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ORIGINAL ARTICLE

# Liver Fibrosis Regression After Direct-Acting Antivirals for Hepatitis C Virus: A Prospective Study

Fahmy H Hablass[1], MD; Sameh A. Lashen[1*], MD, PhD, Eman A. Mohamed[1], MD

1 Department of Internal Medicine (Hepatology and Gastroenterology division), Faculty of Medicine, University of Alexandria, Alexandria, Egypt.

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Correspondence to: Sameh A. Lashen, Department of Internal Medicine (Hepatology and Gastroenterology division), Faculty of Medicine, University of Alexandria, Alexandria, Egypt.
Email: sameh.lashen@alexmed.edu.eg
ORCID ID: 0000-0002-8599-1338

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## ABSTRACT

**BACKGROUND AND AIM:** The impact of hepatitis C virus (HCV) elimination on liver fibrosis has been a hot topic since the introduction of direct-acting antivirals (DAAs). Liver stiffness (LS) can be evaluated non-invasively by transient elastography (TE). We aimed at evaluation of liver stiffness changes by FIB-4 and TE after HCV clearance.

**PATIENTS AND METHODS**: Prospectively, 137 patients were included (per-protocol analysis). Baseline liver test profile, LS by TE, and FIB-4 were done. Sustained virologic response was evaluated at 12 weeks after DAAs treatment (SVR12). LS and liver test profiles were re-evaluated after 12 months of follow-up.

**RESULTS:** An SVR12 was achieved among 97.3% of patients. In all patients, the FIB-4 and TE values after HCV elimination was significantly lower than its mean values at baseline (2.20 ± 1.30 vs 3.76 ± 2.23, and 8.32 ± 3.16 v 11.75 ± 5.47 kPa, $p < 0.001$ respectively). For patients with ≥ F2, 69.6% have fibrosis regression while cirrhosis regressed among 56.1% of patients with F4 at baseline. LS of 17.6 kPa could identify patients with a higher possibility of fibrosis regression (sensitivity= 94.4%, specificity= 82.6%, area under the curve = 0.88, $p < 0.001$). Fibrosis regression was associated with improvement in aminotransferases, serum albumin, bilirubin, and INR. Gender, age, platelet count, serum bilirubin, Child-Turcotte-Pugh score, and baseline fibrosis stage were the independent predictors for fibrosis regression.

**CONCLUSION**: Achieving an SVR after DAAs therapy is associated with regression of fibrosis. Baseline clinicolaboratory parameters could predict the likelihood of fibrosis regression with an LS of 17.6 kPa is a suggested cut-off value.

**Key words**: Liver stiffness; Transient Elastography; Direct-antivirals; FIB-4; Fibrosis



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## INTRODUCTION

Recently, the development of direct-acting antiviral (DAAs) drugs represented a revolution in hepatitis C virus (HCV) treatment; the commonest cause of liver fibrosis/cirrhosis worldwide, with surprising efficacy and safety[1]. Interferon (IFN) treatment was not allowed for cirrhotic patients because of its adverse events and the risk of hepatic decompensation. However, in the eligible subgroup, IFN-based HCV elimination was found to induce fibrosis regression, but it was unclear whether it was due to the antifibrotic potentials of IFN, or was due to HCV elimination. Also, data about patients with cirrhosis were lacking[2,3]. With the introduction of

DAAs, cirrhotic patients could be safely treated. The impact of HCV elimination on liver fibrosis has been a hot topic since that. Several reports have addressed the possibility of reversal of hepatic fibrosis after HCV treatment[4,5]. The gold standard tool for evaluation of the degree of liver fibrosis is the liver biopsy, but due to its invasive nature, the search for other tools to properly evaluate liver fibrosis was of clinical interest[5]. Among the non-invasive tests, the FIB-4 could accurately discriminate between mild/moderate fibrosis and bridging fibrosis. Also, its utilization could decrease the need for liver biopsy in ~ 70% of patients with an accuracy of ~ 87%[5,6]. Transient elastography (TE) is currently an approved non-invasive tool for evaluation of the degree of liver fibrosis with accepted accuracy and reproducibility[7]. The current study aimed to evaluate the impact of DAAs-achieved HCV elimination on liver fibrosis using the TE and FIB-4 test.

## MATERIALS AND METHODS

**Setting and study design**

The current prospective study included 150 treatment-naïve chronic genotype 4 HCV-infected patients who attended the hepatitis C treatment center at the Internal Medicine Department, Faculty of Medicine (a tertiary care hospital), University of Alexandria, for DAAs therapy.

All the included patients were subjected to clinical evaluation and laboratory investigations including complete blood picture (CBC), liver profile test, serum creatinine, hepatitis B markers, serum alfa-fetoprotein (AFP), and HCV RNA quantification [automated Cobas Amplicor Analyzer (Roche Molecular Diagnostics, California, USA] with a detection limit of 15 IU/mL = $1.17Log_{10}$. Abdominal ultrasound was performed to assess the presence or absence of cirrhosis and ascites, as well as to screen for focal hepatic lesions (FHL). A triphasic CT scan of the liver was done if indicated. The severity of liver disease was estimated by the Child-Turcotte-Pugh (CTP) score. After an initial evaluation, all the eligible patients were assigned to either Sofosbuvir 400 mg plus Daclatasvir 60 mg±weight-based Ribavirin, or Sofosbuvir 400 mg/Ledipasvir 90mg single-pill combination±weight-based Ribavirin for 12 or 24 weeks. During the time of patient enrolment, the Clinical Practice Guidelines of the European Association for the Study of the Liver (EASL) 2015 were being adopted by our hospital.

Follow-up laboratory investigations (including HCV RNA quantification) were assessed at the end of treatment (EOT) and 12 weeks later to assess the sustained virologic response (SVR12).

The degree of liver fibrosis was evaluated before starting DAAs, and 12 months after the EOT using the FIB-4 score and liver stiffness (LS) by Fibroscan (Echosens, Paris, France). The staging of liver fibrosis by FIB-4 score was as followings; F0-F1 = score < 1.45, F2 = 1.45 - 3.25, F3-F4 = score > 3.25[5], and for Fibroscan results as followings: F0-F1 = LS of < 7 kPa, F2 = LS of 7-9.4 kPa, F3 = LS of 9.5-12.4 kPa, and F4 = LS ≥ 12.5 kPa[8]. F0-2 was designated as non-significant fibrosis, while F3 and F4 as a significant fibrosis stage. Changes in the degree of liver fibrosis were defined as follows (based on Fibroscan): Improvement: at least one step-down in the fibrosis stage; Stationary: no change in comparison to the baseline reading; Progression: at least one step-up in the fibrosis stage compared to the baseline reading. Also, we calculated the change in liver stiffness reading (Δ LS) by subtraction of the "after" reading from the "baseline" reading.

All patients with HCV-HBV/HIV co-infection, chronic kidney disease, Child score ≥ B/8, patients with ascites, other causes of chronic liver disease, history of hepatocellular carcinoma (HCC), or undetermined FHL, previous antiviral or interferon treatment, liver or kidney transplant, hematological or solid organ malignancy, and body mass index ≥ 35 kg/m$^2$ were excluded from the study.

**Ethics & Consents**

Our study was performed in agreement with the revised Declaration of Helsinki (2013), and with Good Clinical Practice guidelines. The study was approved by our institutional ethical committee, and informed consent was obtained from every patient included in the study.

**Statistical analysis**

Data were analyzed using Statistical Package for Social Sciences (IBM SPSS version 26.0) software. The data were expressed as mean ± standard deviation (SD) or proportions. The student's *t*-test was used to compare means. Chi-square ($\chi^2$) test or Fisher's Exact test (*FET*) test were used as appropriate. The one-way ANOVA test was used for comparing the subgroups with post hoc analysis. The sensitivity and specificity of LS measurement were assessed by plotting a receiver-operating characteristic (ROC) curve. Correlations between variables were analyzed by using Pearson's correlation coefficient or Spearman's rank test as appropriate. Multivariate analysis was done. Statistical significance was assessed at $p < 0.05$. All calculated P values were two-tailed.

## RESULTS

At 12 weeks after the EOT, 146 patients achieved an SVR12 (97.3%). During the follow-up, data of nine patients were lost, leaving the analysis for only 137 patients (Per-protocol analysis). The follow-up period was 12 months after DAAs treatment for all patients. There was high degree of inter-rater reliability for both FIB-4 test and Fibroscan for stratifying liver fibrosis stage (ICC = inter-class correlation coefficient = 0.91, $p < 0.001$, 95% CI: 0.77-0.96), the inter-rater degree of agreement between Fibroscan and FIB-4 was significant (Cohen's kappa = 0.73, $p < 0.001$). At baseline, patients with significant fibrosis were significantly older than patients with non-significant fibrosis. Also, they have higher baseline bilirubin, INR, AFP, and CTP score, and lower serum albumin, platelets, hemoglobin, and white blood cell count compared to patients with non-significant fibrosis ($p < 0.001$) (Table 1).

**Changes in the fibrosis scores after HCV elimination**

In all patients, the Mean±SD of FIB-4 values after HCV elimination was significantly lower than its mean values at baseline (2.20 ± 1.30 vs. 3.76 ± 2.23, $p < 0.001$, 95% CI: 1.32-1.81). Also, in all patients, the Mean±SD of liver stiffness measurements by Fibroscan after HCV elimination was significantly lower than its mean values at baseline (8.32 ± 3.16 vs. 11.75 ± 5.47 Kpa, $p < 0.001$, 95% CI: 2.89-3.97). The frequency (%) of F3 and F4 fibrosis has declined significantly after the follow-up (Figure 1-a through d).

Among patients with fibrosis stage ≥ F2 ($n = 115$), fibrosis regression occurred in 80 (69.6%), while 26 (22.6%) patients remained unchanged. Progression occurred in nine (7.8%) patients. Fibrosis stage-specific dynamic changes showed that there was a significant difference as regards the regressive, stationary, or progressive course between different baseline fibrosis categories. The highest percentage of fibrosis regression was obtained among F2-F3 stages (87.2%, and 67.6% respectively), while cirrhosis regression occurred in 56.1% of patients ($p = 0.016$) (Figure 2).

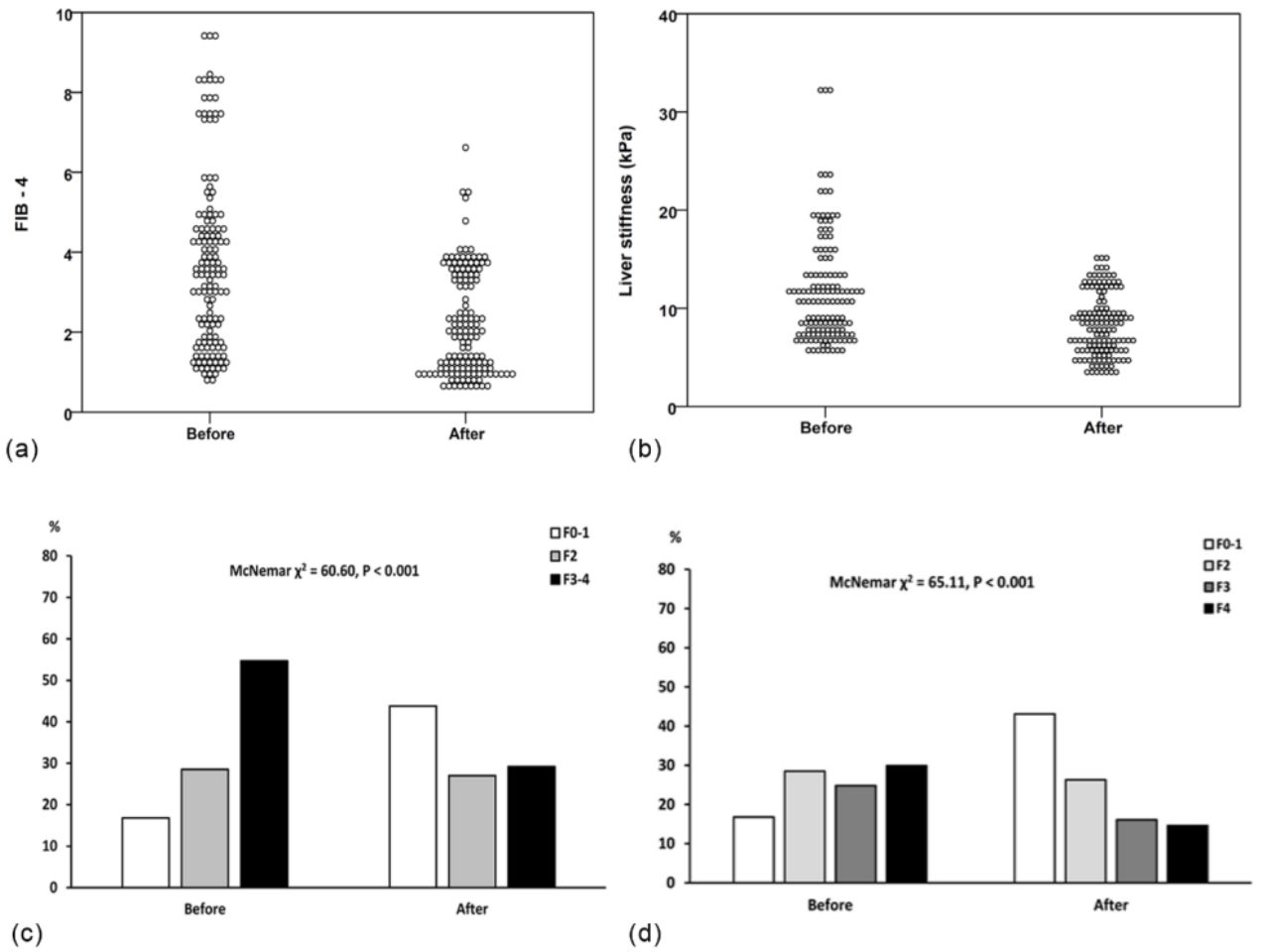


**Figure 1** Comparisons between study cohort before and after hepatitis C treatment as regards (a) FIB-4 score; (b) Liver stiffness using Fibroscan; (c) Fibrosis stage by FIB-4 test; and (d) Fibrosis stage by Fibroscan.

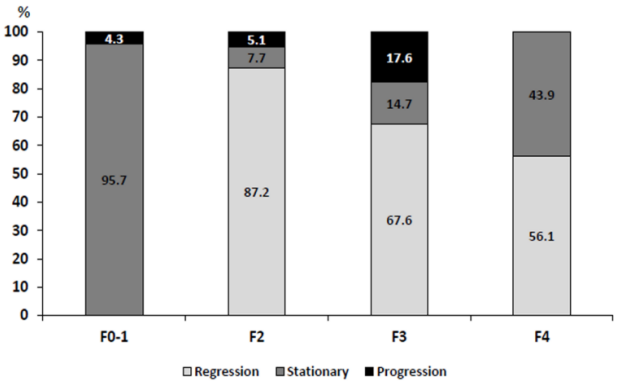


**Figure 2** Dynamic changes in different fibrosis grades after hepatitis C treatment.

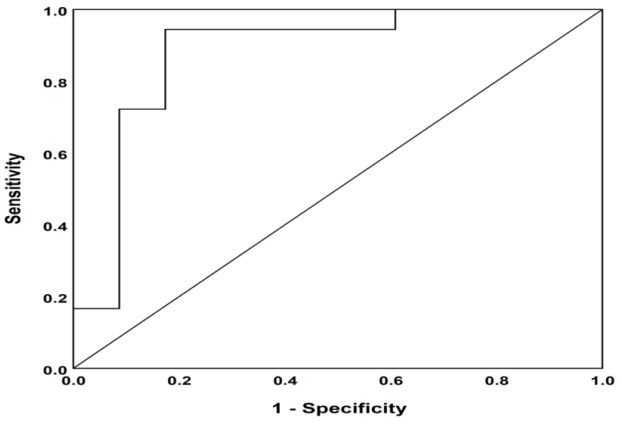


**Figure 3** ROC curve analysis for the sensitivity and specificity of liver stiffness in determining the likelihood of fibrosis regression.

**ROC curve analysis**

In the subgroup of cirrhosis (F4 by Fibroscan, $n = 41$), a ROC curve analysis was run to determine the cut-off point at which fibrosis regression is unlikely. LS of 17.6 Kpa could identify patients with a higher possibility of fibrosis regression with a sensitivity of 94.4%, a specificity of 82.6%, a positive predictive value of 81%, and a negative predictive value of 95% (area under the curve = 0.88, $p < 0.001$, 95% CI: 0.77-0.99) (Figure 3).

**Changes in the laboratory parameters after HCV elimination**

Patients who cleared HCV have a significant rise in serum hemoglobin, platelets, WBCs, and serum albumen ($p < 0.001$), and a significant decrease in serum bilirubin, INR, liver aminotransferases, serum AFP, and FBS ($p < 0.001$) (Table 2).

**Comparison between patients with and without fibrosis regression as regards baseline parameters**

After the exclusion of patients with stationary F0-1, a comparison between patients who have fibrosis regression ($n = 80$) and patients without regression (sum of progression plus stationary F2-4, $n = 35$)

**Table 1** Shows the baseline clinical and laboratory data and their comparisons

| Parameter | F0-1 (*n* = 23) | F2 (*n* = 39) | F3 (*n* = 37) | F4 (*n* = 41) | P |
|---|---|---|---|---|---|
| Sex: n (%) | | | | | |
| Male | 13 (56.5) | 13 (33.3) | 19 (55.9) | 32 (78) | 0.001 |
| Female | 10 (43.5) | 26 (66.7) | 14 (44.1) | 9 (22) | |
| Age (years) | 27.74 ± 5.23 [bc] | 30.08 ± 6.44 [bc] | 43.09 ± 6.13 | 45.95 ± 9.95 | <0.001 |
| Hb (g/dl) | 12.97 ± 1.08 [bc] | 12.65 ± 1.42 [c] | 12.17 ± 0.99 [c] | 11.65 ± 0.93 | <0.001 |
| Platelets x$10^3$ | 158.13 ± 24.95 [abc] | 146.33 ± 20.10 [bc] | 115.65 ± 21.47 [c] | 81.1 ± 12.90 | <0.001 |
| WBCs (c/ccm) | 8.28 ± 0.96 [bc] | 7.86 ± 1.09 [bc] | 5.14 ± 0.73 [c] | 3.90 ± 0.48 | <0.001 |
| ALT (IU/l) | 98.09 ± 14.94 [abc] | 78.90 ± 24.85[c] | 74.41 ± 17.22 [c] | 62.22 ± 11.70 | <0.001 |
| AST (IU/l) | 64.96 ± 12.23 [abc] | 92.90 ± 25.27 | 95.24 ± 15.13 [c] | 86.27 ± 11.73 | <0.001 |
| Albumen (g/dl) | 3.63 ± 0.15 [bc] | 3.57 ± 0.14 [bc] | 3.39 ± 0.19 [c] | 3.12 ± 0.13 | <0.001 |
| Bilirubin (mg/dl) | 1.33 ± 0.29 [bc] | 1.49 ± 0.30 [bc] | 2.18 ± 0.38 | 2.31 ± 0.36 | <0.001 |
| INR | 1.28 ± 0.09 [bc] | 1.31 ± 0.12 [bc] | 1.44 ± 0.13 [c] | 1.56 ± 0.14 | <0.001 |
| CTP class A | 23 (100) | 39 (100) | 10 (29.4) | 8 (19.5) | <0.001 |
| CTP class B | 0 (00) | 0 (00) | 24 (70.6) | 33 (80.5) | |
| CTP score | 5.39 ± 0.49 [bc] | 5.46 ± 0.50 [bc] | 6.65 ± 0.60 | 6.80 ± 0.40 | <0.001 |
| AFP (ng/ml) | 10.63 ± 2.50 [bc] | 13.76 ± 2.84 [bc] | 19.19 ± 6.68 [c] | 30.99 ± 10.61 | <0.001 |
| PCR $Log_{10}$ | 5.88 ± 0.40 [ac] | 5.49 ± 0.47 [b] | 5.87 ± 0.49 [c] | 5.55 ± 0.48 | <0.001 |
| FBS (mg/dl) | 96.22 ± 12.34 | 96.43 ± 12.79 | 95.08 ± 13.40 | 99.07 ± 12.03 | 0.57 |
| BMI (kg/$m^2$) | 22.85 ± 1.06 [c] | 22.21 ± 1.46 | 22.22 ± 1.29 | 21.85 ± 1.42 | 0.05 |

AFP: Alfa-fetoprotein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; CI: Confidence interval; CTP: Child-Turcotte-Pugh score; FBS: Fasting blood sugar; F: Fibrosis stage; Hb: Hemoglobin; INR: International normalization ratio; PCR: Polymerase chain reaction; WBCs: White blood cells; a: Significant difference from F2; b: Significant difference from F3; c: Significant difference from F4

**Table 2** Shows a comparison between the baseline parameters before and after hepatitis C clearance.

| Parameter | Before | After | P | 95% CI | |
|---|---|---|---|---|---|
| Hb (g/dl) | 12.29 ± 1.22 | 13.03 ± 0.93 | <0.001 | -0.84 | -0.64 |
| Platelets x $10^3$ | 121.19 ± 35.73 | 136.42 ± 29.53 | <0.001 | -17.58 | -12.88 |
| WBCs (c/cmm) | 6.07 ± 2.01 | 7.04 ± 1.82 | <0.001 | -1.31 | -0.62 |
| ALT (IU/l) | 76.01 ± 21.53 | 24.58 ± 8.07 | <0.001 | 47.64 | 55.23 |
| AST (IU/l) | 86.80 ± 20.19 | 32.94 ± 9.46 | <0.001 | 50.51 | 57.22 |
| Albumen (g/dl) | 3.42 ± 0.25 | 3.72 ± 0.32 | <0.001 | -0.35 | -0.28 |
| Bilirubin (mg/dl) | 1.88 ± 0.53 | 1.12 ± 0.33 | <0.001 | 0.68 | 0.83 |
| INR | 1.42 ± 0.17 | 1.21 ± 0.15 | <0.001 | 0.18 | 0.22 |
| CTP score | 6.15 ± 0.82 | 5.36 ± 0.59 | <0.001 | 0.66 | 0.91 |
| AFP (ng/ml) | 19.74 ± 10.47 | 13.26 ± 7.43 | <0.001 | 5.71 | 7.25 |
| FBS (mg/dl) | 96.85 ± 12.61 | 91.70 ± 9.63 | <0.001 | 2.62 | 7.68 |
| BMI (kg/$m^2$) | 22.21 ± 1.37 | 22.74 ± 1.32 | 0.001 | -0.61 | -0.44 |

AFP: Alfa-fetoprotein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; CI: Confidence interval; CTP: Child-Turcotte-Pugh score; FBS: Fasting blood sugar; Hb: Hemoglobin; INR: International normalization ratio; WBCs: White blood cells.

was done. Patients without fibrosis regression have baseline male sex predominance, lower mean Hb, WBCs, platelets count, ALT, AST, and serum albumen, and have a higher mean age, CTP score and class, INR, serum bilirubin, FIB-4, and liver stiffness measurement ($p < 0.05$), while there was no significant difference as regards the baseline viral load, FBS, and body mass index (BMI) (Table 3).

**Predictors for fibrosis regression**

By univariate analysis, age, gender, high serum aminotransferases, platelet count, serum albumin, bilirubin, and INR, Child-Pugh score, and fibrosis stage at baseline were independent predictors for fibrosis regression. However; with multivariate logistic regression analysis, gender, age, platelet count, serum bilirubin, Child-Pugh score, and fibrosis stage at baseline were the independent predictors for reversion of fibrosis (Table 4).

**Table 3** Shows a comparison between patients with and without fibrosis regression as regards baseline parameters

| Parameter | Fibrosis regression (n=80) | Fibrosis progression (n=35) | P |
|---|---|---|---|
| Sex: n (%) | | | |
| Male | 37 (46.3) | 28 (80) | 0.001 |
| Female | 43 (53.7) | 7 (20) | |
| Age (years) | 36.26 ± 9.49 | 47.03 ± 8.84 | < 0.001 |
| Hb (g/dl) | 12.34 ± 1.26 | 11.77 ± 0.98 | 0.01 |
| Platelets x$10^3$ | 122.19 ± 31.83 | 95.11 ± 27.05 | < 0.001 |
| WBCs (c/ccm) | 5.95 ± 1.94 | 4.97 ± 1.61 | 0.007 |
| ALT (IU/l) | 76.18 ± 21.18 | 62.51 ± 14.77 | < 0.001 |
| AST (IU/l) | 94.59 ± 20.03 | 83.49 ± 11.18 | < 0.001 |
| Albumen (g/dl) | 3.42 ± 0.23 | 3.19 ± 0.19 | < 0.001 |
| Bilirubin (mg/dl) | 1.88 ± 0.49 | 2.24 ± 0.42 | < 0.001 |
| INR | 1.40 ± 0.16 | 1.53 ± 0.13 | < 0.001 |
| CTP class A | 47(58.8) | 11 (31.4) | 0.007 |
| CTP class B | 33 (41.2) | 24 (68.6) | |
| CTP score | 6.12 ± 0.83 | 6.68 ± 0.47 | < 0.001 |
| AFP (ng/ml) | 18.26 ± 7.62 | 28.81 ± 12.53 | < 0.001 |
| PCR $Log_{10}$ | 5.59 ± 0.52 | 5.7 ± 0.45 | 0.27 |
| FIB-4 | 3.61 ± 1.53 | 5.76 ± 2.43 | < 0.001 |
| Liver stiffness (kPa) | 11.25 ± 3.70 | 16.29 ± 6.86 | < 0.001 |
| FBS (mg/dl) | 96.63 ± 12.04 | 98.08 ± 14.18 | 0.57 |
| BMI (kg/$m^2$) | 22.10 ± 1.45 | 22.08 ± 1.26 | 0.94 |

AFP: Alfa-fetoprotein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; CI: Confidence interval; CTP: Child-Turcotte-Pugh score; FBS: Fasting blood sugar; F: Fibrosis stage; Hb: Hemoglobin; INR: International normalization ratio; PCR: Polymerase chain reaction; WBCs: White blood cells

## DISCUSSION

In addition to the removal of the etiology behind chronic liver disease, the reversal of liver fibrosis remained as an ultimate goal of treatment in the management of chronic liver diseases. In the context of HCV infection, the recently introduces DAAs showed a high SVR with a wide range of safety. Also, they open the scope for treatment of cirrhotic patients who were not eligible for interferon-based

treatment.

The first observation in our study is the high degree of agreement between Fibroscan and FIB-4 test emphasizing the accuracy of Fibroscan is a non-invasive method for assessing liver fibrosis. This finding is in agreement with results obtained in previous researches[9-11].

In the current study, an SVR12 of 97.3%, emphasizing the potency of available DAAs in Egypt. Also, in the current study, the elimination of HCV resulted in improvement in liver fibrosis as measured by the FIB-4 test and liver stiffness measurement. Although the current DAAs were developed to treat HCV not to ameliorate liver fibrosis, the clearance of HCV resulted in amelioration of the necro-inflammatory process driven by viral replication. The necro-inflammatory reaction is the main drive for stellate cell trans-differentiation and laydown of collagen with fibrosis formation. However, this process doesn't resolve rapidly after treatment of HCV, but over a long period, emphasizing the importance of long-term follow-up after viral clearance[11,12].

In this regard, during the interferon era, the biggest histological study goes back to 2002 and incorporated the findings of four main prospective trials wherein patients obtained their repeat liver biopsy 6 months after interferon therapy was discontinued. Patients with an SVR had their fibrosis regressed among 50% of the F4 fibrosis stage[13].

Similarly, our findings are in agreement with different researches about fibrosis regression after DAAs. Martini et al. found that the achievement of an SVR was associated with improvement in fibrosis scores including APRI score, FIB-4 index, and LS by elastography at 48 weeks post-treatment. This improvement was obtained among 42% of F4 and 66.7% of F3 patients[14]. Also, in a meta-analysis and systematic review that included 24 studies, patients who achieved an SVR, compared to those who didn't, could obtain a 2.4 kPa decline in LS at the end of antiviral treatment, which increased to 4.1 kPa after one year. Moreover, this improvement was greater for DAAs-treated compared to interferon-treated patients[12]. Also, liver fibrosis declined after DAAs treatment in other studies as estimated by FIB-4, and APRI scores with a median decrease of 0.75 and 0.67 points respectively[15]. Many explanations have been proposed to explain the greater decline in LS after DAAs. This could be secondary to the rapid elimination of viremia after the commencement of DAAs, with an associated rapid decrease in the necro-inflammation and fibrogenesis. Also, the ability to treat cirrhotic patients and patients with higher stiffness with DAAs has led to a higher magnitude of stiffness amelioration[12].

We also found a fibrosis regression among 56.1% of patients with F4, and a cut-off value of 17.6 kPa was the point of no return for fibrosis regression among our cohort with high sensitivity and specificity. As long as fibrosis regression is not achieved in all patients with advanced fibrosis, long-term follow-up is still needed in a substantial group of patients who are at risk of ongoing liver disease progression, decompensation, and HCC. Identifying these groups is a cost-effective approach especially in limited-resource areas. From the clinical aspect, this suggests a point at which the clearance of HCV is too late and disease progression will still occur. This finding in our study is in agreement with the Baveno VI statement where patients with LS greater than or equal to 17 kPa are considered to have clinically significant portal hypertension and are indicated for maintained regular evaluation[16].

In our study, the changes in liver fibrosis measurement were reflected as clinical improvement in laboratory parameters. We observed an overall improvement in hemoglobin, platelets, WBCs, serum albumin, bilirubin, INR, liver aminotransferases, AFP, and FBS among patients who achieved an SVR12 and decline in LS. However; this was not evident in the CTP score due to selection criteria in our study. In agreement with our study, Attia et al. also observed a significant improvement in the aminotransferases after DAAs treatment[17]. Similarly, the fibrosis regression has been linked to a decrease in portal pressure on long term follow up, as well as a decrease in the rate of de novo emergence of HCC[18]. These data were confirmed in previous studies[4,14,19].

**Table 4** Shows the univariate and multivariate analysis for predictors of fibrosis regression.

| | Univariate analysis | Multivariate analysis | | |
|---|---|---|---|---|
| | P | P | OR | 95% CI |
| Age | <0.001 | 0.014 | 1.25 | 1.10 – 1.5 |
| Male sex | 0.001 | < 0.001 | 1.14 | -2.28 |
| ALT | 0.01 | 0.13 | - | - |
| AST | 0.001 | 0.89 | - | - |
| Platelets | <0.001 | < 0.001 | 0.39 | -0.04 |
| Albumen | <0.001 | 0.41 | - | - |
| Bilirubin | <0.001 | 0.02 | 4.7 | 1.62 – 1.93 |
| INR | <0.001 | 0.48 | - | - |
| CTP score | <0.001 | 0.04 | 0.81 | 0.02-1.60 |
| PCR | 0.27 | 0.78 | - | - |
| Baseline Fibrosis stage | <0.001 | 0.005 | 3.8 | 23.1-64.2 |

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CI: Confidence interval; CTP: Child-Turcotte-Pugh score; INR: International normalization ratio; OR: Odd's ratio; PCR: Polymerase chain reaction.

In the current study, gender, age, baseline platelet count, serum bilirubin, Child-Pugh score, and fibrosis stage could independently predict fibrosis reversion. Attia et al. also showed that baseline bilirubin, INR, and albumen were predictors for fibrosis reversion. [17] Besides, Soliman et al. concluded that LS, hepatic steatosis, and MBI were the independent predictors[20]. The influence of these factors in our cohort on the fibrosis dynamics could be attributed to their reflection on more fibrotic changes in the liver parenchyma. Elder age is related to longer disease duration before initiation of DAAs. Gender has been also linked to the rate of fibrosis progression[21]. Lastly, previous studies found that the rate of fibrosis regression is more evident in those with higher baseline fibrosis grade[12]. However, fibrosis regression can be influenced by other factors. Alcohol use, diabetes mellitus, and/or overweight can maintain hepatic inflammation and fibrosis following HCV eradication[22]. Recently, higher body mass index (BMI) was negatively associated with the post-SVR platelet count improvement among patients with advanced hepatic fibrosis[23,24].

***In conclusion***; obtaining an SVR after DAAs therapy is associated with regression of fibrosis. Fibrosis regression is more evident in the group of patients with early fibrosis at baseline.

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