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Original Article

# FibroScan, APRI, FIB4, and GUCI: Role in prediction of fibrosis and response to therapy in Egyptian patients with HCV infection

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ABSTRACT

*Background and study aims:* Multiple noninvasive methods have been used successfully in the prediction of fibrosis. However, their role in the prediction of response to hepatitis C virus (HCV) antiviral therapy is debatable. The aim of this study was to validate and compare the diagnostic performance of FibroScan, APRI (aspartate aminotransferase (AST)-to-platelet ratio index), FIB4, and GUCI (Göteborg University Cirrhosis Index) for the prediction of hepatic fibrosis and treatment outcome in HCV-infected patients receiving pegylated interferon and ribavirin (PEG-IFN/ribavirin).

*Patients and methods:* This study included 182 Egyptian patients with chronic HCV infection. They were classified into two groups based on the stages of fibrosis: mild to significant fibrosis (F1–F2) and advanced fibrosis (F3–F4). The APRI, FIB4, and GUCI scores were calculated before the antiviral treatment. The FibroScan was performed for all patients before treatment.

*Results:* Stiffness and FIB4 have greater sensitivity and specificity in detecting advanced fibrosis of 80%, 77% and 88%, 84%, respectively. Based on multivariate regression analysis, FIB4, body mass index (BMI), and alpha-fetoprotein (AFP) level were found to be statistically significant predictors of advanced fibrosis ($p$-value: 0.000, 0.011, and 0.001, respectively) with odds ratio (OR: 3.184, 1.170, and 1.241, respectively). With respect to virological response, the stiffness, APRI, FIB4, and GUCI were significantly lower in sustained virological responders. However, these are not good predictors of response to PEG-IFN/ribavirin therapy. AFP was the only statistically significant predictor of response ($p = 0.002$) with OR of 1.141 in multivariate regression analysis.

*Conclusion:* FibroScan and noninvasive scores such as APRI, FIB4, and GUCI can be used as good predictors of liver fibrosis in chronic hepatitis C. However, they are not good predictors of response to PEG-IFN/ribavirin therapy.



## Introduction

Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease worldwide. The long-term impact of HCV infection varies, from minimal histological changes to advanced fibrosis with or without hepatocellular carcinoma (HCC) [1].

About 160 million people worldwide are known to be chronically infected, although most are unaware of their infection [2].

Until 2011, the combination of pegylated interferon (PEG-IFN)-α and ribavirin for 24 or 48 weeks was the approved treatment for chronic hepatitis C (CHC) [3]. With recent advances, many direct antiviral agents (DAA) have been developed, which show potential therapeutic effect in HCV infection [4].

Despite the emergence of the new oral directly acting antiviral agents (DAAs), the PEG-IFN/RBV combination remains a part of the triple therapy with sofosbuvir in Egypt according to the national guidelines, which is available in limited amounts and at high costs. Thus, the predictors of response to PEG-IFN/ribavirin therapy must be explored for better selection of patients receiving triple therapy and for better response using simple, easily used and calculated noninvasive measures.

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Several laboratory tests, scores, and indices have been proposed for noninvasive prediction of hepatic fibrosis in HCV-infected patients. Amongst these, aspartate aminotransferase (AST)-to-platelet ratio (APRI), FIB4, and Göteborg University Cirrhosis Index (GUCI) are based on routine laboratory parameters and are readily available in clinical practice with significant accuracy for diagnosing hepatic fibrosis [5].

The aim of the present study was to evaluate the role of FibroScan, APRI, FIB4, and GUCI as predictors of liver fibrosis in patients with chronic HCV infection, as well as to assess the value of these noninvasive measures in the prediction of virological response to PEG-IFN/ribavirin therapy in Egyptian patients with chronic HCV infection.

## Patients and methods

### *Patient population*

This study enrolled 182 patients with chronic HCV infection who underwent antiviral treatment as part of the national programme for combating viral hepatitis in Egypt. Patients were subjected to history taking, clinical examination, and routine pretreatment laboratory workup. The diagnosis of CHC was established by the presence of HCV RNA using polymerase chain reaction (PCR) assays. All patients underwent a pretreatment liver biopsy within 6 months before the initiation of therapy. All patients underwent a pretreatment FibroScan examination, and their fibrosis scores were calculated. Patients with HCV genotype other than genotype 4, chronic liver disease other than HCV, decompensated liver cirrhosis, HCC, and liver biopsy contraindication, and those unsuitable for the combined interferon and ribavirin treatment due to persistent haematological abnormalities were excluded from the study.

All patients received the standard of care with weekly pegylated interferon plus ribavirin for 48 weeks. Peg-interferon alfa-2b (Peg-Intron-MSD) in a dose of 1.5 mg/kg subcutaneous injection once/week and ribavirin (Rebetol, MSD) (SOC) as ribavirin dose determined by patient weight <75 kg = 1,000 mg/day; ⩾75 kg = 1,200 mg/day in two separate oral doses after meals in the morning and at night for 48 weeks and all patients were adherent to treatment and follow up.

Sustained virological response (SVR) was defined by undetectable serum HCV RNA by qualitative PCR assay (Cobas Amplicor, HCV Roche, Branchburg, NJ, USA, v 2.0, detection limit 50 IU/mL) 24 weeks after the end of therapy.

The study was conducted according to the principles of the Declaration of Helsinki. Institutional Review Board (IRB) approval was obtained before the study was begun, and signed informed consent was obtained from all study patients.

### *Laboratory tests and calculated scores*

Pretreatment blood samples were collected, and laboratory tests in the form of complete blood cell counts, liver function test, kidney function test, and alpha-fetoprotein (AFP) in addition to the HCV PCR were performed. A HCV PCR reaction was carried out again at the end of treatment and 6 months after.

AST-to-platelet ratio index, FIB4 score, and GUCI were calculated according to the following equations:

- The APRI score was calculated using Wai's formula [6]:
  (AST/upper limit of normal)/platelet count (expressed as platelets $\times 10^9$/L) $\times$ 100.
- The FIB4 score was calculated using Sterling's formula [7]:
  Age (years) $\times$ AST (IU/L)/platelet count ($\times 10^9$/L) $\times \sqrt{}$ALT (IU/L)).
- GUCI was calculated using the equation [8]:

  Normalized AST $\times$ INR $\times$ 100/platelet count ($\times 10^9$/L).

### *Histological classification*

Ultrasound-guided percutaneous liver biopsy was performed using 16-guage semiautomated biopsy needles. The biopsy specimens were subject to histopathological examination. First, liver specimens of a minimum of 15-mm length with at least four portal tracts were fixed in 10% neutral formalin, processed, and then embedded in paraffin. The sections were stained with haematoxylin–eosin and Masson's trichrome for the detection of fibrosis. Histopathological examination according to the METAVIR scoring system demonstrated different stages of fibrosis (F0–F4) and grades of necroinflammatory changes activity (A0–A3) [9]. The histopathological examination of all liver biopsy samples was performed by a single expert pathologist. Patients were further grouped according to the degree of hepatic fibrosis: (i) mild to significant fibrosis ⩽F2 and (ii) advanced fibrosis >F2.

### *FibroScan (ultrasound transient elastography)*

Liver stiffness measurements were performed for all patients using FibroScan® (ECHOSENSE, FIBROSCAN 502, Paris, France) at the Kasr Alainy Viral Hepatitis Center, Cairo University. Ten valid measurements were performed, and the median of liver stiffness expressed in kilopascals (kPa) was reported [10]. Only examinations with a success rate of >60% and an interquartile range (IQR) <30% were included in this study and were considered reliable. The cutoffs described in Ref. [11] were used as follows:

>5.5 kPa = F0
5.5–5.9 = F0–F1
6–6.9 = F1
7–8.7 = F1–F2
8.8–9.4 = F2
9.5–12.4 = F3
12.5–14.4 kPa = F3–F4
⩾14.5 = F4

### *Statistical analysis*

The data of all patients were tabulated and processed using SPSS version 10.0 for Windows XP (SPSS, Chicago, IL, USA). The quantitative data were described as mean, standard deviation, or range, and then compared by Student's *t*-test. Pearson's correlation was conducted to correlate continuous parameters.

Multivariate forwards stepwise binary logistic regression analysis with significant fibrosis (⩾F2), advanced fibrosis (⩾F3), and cirrhosis (F4) – as the dependent factor – were performed in comparison to the selected scores. The receiver–operator curve (ROC) was generated by plotting the relationship of the true positivity (sensitivity) and the false positivity (1 − specificity) at various cutoff points of the tests. An area under the ROC (AUC) of 1.0 is characteristic of an ideal test, whereas 0.5 indicates a test of no diagnostic value. Considering sensitivity and specificity, the cutoff points were selected according to the maximum values of sensitivity and specificity. The diagnostic accuracy, sensitivity, specificity, and positive and negative predictive values were also calculated. A $p$-value < 0.05 was considered significant.

## Results

A statistically significant difference was noted between both fibrosis groups in terms of age, BMI, AST, alanine transaminase