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# Liver Stiffness Predicts Relapse after Direct Acting Antiviral Therapy Against Chronic Hepatitis C Virus Infection

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## Abstract

*Background:* Assessment of fibrosis in chronic hepatitis has always been considered of utmost relevance for patient care in clinical hepatology. Over the last years, multiple non-invasive methods were used for diagnosis of hepaic fibrosis, including transient Elastography in addition to clinical and biochemical parameters or combinations of both methods. Serum markers and elastography are considered useful techniques for diagnosing severe liver fibrosis and cirrhosis and for excluding significant fibrosis in hepatitis C virus infected patients. Also, liver stiffness may help to foretell treatment response to antiviral therapy.

*Aim of Study:* This study aimed to evaluate changes of Transient elastography values as well as serum fibronectin and AST to platelet ratio index in patients (APRI) treated with sofosbuvir-based treatment regimen.

*Methods:* This is a follow-up study including 100 chronic HCV Egyptian patients treated with Sofosbuvir-based treatment regimen. Transient elastography values were recorded as well as serum fibronectin and APRI were calculated at baseline and SVR12.

*Results:* There was a significant improvement of platelets counts, ALT and AST levels, which in turn cause significant improvement in APRI scores at SVR12. Liver stiffness measurements were significantly lower at SVR12 (15.40±8.96 vs. 8.82±4.74 kPa, $p$=0.000). There was significant decline in serum fibronectin from baseline to SVR 12 (524.14±237.61 vs. 287.48±137.67, $p$=0.000).

***Key Words:*** *Hepatitis C Virus – Liver stiffness – Transient Elastography – Fibronectin.*

## Introduction

**HEPATITIS C** Virus (HCV), and its long-term resultant consequences, is a major endemic medical health problem in Egypt. Having taken a representative sample of the country, from both urban and rural areas, an Egyptian demographic health survey conducted in 2008 concluded that 14.7% of the population have been infected, making this the highest prevalence in any population in the world [1,2]. In the Nile Delta and Upper Egypt, infection rates can be much higher at around 26% and 28%, respectively [3]. With incidence rates between 2 and 6 per 1000 every year, this leads to an estimated 170,000 new cases every year to add to the 11.5 million patients suffering from the disease [3].

Guidelines for the therapy of Chronic Hepatitis C (CHC) recommend evaluating liver fibrosis which helps in selecting treatment options and the perfect choice of treatment timing [4].

Achievement of a sustained viral response is associated with fibrosis regression even in patients with severe fibrosis and cirrhosis [5,6] suggesting that evaluation of fibrosis after antiviral therapy could be of clinical importance for the management of these patients.

Liver biopsy is considered the "gold standard" for the evaluation of hepatic fibrosis. In the last years, Transient Elastography (TE) and Magnetic Resonance (MR) Elastography have also been used as non-invasive tools for the diagnosis of hepatic fibrosis [7,8]. Additionally, transient elastometry represents a non-invasive tool to identify patients with persistent clinically significant portal hypertension after achieving SVR. However, the median levels of LS differ considerably between clinical trials and studies aimed at evaluating the efficacy and safety of therapy against HCV infection in patients with cirrhosis. In addition, response according to the level of LS have scarcely been analysed in cirrhotic subjects receiving DAA-based combinations, in spite of the fact that the degree of LS was independently associated with the likelihood to achieve SVR to dual therapy with Peg-IFN/RBV within this subset [9].

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Indirect markers" are combination of clinical and biochemical parameters not directly related to extracellular matrix metabolism which have been utilized for their ability to anticipate and differentiate different stages of liver fibrosis. Among them, Forns test, the AST-to-platelet ratio index (APRI) test and FibroTest (FT) have shown an acceptable diagnostic accuracy for the detection of significant and/or advanced degrees of fibrosis and cirrhosis **[10,11]**.

Fibronectin (FN) is a high-molecular weight (~440kDa) glycoprotein of the Extracellular Matrix (ECM) that binds to membrane-spanning receptor proteins called integrins **[12]**. FN is synthesized by many cell types. A large portion of circulating FN is produced by hepatocytes, in which it exists in two forms, termed cellular FN (cFN) and plasma FN (pFN). In healthy subjects, the human plasma FN level is ~300 ± 100 μg/ml **[13,14]**. pFN levels decrease over the course of acute and chronic hepatitis, and are associated with these levels of protease and activity, increased consumption of FN and the reduction of synthesis **[14]**.

## Patients and Methods

This is a follow-up study including 100 Chronic Hepatitis C (CHC) patients attending the outpatient clinics of the Tropical Medicine & Gastroenterology and the Internal Medicine Departments-Qena University Hospital. All eligible patients were included according to inclusion criteria approved by the National Committee for Control of Viral Hepatitis (NCCVH): Age 18-75 years, HCV RNA positivity, any BMI (weight in kilograms/squared height in meters), treatment-naïve patients only were included in this study. Exclusion criteria included HBV co-infection, HIV, decompensated liver cirrhosis, inadequately controlled diabetes mellitus (HbA 1 c >9%), hepatocellular carcinoma or extra-hepatic malignancy. Diagnosis of liver cirrhosis was on clinical basis involving laboratory tests and ultrasonography findings of liver cirrhosis and/or liver stiffness measurement ≥ 12.5kPa **[15]**.

Patients were subjected to history taking, clinical examination and routine laboratory work up. All patients underwent Transient Elastography (TE) within two weeks before treatment initiation as well as serum fibronectin measurement and APRI was calculated.

All study patients were treated with Sofosbuvir-based treatment regimens according to the approved treatment recommendation of EASL **[16]**. Patients were assessed for HCV RNA at week zero (baseline), end of treatment and 12-weeks after end of treatment (SVR12). Undetectable HCV RNA by quantitative polymerase chain reaction assay (Cobas Amplicor, HCV Roche, Branchburg, NJ, USA, V2.0, detection limit 15IU/mL) 12-weeks after end of treatment was defined as SVR12, which is the main indicator of successful treatment.

The study was approved by Ethical Committee of Qena Faculty of Medicine, South Valley University. Written informed consent was obtained from all patients before treatment.

*Laboratory tests:*

Complete blood cell counts, kidney and liver function tests together with HCV RNA by PCR were done for all patients participating in this study. HCV RNA by PCR was done again at end of treatment and SVR12.

Aspartate aminotransferase-to-platelet ratio index (APRI) was calculated using Wai's formula at baseline and SVR12 according to the following equation **[11]**:

(AST/upper limit of normal)/platelet count (expressed as platelets X $10^9$/L) X 100.

APRI cutoff greater than 1.0 predict cirrhosis while cutoff greater than 0.7 predict significant hepatic fibrosis **[17,18]**.

The Fibronectin enzyme-linked immunosorbent assay (ELISA; eBioscience, Vienna, Austria) uses a double-antibody sandwich ELISA to determine the level of human fibronectin in the samples. The serum samples, biotin-conjugate and standards were added to the wells, which were pre-coated with human fibronectin monoclonal antibody and allowed to incubate for 2h at 23ºC. Unbound material was washed out. Fibronectin combined with streptavidin-horseradish peroxidase (eBioscience, Vienna, Austria) were added to form an immune complex and were then allowed to incubate for 1h at 23ºC. Unbound material was washed out. Chromogen solution (eBioscience) was added and incubated for ~10min in the dark for the conversion of the colorless solution to a blue solution, the intensity of which was proportional to the quantity of fibronectin in the sample. Following the addition of the 100 μl acidic stop solution (eBioscience), the color changed to yellow. The intensity of the colored reaction product was measured using an automated ELISA reader (RT-1904C Chemistry Analyzer; Rayto, Atlanta, GA, USA) at 450nm. The results were expressed as ng/ml.

*Transient Elastography:*

Liver Stiffness (LS) measurements were done for all study patients with Transient Elastography

(Echosens, Fibroscan 502, Paris, France) using both the M and Xl probes. 10 valid measurements were done for every patient. The ratio of the valid measurements to total acquisitions numbers was used as an indicator for the success rate and median of liver stiffness expressed in kilopascals (kPa) was considered to be representative of the elastic modulus of the liver [19]. Reliable examination was considered if a success rate of 60% and interquartile range (variability in the validated measures) <30% of the median elasticity. All patients did ultrasound transient elastography examination at the start of treatment and at 12-weeks after end of treatment. Results of transient elastography were correlated to different stages of liver fibrosis according to the histological staging system of METAVIR. The used cut-off values were [20,21]:

- <7.1kPa=non-significant fibrosis (<F2).
- From ≥7.1 kPa to <9.5kPa=significant fibrosis (≥F2).
- ≥9.5kPa for advanced fibrosis (≥F3) and ≥12.5 kPa for cirrhosis (F4).

*Statistical analysis:*

Data was analyzed using SPSS advanced statistics Version 22 (SPSS Inc., Chicago, IL). Numerical data were described as mean, standard deviation or range and compared by Student's *t*-test. The Pearson's correlation coefficient was used to analyze the correlations between liver elastography values and APRI at baseline and SVR12. Stepwise multiple linear regression analysis was used to determine which variables at baseline of treatment were associated with improvement in liver stiffness measurement.

## Results

The demographic criteria of the studied patients showed a mean age of 45±12 years with male predominance (69%). 80% of the studied patients were noncirrhotic. Regarding Liver Stiffness (LS) measurement, 17% had non-significant fibrosis (<7.1kPa) (<F2), 12% had mild to significant fibrosis (≥7.1-<9.5kPa) (≥F2-<F3), 31% had advanced fibrosis (≥9.5kPa) (≥F3) and 40% of studied population had cirrhosis (≥12.5kPa) (F4). The mean value of liver stiffness measurement was 15.40±8.96kPa while the mean value of fibronectin level was 524.14±237.61 and the mean value of APRI was 0.91±0.62. At end of treatment, all patients were responders while 12-weeks after end of treatment, 94% of patients achieved SVR while 6% of patients were relapsers.

In all studied patients, there is significant decline in ALT, AST, APRI and serum fibronectin level from baseline to SVR 12 with statistically significant difference in noncirrhotic patients and at SVR 12 ($p$=0.000).

Significant decline in liver stiffness measurements was observed in all studied patients whether cirrhotic or not from baseline to SVR 12 with statistically significant difference at SVR 12 ($p$= 0.000).

There is significant improvement of platelets count in all studied patients with significant improvement in noncirrhotic and SVR12 patients ($p$=0.000). Our study results revealed strong positive correlation between serum fibronectin with ALT, AST, APRI score, liver stiffness and liver status (whether cirrhotic or not) while strong negative correlation was found between serum fibronectin with platelets' count and gender of the patient.

Liver stiffness measurements with a cutoff value 12Kpa was able to predict relapse among treated patients with AUC 0.90 and specificity of 85% together with AST (AUC 0.95 and specificity of 88%), ALT (AUC 0.80 and specificity of 94.6%) and baseline liver status (AUC 0.92 and specificity of 85%), all can predict relapse after treatment by DAAs.

Table (1): Demographic data in studied group.

| Demographics | Mean ± SD, (n %) |
|---|---|
| Age | 45±12 |
| *Sex, n (%):* | |
| Male | 69 |
| Female | 31 |
| *Presence or absence of baseline cirrhosis, n (%) :* | |
| Non-cirrhotic | 80 |
| Cirrhotic | 20 |
| *Baseline liver stiffness values in kPa, n (%):* | |
| >7.1kPa | 37 |
| ≤7.1kPa | 22 |
| ≤9.5kPa | 21 |
| ≤12.54kPa | 20 |
| *Baseline APRI, n (%):* | |
| <1 | 65 |
| >1 | 35 |
| Baseline liver stiffness measurement (kPa) | 9.03±5.49 |
| Baseline fibronectin level | 524.14±237.61 |
| Baseline APRI | 0.91±0.62 |
| *Response at 12-weeks after EOT (SVR12), n (%):* | |
| Sustained responders | 94 |
| Relapsers | 6 |

Table (2): ALT.

| | Total studied patients | Non-cirrhosis | Cirrhosis | Sustained responders | Relapsers |
|---|---|---|---|---|---|
| Baseline (Mean ± SD) | 40.83±15.46 | 36.98±14.13 | 56.25±10.08 | 39.63±14.80 | 59.67±14.25 |
| SVR12 (Mean ± SD) | 26.73±14.77 | 23.84±14.84 | 38.30±6.68 | 26.26±15.11 | 34.17±2.48 |
| *p*-value | 0.000 | 0.000 | 0.091 | 0.000 | 0.119 |

Table (3): AST.

| | Total studied patients | Non-cirrhosis | Cirrhosis | Sustained responders | Relapsers |
|---|---|---|---|---|---|
| Baseline (Mean ± SD) | 44.54±17.04 | 39.86±13.89 | 63.25±15.78 | 42.68±15.67 | 73.67±9.95 |
| SVR12 (Mean ± SD) | 27.37±11.81 | 25.68±11.02 | 34.15±12.68 | 27.85±11.96 | 19.83±5.12 |
| *p*-value | 0.000 | 0.000 | 0.978 | 0.000 | 0.635 |

Table (4): Platelets.

| | Total studied patients | Non-cirrhosis | Cirrhosis | Sustained responders | Relapsers |
|---|---|---|---|---|---|
| Baseline (Mean ± SD) | 156.25±61.65 | 171.69±59.20 | 94.50±14.59 | 159.63±61.89 | 103.33±20.90 |
| SVR12 (Mean ± SD) | 208.42±59.90 | 223.19±57.18 | 149.35±22.60 | 210.98±60.81 | 168.33±14.72 |
| *p*-value | 0.000 | 0.000 | 0.360 | 0.000 | 0.790 |

Table (5): Liver stiffness (Elastography).

| | Total studied patients | Non-cirrhosis | Cirrhosis | Sustained responders | Relapsers |
|---|---|---|---|---|---|
| Baseline (Mean ± SD) | 9.03±5.49 | 6.66±2.88 | 18.47±2.20 | 8.51±5.19 | 17.08±3.57 |
| SVR12 (Mean ± SD) | 7.09±3.97 | 5.47±2.23 | 13.60±2.37 | 6.60±3.48 | 14.83±3.13 |
| *p*-value | 0.000 | 0.000 | 0.157 | 0.000 | 0.031 |

Table (6): Fibronectin level.

| | Total studied patients | Non-cirrhosis | Cirrhosis | Sustained responders | Relapsers |
|---|---|---|---|---|---|
| Baseline (Mean ± SD) | 524.14±237.61 | 478.17±211.45 | 708±252.60 | 518.23±228.05 | 616.67±373.72 |
| SVR12 (Mean ± SD) | 287.48±137.67 | 256.35±121.16 | 412±131.57 | 279.77±134.24 | 408.33±146.34 |
| *p*-value | 0.000 | 0.000 | 0.598 | 0.000 | 0.963 |

Table (7): APRI.

| | Total studied patients | Non-cirrhosis | Cirrhosis | Sustained responders | Relapsers |
|---|---|---|---|---|---|
| Baseline (Mean ± SD) | 0.91±.62 | 0.71±0.47 | 1.71±0.49 | 0.85±0.57 | 1.86±0.51 |
| SVR12 (Mean ± SD) | 0.38±0.24 | 0.33±0.21 | 0.59±0.24 | 0.39±0.25 | 0.30±0.08 |
| *p*-value | 0.000 | 0.000 | 0.750 | 0.000 | 0.942 |

Table (7): Association of baseline serum fibronectin with baseline demographic factors in the study population.

| Variable | Fibronectin |
|---|---|
| Spearman's r | *p*-value |
| –0.640 | 0.000 |
| 0.572 | 0.000 |
| 0.614 | 0.000 |
| –0.627 | 0.000 |
| 0.655 | 0.000 |
| 0.541 | 0.000 |
| 0.364 | 0.000 |

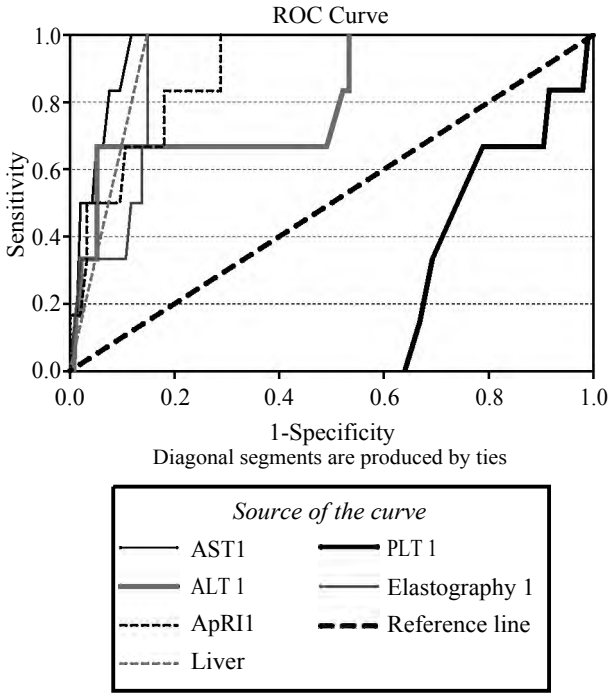


Fig. (1): ROC curve showing predictors of relapse after treatment.

## Discussion

Non-pegylated interferon (IFN) or pegylated IFN (PEG-IFN) in combination with ribavirin (RBV) were the main drugs used for the management of HCV infection [22,23]. In 2011, the use of the first-generation direct acting antivirals (DAAs) boceprevir and telaprevir with PEG-IFN and RBV increased the overall SVR rates to 68%-75% for naive patients and to 59%-88% for treatment-experienced patients, even if these regimens were used only for the treatment of genotype 1 HCV infection [24,25].

Despite the positive effect of HCV infection eradication on patients' prognosis, few data about liver cirrhosis/fibrosis regression are accessible. Liver fibrosis regression as a consequence of viral eradication is supported by the reduction of inflammatory mediators that leads to apoptosis of myofibroblasts, and occurs by the inactivation of stellate cells. The downregulation of inflammation, as well as hepatocyte regeneration, microvascular remodeling and degradation of extracellular matrix lead to the generation of new hepatic tissue [26].

Our study showed improvement of liver stiffness measurements 12 weeks after end of treatment as well as significant improvement in AST, ALT and platelets count with subsequent improvement of APRI score which signifies notable improvement of hepatic necroinflammation and fibrosis following antiviral treatment.

This was in accordance with Bachofner et al., who reported that patients with SVR after DAA therapy showed significant regression of TE values and rapid decrease in TE was in concordance with regression of APRI fibrosis score [27]. Also our results agreed with Elsharkawy et al., 2017 who revealed that Sofosbuvir-based treatment resulted in a clinically significant improvement in parameters of liver fibrosis [28].

This study showed significant improvement in serum fibronectin levels after antiviral treatment with statistically significant difference in SVR12 patients.

Due to the high response rates of DAA-based regimens, few studies have addressed the impact of liver stiffness on relapse rates with DAA regimens. Our study results revealed that high Liver Stiffness (LS) was able to predict relapse among DAA treated patients with a cutoff value 12Kpa and this was in agreement with Neukam et al., who declared that the degree of LS impacts on the relapse rate to DAA-based therapy in the clinical practice. However in Neukam et al., 2017 study, LS measurements more than 2 1Kpa was associated with relapse which can be explained by the large number of cirrhotic patients who were included in his study [29]. We also found that each of ALT, AST and baseline liver status (cirrhotic or noncirrhotic) can predict relapse in HCV treated patients.

In conclusion, compared to pre-treatment values, SVR12 LS scores are significantly reduced which reflects improved liver fibrosis parameters with available DAAs. Also, high LS measurements before treatment can be a predictor of relapse and so LS can be used to guide treatment duration by prolonging duration of treatment but more trials are needed.

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# صلابة الكبد تتنبآ بالإنتكاسة بعد العلاج المباشر المضاد للفيروسات ضد الإلتهاب الكبدى الفيروسى (سى) المزمن

المقدمة والهدف من البحث: إن تقييم التليف فى حالات إلتهاب الكبد المزمن يعتبر ذو آهمية قصوى فى علاج ومتابعة هذه الحالات. وعلى مدى السنوات الآخيرة، تم إستخدام العديد من الطرق غير الغازية لتشخيص تليف الكبد، بما فى ذلك Elastography بالإضافة إلى المعلمات السريرية والكيميائية الحيوية آو مزيج من كلتا الطريقتين. هذا وتعد علامات المصل elastography تقنيات مفيدة لتشخيص تليف الكبد كما تساعد على إستبعاد وجود التليف فى المرضى المصابين بفيروس إلتهاب الكبد (سى). آيضا، بالإضافة إلى آن قياس تصلب الكبد يساعد على التنبؤ بالإستجابة للعلاج المضاد للفيروسات. لقد هدفنا من خلال هذا البحث إلى تقييم التغيرات فى قيم elastography وكذلك فبرونيكتين فى الدم ومؤشر إنزيم الكبد AST إلى نسبة الصفائح الدموية فى المرضى الذين يتم علاجهم بالعلاج القائم ع عقار السوفوسبوفير.

هذه دراسة متابعة تشمل ١٠٠ مريض مصاب بمرض إلتهاب الكبد الفيروسى (سى) المزمن الذين تذ علاجهم بنظام العلاج القائم على السوفوسبوفير وتم تسجيل قيم elastography وكذلك تم حساب نسبة فبرونيكتين ومؤشر إنزيم الكبد AST إلى نسبة الصفائح الدموية فى بداية العلاج وبعد إنتهاء العلاج ب ١٢ إسبوع.

نتائج الدراسة: كان هناك تحسن كبير فى عدد الصفائح الدموية، ومستويات إنزيمات الكبد ALT وAST، مما يؤدى بدوره إلى حدوث تحسن كبير فى درجات مؤشر إنزيم الكبد AST إلى نسبة الصفائح الدموية (APRI) عند الإسبوع الثانى عشر بعد إنتهاء العلاج كما كانت قياسات تصلب الكبد آقل بكثير عند الإسبوع الثانى عشر بعد إنتهاء العلاج 15.40±8.96 مقابل 8.82±4.74 كيلو باسكال. كما وجد إنخفاضا كبيرا فى نسبة فيبرونكتين بالدم من بداية العلاج (524.14±237.61) مقابل (287.48±137.67, $p$=0.000).