.22 ± 0.19	1.23# ± 0.18	1.23# ± 0.16	5.092*
Median (Min. – Max.)	1.1 (0.9 – 1.8)	1.2 (1 – 1.9)	1.2 (1 – 2.1)	1.2 (1 – 1.9)	1.2 (1 – 1.8)	(0.005*)
t (p)	0.023 (0.982)	0.907 (0.365)	0.836 (0.403)	1.537 (0.125)	3.888(<0.001*)	

SD: Standard deviation**; U:** Mann Whitney test**; t:** Student t-test**; Fr:** Friedman test**, Sig. bet.** periods were done using Post Hoc Test (Dunn's)**;** p_0**:** p value for comparing between the studied periods**; p:** p value for comparing between Responder and Non-Responder**; *:** Statistically significant at $p \leq 0.05$; **#:** Significant with Before treatment

Table 3. Comparison between the different studied periods according to hemoglobin concentration, white blood cell count and platelet count in each group

	Before treatment	End of treatment	After 12 weeks	After 24 weeks	After one year	F (p_0)
Hemoglobin concentration (g/dl)						
Responder	(n = 454)	(n = 454)	(n = 454)	(n = 454)	(n = 454)	
Mean ± SD.	12.44 ± 1.97	11.97# ± 1.82	11.7# ± 1.78	11.98# ± 1.74	11.94# ± 1.91	46.773*
Median (Min. – Max.)	12.5 (8 – 18.8)	12 (7.2 – 16.5)	11.5 (3 – 16.1)	12 (7.5 – 17.8)	12 (7.3 – 17.5)	(<0.001*)
Non-Responder	(n = 39)	(n = 39)	(n = 39)	(n = 39)	(n = 39)	
Mean ± SD.	12.88 ± 1.67	12.13# ± 1.43	12.18# ± 1.39	12.6 ± 1.61	11.91# ± 1.45	8.795*
Median (Min. – Max.)	13.2 (9.1-15.2)	12 (9.1-14.6)	12.5 (9.4-14.5)	12.5 (9.1-16.3)	12 (9.2 – 15.2)	(<0.001*)
t (p)	1.338 (0.181)	0.489 (0.625)	1.663 (0.097)	2.151* (0.032*)	0.128 (0.899)	
White blood cells (×10³/µl)						
Responder	(n = 454)	(n = 454)	(n = 454)	(n = 454)	(n = 454)	
Mean ± SD.	5.54 ± 1.71	5.57 ± 1.83	5.98 ± 2.52	5.99 ± 2.02	6.01 ± 2.22	39.869*
Median (Min. – Max.)	5.2 (2.6 – 12.8)	5.2 (2.3 – 15.6)	5.6# (3 – 14.8)	5.5# (2.6 – 13.5)	5.6# (2.5 – 20.8)	(<0.001*)
Non-Responder	(n = 39)	(n = 39)	(n = 39)		(n = 39)	

Mean ± SD.	5.67 ± 1.90	5.49 ± 1.95	5.61 ± 1.52	5.63 ± 1.99	5.63 ± 2.15	0.692 (0.952)
Median (Min. – Max.)	5.2 (3.6 – 11.6)	4.5 (2.5 – 11.5)	5.3 (2.8 – 8.9)	5.3 (2.4 – 11.5)	4.8 (1.9 – 10.5)	
U (p)	8691.0 (0.849)	8353.5 (0.558)	8305.5 (0.521)	7996.50 (0.315)	7863.00 (0.246)	
Platelet count(×10³/µl)						
Responder	(n = 454)	(n = 454)	(n = 454)	(n = 454)	(n = 454)	
Mean ± SD.	133.7 ± 66.6	135.5 ± 68.3	135.4 ± 68.3	135.7 ± 65.7	145.8# ± 68.3	30.328* (<0.001*)
Median (Min. – Max.)	120 (43 – 492)	121.5 (21 – 450)	122 (30 – 588)	122.5 (28 – 455)	133 (40 – 468)	
Non-Responder	(n = 39)	(n = 39)	(n = 39)	(n = 39)	(n = 39)	
Mean ± SD.	135.5 ± 68.8	136.3 ± 70.8	132.1 ± 61.2	127.7 ± 61.1	119.6 ± 55.2	3.390* (0.028*)
Median (Min. – Max.)	125 (54- 320)	125 (50- 352)	122 (42- 305)	120 (39- 305)	111 (44-314)	
t (p)	0.159 (0.873)	0.074 (0.941)	0.292 (0.771)	0.737 (0.462)	2.333* (0.020*)	

SD: Standard deviation**; U:** Mann Whitney test**; t:** Student t-test**; Fr:** Friedman test**, Sig. bet.** periods were done using Post Hoc Test (Dunn's)**;** p_0**:** p value for comparing between the studied periods**; p:** p value for comparing between Responder and Non-Responder**; *:** Statistically significant at $p \leq 0.05$; **#:** Significant with Before treatment

Table 4. Comparison between the different studied periods according to FIB4 and APRI scores in each group

	Before treatment	End of treatment	After 12 weeks	After 24 weeks	After one year	Fr (p0)
FIB4 index						
Responder	(n = 454)	(n = 454)	(n = 454)	(n = 454)	(n = 454)	
Mean ± SD.	3.89 ± 2.47	3.41 ± 2.08	3.31 ± 1.92	3.43 ± 2.12	3.23 ± 2.46	
Median (Min. – Max.)	3.3 (0.4- 16.5)	2.9# (0.4- 14.2)	2.8# (0.5- 14.4)	3# (0.4 – 13.3)	3.3# (0.4- 16.5)	76.466* (<0.001*)
Non-Responder	(n = 39)	(n = 39)	(n = 39)	(n = 39)	(n = 39)	
Mean ± SD.	4.06 ± 2.91	3.56 ± 2.17	3.44 ± 2.01	3.83 ± 1.99	3.93 ± 2	
Median (Min. – Max.)	3.7 (0.9- 14.8)	3.1 (0.7 – 9.3)	3.1 (0.7 – 10.3)	3.7 (0.8 – 9.1)	3.7 (0.9 – 14.8)	6.283 (0.179)
U (p)	8739.0 (0.894)	8557.0 (0.729)	8531.0 (0.706)	7476.0 (0.107)	6242.0* (0.002*)	
APRI score						
Responder	(n = 454)	(n = 454)	(n = 454)	(n = 454)	(n = 454)	
Mean ± SD.	1.33 ± 1.03	1.02 ± 0.82	0.91 ± 0.61	0.90 ± 0.66	0.81 ± 0.72	253.012* (<0.001*)
Median (Min. – Max.)	1.01 (0.1-6.6)	0.77# (0.1-5.6)	0.75# (0.1-3.8)	0.71# (0.1- 4)	0.63# (0.1-9.3)	
Non-Responder	(n = 39)	(n = 39)	(n = 39)	(n = 39)	(n = 39)	
Mean ± SD.	1.41 ± 1.03	1.17 ± 0.87	1.11 ± 0.77	1.28 ± 1.04	1.32 ± 0.99	4.884 (0.299)
Median (Min. – Max.)	1.20 (0.2- 4.1)	0.91 (0.2- 3.6)	0.92 (0.1- 3.2)	1.04 (0.3- 5.9)	1.03 (0.3- 5.5)	
U (p)	8400.0 (0.596)	7780.5 (0.209)	7545.0 (0.126)	6513.0 (0.006*)	4990.0 (<0.001*)	

SD: Standard deviation**; U:** Mann Whitney test**; t:** Student t-test**; Fr:** Friedman test**, Sig. bet.** periods were done using Post Hoc Test (Dunn's)**;** p_0**:** p value for comparing between the studied periods**; p:** p value for comparing between Responder and Non-Responder**; *:** Statistically significant at $p \leq 0.05$; **#:** Significant with Before treatment

Table 5. Comparison between the two studied groups according to sub-classifications of FIB4 and APRI scores

		Total (n = 493)	Responder (n = 454)	Non-Responder (n = 39)	χ^2	p
FIB4	**Before treatment**					
	<1.45	55 (11.2%)	51 (11.2%)	4 (10.3%)	1.030	0.598
	1.45 – 3.25	185 (37.5%)	173 (38.1%)	12 (30.8%)		
	>3.25	253 (51.3%)	230 (50.7%)	23 (59%)		
	After one year					
	<1.45	72 (14.6%)	70 (15.4%)	2 (5.1%)	9.230	0.010*
	1.45 – 3.25	237 (48.1%)	223 (49.1%)	14 (35.9%)		

	>3.25	184 (37.3%)	161 (35.5%)	23 (59%)		
	MH (p_0)	399.0* (<0.001*)	383.0 (<0.001*)	16.0 (0.527)		
APRI	**Before treatment**					
	<0.5	94 (19.1%)	88 (19.4%)	6 (15.4%)	0.512	0.774
	0.5 – 1.5	242 (49.1%)	221 (48.7%)	21 (53.8%)		
	>1.5	157 (31.8%)	145 (31.9%)	12 (30.8%)		
	After one year					
	<0.5	174 (35.3%)	170 (37.4%)	4 (10.3%)	12.519*	0.002*
	0.5 – 1.5	262 (53.1%)	235 (51.8%)	27 (69.2%)		
	>1.5	57 (11.6%)	49 (10.8%)	8 (20.5%)		
	MH (p_0)	480.0* (<0.001*)	461.0 (<0.001*)	19.0 (0.527)		

χ^2: Chi square test**; MH:** Marginal Homogeneity Test**; p:** p value for comparing between Responder and Non-Responder**; p_0:** p value for comparing between Before treatment and after one year**; ***: Statistically significant at p <0.05

Table 6: Comparison between two studied groups according to fibro scan, Child score and MELD score at (baseline) before and after 1-year treatment

		Total	**Responder**	**Non-Responder**	**Test of Sig. (p)**
Fibro scan	**Before treatment**	(n = 493)	(n = 454)	(n = 39)	
	Mean ± SD.	20.65 ± 6.29	20.59 ± 6.16	21.39 ± 7.71	U=8561.5 (0.733)
	Median (Min. – Max.)	20 (11.7 – 45)	20 (12 – 42.5)	20.2 (11.7 – 45)	
	After one year	(n = 493)	(n = 454)	(n = 39)	
	Mean ± SD.	17.79 ± 5.94	17.58 ± 5.94	20.19 ± 5.40	U=6191.50 (0.002*)
	Median (Min. – Max.)	16 (7.5 – 44)	15.3 (7.5 – 36)	20.50 (12.50 – 44)	
	Z (p_0)	13.208* (<0.001*)	13.357* (<0.001*)	1.354 (0.176)	
Child score	**Before treatment**	(n = 493)	(n = 454)	(n = 39)	
	A	394 (79.9%)	366 (80.6%)	28 (71.8%)	χ^2=1.742 (0.187)
	B	99 (20.1%)	88 (19.4%)	11 (28.2%)	
	C	0 (0%)	0 (0%)	0 (0%)	
	Mean ± SD.	5.69 ± 1	5.68 ± 0.99	5.85 ± 1.14	U=8291.0 (0.455)
	Median (Min. – Max.)	5 (5 – 9)	5 (5 – 9)	5 (5 – 9)	
	After one year	(n = 493)	(n = 454)	(n = 39)	
	A	418 (84.8%)	396 (87.2%)	22 (56.4%)	χ^2=27.290* (<0.001*)
	B	65 (13.2%)	51 (11.2%)	14 (35.9%)	
	C	10 (2%)	7 (1.5%)	3 (7.7%)	
	Mean ± SD.	5.82 ± 1.19	5.74 ± 1.14	6.72 ± 1.41	U=4489.50* (<0.001*)
	Median (Min. – Max.)	5 (5 – 12)	5 (5 – 12)	6 (5 – 11)	
	Z (p_0)	2.234* (0.025*)	0.707 (0.479)	4.685* (<0.001*)	
MELD	**Before treatment**	(n = 493)	(n = 454)	(n = 39)	
	Mean ± SD.	8.06 ± 2.27	8.04 ± 2.23	8.31 ± 2.71	U=8657.5 (0.817)
	Median (Min. – Max.)	8 (6 – 18)	8 (6 – 18)	8 (6 – 15)	
	After one year	(n = 493)	(n = 454)	(n = 39)	
	Mean ± SD.	8 ± 1.87	7.82 ± 1.65	10.05 ± 2.83	U=4459.5* (<0.001*)
	Median (Min. – Max.)	8 (6 – 18)	8 (6 – 17)	10 (6 – 18)	
	Z (p_0)	0.860 (0.390)	2.197* (0.028*)	3.517 (<0.001*)	
	ΔMELD (MELD score changes)	(n = 493)	(n = 454)	(n = 39)	
	Decline (≤ -2)	112 (22.7%)	107 (23.6%)	5 (12.8%)	χ^2=31.150* (<0.001*)
	Stable (-2 < – <2)	276 (56%)	264 (58.1%)	12 (30.8%)	
	Increase (≥2)	105 (21.3%)	83 (18.3%)	22 (56.4%)	
	Mean ± SD.	-0.06 ± 2.29	-0.22 ± 2.18	1.74 ± 2.75	U=5113.50 (<0.001*)
	Median (Min. – Max.)	0 (-6 – 10)	0 (-6 – 8)	2 (-4 – 10)	

SD: Standard deviation**; U:** Mann Whitney test; **Z:** Wilcoxon signed ranks test; **χ^2:** Chi square test; **MC:** Monte Carlo; **p:** p value for comparing between Responder and Non-Responder; **p_0:** p value for comparing between the studied periods; *****: Statistically significant at p < 0.05

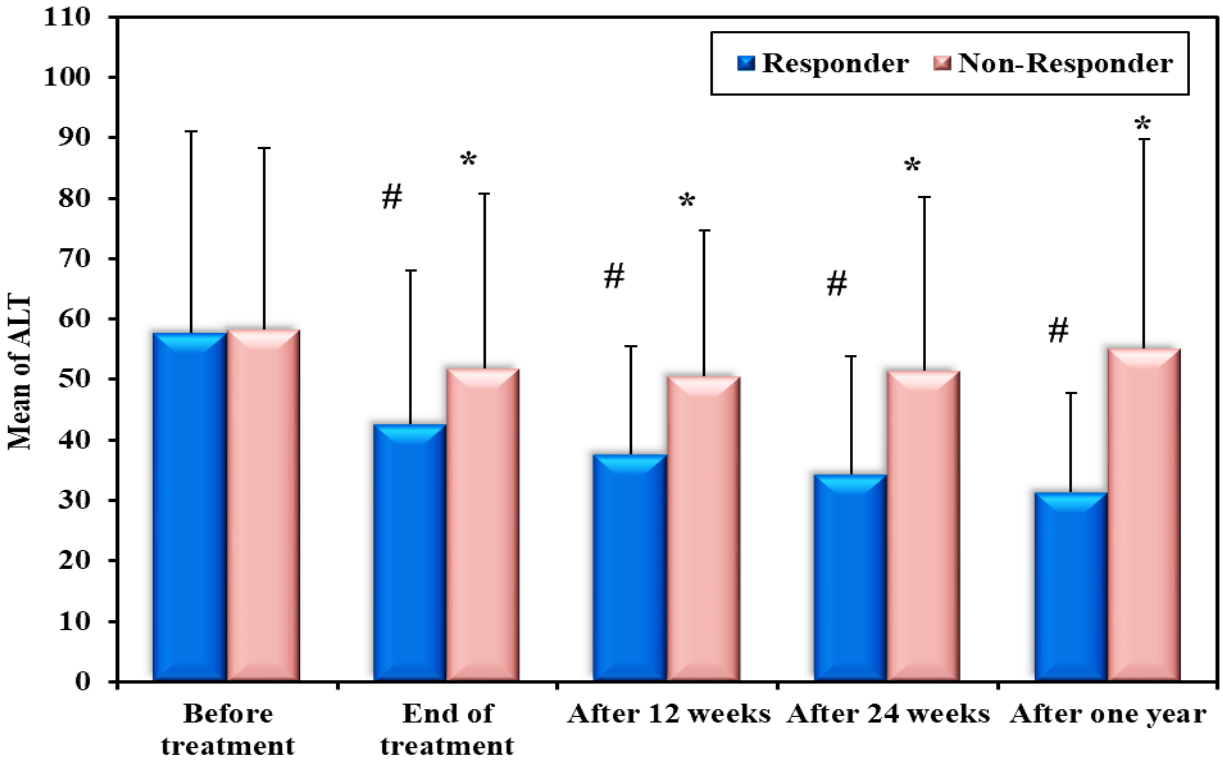

Figure 1: Comparison between the different studied periods according to ALT in each group. #: Significant with Before treatment**; *:** Significant between Responder and Non-Responder in each period

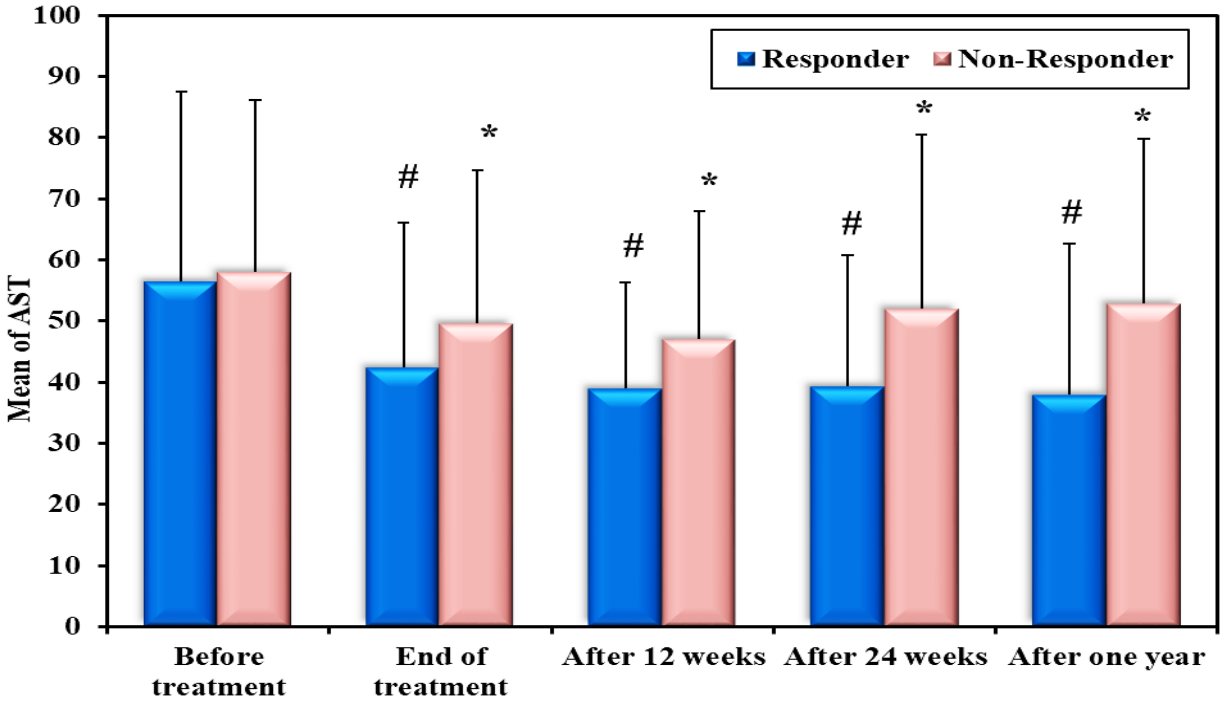

Figure 2: Comparison between the different studied periods according to AST in each group. #: Significant with Before treatment**; *:** Significant between Responder and Non-Responder in each period

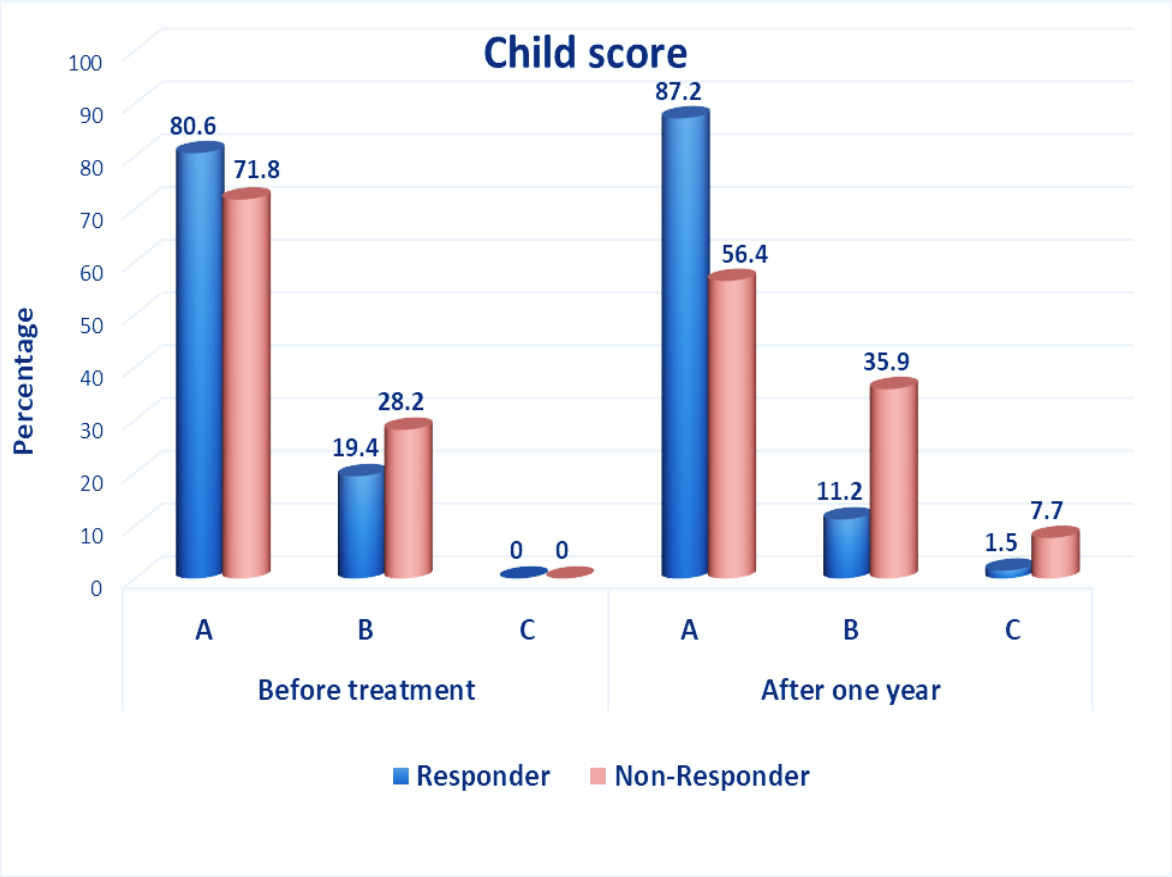

Figure 3: Comparison between two studied groups according to child grade before and 1-year EOT

Discussion

Egypt has experienced the highest prevalence of Hepatitis c in the world for so long, but has begun taking the most significant step toward eliminating the disease so far, with the most extensive treatment campaigns throughout the world applying remarkably effective regimens of direct-acting antiviral therapy, leading to massive treatment of nearly two and a half million Egyptian HCV patients [15]. The availability of highly effective all-oral, interferon free, DAA medications for patients with cirrhosis has transformed the treatment options for infected HCV patients and most patients can now achieve viral clearance. In our study, from 500 HCV patients, 493 patients completed the study of whose PCR for HCV turned negative in 462 patients (93.7%) after 12 weeks of treatment (SVR12), and 454 (92.1%) patients maintained negative after one-year end of treatment.

In this work we noticed that obtaining SVR12 was linked to considerable increase in PLT count, which begins at the end of treatment and lasts for up to 12 months. Come online with our findings Elabd et al has reported significant elevation of platelet count after achieving HCV eradication by DAAs [16]. Additionally, Sayyar et al. has concluded that PLT improvement following HCV eradication is most likely due to viral eradication and should not be used or construed as a measure of liver fibrosis or portal hypertension improvement only [17].

Moreover, in our study we noticed progressive improvement of liver functions (including considerable reduction of serum transaminases, serum bilirubin, prothrombin time and INR together with significant elevation of serum albumin in HCV patients achieving SVR during the period of follow up compared to patients that failed to achieve SVR who showed either non-significant changes or even worsening in liver functions. This was evident on statistical analysis which demonstrated significant differences in theses parameters, besides significant lowering in MELD score in patients achieving SVR, as the mean value of MELD was decreased from 8.04 before treatment to 7.82 after one-year EOT with statistically significant difference (p value = 0.028). However, Child score did not show significant improvement in these patients but still there was a trend towards improvement. Where Child grades before treatment were Child A, B and C 366 (80.6%), 88 (19.4%), and 0 (0%) respectively, while one year after HCV eradication they were 396 (87.2%), 51 (11.2%), and 7 (1.5%) respectively. These results are in agreement with those of Cheung and his colleagues who reported that there is an improvement in Child and MELD scores after DAAs therapy [18].

Rapid and sustained reduction of ALT and AST after initiating therapy and later on after cessation of antiviral agents during the period of a year of follow up indicate liver inflammation resolution in parallel with HCV clearance. In

the previous study by Cheng et al. histological findings regarding necroinflammatory activity in the liver were observed in patients achieving SVR [19]. They have found histological improvement in hepatic inflammation in 71.4% patients, where the mean HAI (Histological Activity Index) scores lowered from 6.9 to 5.0 after HCV eradication by DAAs. Additionally, several preceding studies likewise have demonstrated the positive impacts of HCV eradication on liver inflammation [20,21]. Reduced hepatic inflammation appears to be a factor linked to fibrosis regression.

To better understand how antiviral medication affects hepatic fibrosis, it is crucial to comprehend the natural course and pathophysiology of chronic hepatitis C infection. Increased synthesis and deposition of extracellular matrix, inflammation and production of numerous cytokines, and proliferation of myofibroblasts are all part of the pathophysiology of fibrosis after hepatocyte injury. Inflammation, in particular, is a primary driver of the fibrogenic response in the HCV-infected liver. Proinflammatory cytokines and profibrogenic substances are secreted by the immune system, resulting in hepatic damage and fibrosis promotion [22].

The gold standard for determining fibrosis is a liver biopsy. Yet, performing a liver biopsy for all patients to determine their fibrosis stage is unfeasible, over and above performing a liver biopsy for follow up and for detecting fibrosis regression after achieving SVR in HCV patients is impractical.

Many non-invasive approaches are commonly employed for determining the fibrosis stage, including imaging technologies and serum biomarkers. Imaging technologies, on the other hand, are costly and unavailable in some medical facilities. Numerous laboratory indices, such as aspartate aminotransferase to platelet ratio index (APRI) and fibrosis-4 (FIB-4) are useful for assessment of liver fibrosis in chronic HCV patients [23,24]. They offer a number of benefits, including ease of use, reproducibility, patient acceptance, cost effectiveness, and the absence of biopsy-related hazards.

In our study, for estimating liver fibrosis we calculated the dynamics of FIB-4 and APRI scores as well as fibroscan for all participants, before and during DAAs then one-year EOT. FIB-4 showed considerable reduction in its mean starting from end of treatment and maintained during follow-up period. Similar findings were obtained in the APRI score. Additionally, concerning classification of FIB-4 showed significant improvement, base line FIB-4 was <1.45, 1.45 – 3.25, and >3.25 in 51 (11.2%), 173 (38.1%), and 230 (50.7%) respectively, that was improved to become 70 (15.4%), 223 (49.1%), and 161 (35.5%) one-year EOT. Comparable findings were recognized regarding APTI score, the baseline APRI scores were <0.5, 0.5 – 1.5 and >1.5 in 88 (19.4%), 221 (48.7%), and 145 (31.9%) respectively which were improved to 170 (37.4%), 235 (51.8%), and 49 (10.8%) respectively.

In their study of 220 HCV patients Cheng and his colleagues has found that both FIB-4 and APRI values decreased considerably at the 4th week of antiviral treatment and maintained during follow up [19]. Given that liver fibrosis is a chronic process, the quick decline in fibrosis scores following DAA medication may actually reflect an improvement in inflammation rather than a true fibrosis regression, as the time period seemed too brief for significant remodeling of hepatocyte. Nevertheless, maintaining the improvement in fibrosis markers one-year EOT may imply real fibrosis regression. A longer duration of viral suppression may be connected with a better histologic response, as according Pockros et al [25].

In terms of the fibroScan outcomes, we identified a considerable reduction of fibroscan results in patients achieving a SVR, in whom mean fibroscan was 20.59 kPa prior to therapy that was lowered to 17.58 kPa one-year EOT. In their earlier work, Lawitz et al. discovered that mean Fibroscan and mean FibroTest scores in both the Child A and B groups generally declined from baseline. They stated that individuals with the highest baseline stiffness fibroscan scores had the greatest improvements in liver stiffness [26]. This could be related to the regression of liver fibrosis or reductions in inflammation following SVR [27].

Previously, liver fibrosis was believed to be permanently irreversible; this is no longer the case. Fibrosis and even cirrhosis are dynamic processes that involves ongoing fibrogenesis and fibrinolysis. As was earlier noted, fibrosis may be reversible in many liver diseases including chronic HBV infection, alcoholic steatohepatitis [28, 29]. In addition, the progression of hepatic fibrosis and inflammation can be decreased or reversed in some HCV patients, with SVR was the key determinant of histological improvement. Numerous interferon-based regiments appear to be equally effective in fibrosis regression [30,31]. In particular, with respect Ogasawara et al earlier 's work showed that liver fibrosis regresses following DAAs-associated SVR, which in turn improves hepatocellular function, lowers portal hypertension, and is linked to a lower risk of hepatic decompensation, liver-related complications, and HCC development [32].

Assuming that regression of liver fibrosis can occur after successful DAAs therapy. The intrahepatic blood flow and hepatocyte functions may improve with fibrosis regression, which would enhance hepatic outcomes.

Our study had some limitations. First, our study had a relatively small sample size. Second, only non-invasive approaches were used to assess liver fibrosis, with no correlation to liver biopsy. Third, we relied solely on fibrosis marker improvement as predictors of histological improvement, despite the fact that liver biopsy is the most accurate tool for assessing histological improvement of liver fibrosis.

Conclusion

In conclusion, achieving a virological suppression by DAAs therapy in HCV patients is linked with regression of liver fibrosis that in turn is associated with improvements in liver functions and better outcome.

Abbreviations
ALT: Alanine transaminase
APRI: Aspartate aminotransferase to platelet ratio index
AST: Aspartate aminotransferase
DAAs: Direct-acting antivirals
ELISA: Enzyme-linked immunoassay
FIB4: Fibrosis-4 Index
HAI: Histological Activity Index
HBVsAg: Hepatitis B virus surface antigen
HCC: Hepatocellular carcinoma
HCV PCR: Hepatitis C virus polymerase chain reaction
HCV-RNA: Hepatitis C virus ribonucleic acid
EOT: End of treatment
INR: International normalized ratio
MELD: Model for end-stage liver disease
PegIFN/RBV: Pegylated interferon / ribavirin
SVR: Sustained virological response
ΔMELD: Delta model for end-stage liver disease

Ethics approval and consent to participate
Before being enrolled in this study, all participants were given a description of the study and given the opportunity to give their informed consent. The study was carried out after approval from the ethical committee of Faculty of Medicine, Menoufia University, Egypt, and according to the Helsinki Declaration**.**
Consent for publication: Not applicable.
Availability of data and material
All data generated or analyzed during this study are included in this published article.
Competing interests
The authors declare that they have no competing interests.
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Authors' contributions
Ali Nada and Naglaa S. Elabd selected the study design, and were responsible for data collections and evaluation of the involved patients. Lmyaa Ata and Amany A. Amer were responsible for samples collection and collecting the clinical and laboratory data of studied patients. Ali Nada performed the fibroScan for patients. All authors participated in writing and revising the paper and approved the final manuscript.
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