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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

Table 1
Demographics and laboratory data of studied groups.

	⩽F2 (Mean ± SD, %)	>F2 (Mean ± SD, %)	*p*-Value
Sex			0.181
Male	72.1%	61.4%	
Female	69.1%	30.9%	
Age (years)	38.5 ± 10.4	44.818 ± 8.8745	0.000
BMI (kg/m^2)	27.3689 ± 3.97046	29.6925 ± 4.01959	0.001
HCV RNA PCR (IU/ml)	893 015.72 ± 1571 254.86	347 974.86 ± 536 542.77	0.23
AST (U/L)	45.13 ± 25.593	88.18 ± 53.619	0.000
ALT (U/L)	53.44 ± 36.891	91.82 ± 67.904	0.000
ALB (gm/L)	4.270 ± 0.4768	4.164 ± 0.4671	0.205
Total bilirubin (mg/dl)	0.837 ± 0.3466	0.939 ± 0.3363	0.039
PC (%)	88.804 ± 9.1359	83.841 ± 11.3546	0.09
INR	1.0819 ± 0.11235	1.1411 ± 0.15369	0.011
Creat. (mg/dl)	0.962 ± 0.2109	0.940 ± 0.2253	0.380
HB (g/dl)	14.102 ± 1.5565	14.280 ± 1.7243	0.523
TLC	6541.18 ± 2122.768	6484.09 ± 2543.111	0.693
PLT (10^3/mm^3)	223,617.65 ± 61,196.231	176,681.82 ± 61,184.347	0.001
AFP (ng/ml)	2.974 ± 2.3949	9.559 ± 8.6411	0.001
Stiffness	6.502 ± 2.2458	18.686 ± 10.8386	0.000
FIB4	1.1932 ± 0.7150	2.5956 ± 1.537	0.000
APRI	0.5505 ± 0.37479	1.44 ± 1.180	0.000
GUCI	0.5966 ± 0.4154	1.7368 ± 1.5887	0.000

(ALT), total bilirubin, international normalized ratio (INR), platelets, and AFP. However, this relation was insignificant in terms of sex, albumin, haemoglobin, and total leukocytic count (Table 1).

According to the results of the liver biopsy, 75.5% of the studied population had liver fibrosis ⩽F2, whereas 24.5% of the studied population had advanced fibrosis >F2 (Table 1).

Liver stiffness and noninvasive scores such as APRI, FIB4, and GUCI were significantly elevated with advanced fibrosis and cirrhosis (Table 1).

An ROC curve was constructed to evaluate the diagnostic accuracy of the different noninvasive methods for predicting advanced fibrosis. The AUC for liver stiffness, FIB4, APRI, and GUCI were 0.90, 0.85, 0.82, and 0.82, respectively, with a p-value < 0.01 for all methods (Fig. 1).

The best cutoff levels for liver stiffness, FIB4, APRI, and GUCI for the prediction of advanced fibrosis were 8.75, 1.67, 0.7, and 0.69, respectively, with sensitivity of 80%, 77%, 73%, and 75%, respectively, and specificity of 88%, 84%, 82%, and 77%, respectively (Fig. 1).

According to the results of the univariate analysis, variables were selected for multivariate regression analysis for the prediction of advanced fibrosis (>F2). FIB4, BMI, and AFP 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) (Table 3).

Six months after the end of treatment, 97 patients showed SVR and 85 patients were nonresponders. No statistically significant difference was found between both responders and nonresponders in terms of age, BMI, sex, and laboratory results, except for thee AST and AFP levels being higher in nonresponders (Table 2).

Nonresponders were significantly more amongst those with advanced stage of fibrosis.

Amongst the different noninvasive methods used (liver stiffness or the calculated scores), only the liver stiffness measurement showed statistically significant difference between responders and nonresponders, which was higher in the latter (Table 2).

The ROC curve was designed to test which noninvasive method could predict the SVR. FIB4, APRI, GUCI, and liver stiffness were not good predictors of virological response with AUROC (0.54, 0.57, 0.57, and 0.59 and p-values of 0.33, 0.08, 0.10, and 0.026, respectively) (Fig. 2).

According to the results of the univariate analysis, variables were selected for multivariate regression analysis for the prediction of virological response. AFP was found to be the only statistically significant predictor of response (p-value 0.002) with odds ratio (OR 1.141) (Table 4).

Discussion

HCV infection is one of the main causes of chronic liver disease worldwide. In Egypt, which has the highest prevalence of chronic HCV, the treatment poses an economic burden on the government [12]. Despite the emergence of new oral antiviral treatments (DAAs), we use PEG-IFN-α/ribavirin as part of triple therapy according to the approved treatment recommendation (EASL 2014) [2] and protocol previously approved by the National Committee for Control of Viral Hepatitis, due to limited amounts and high costs of these new oral antiviral treatments.

Our study aims to evaluate the accuracy of several noninvasive methods for the prediction of hepatic fibrosis severity and treatment outcome in HCV-infected patients receiving PEG-IFN/ribavirin.

Our study showed that older ages were associated with more advanced liver fibrosis. This was in agreement with a previous study that reported the correlation between the rate of fibrotic progression and an older age of onset of infection, irrespective of the duration of infection [13].

Many studies have proposed using multiple scores based on a combination of direct and indirect serum markers such as APRI, FIB4, and GUCI. This is because these markers can be easily calculated from basic inexpensive laboratory equipment; are noninvasive, easily available, accurate, and reproducible; have a role in the staging of fibrosis and tracking of disease progression; and are not susceptible to false-positive results [14,18].

Our study reported that amongst patients with advanced fibrosis (>F2), liver stiffness, pretreatment AST, ALT, and INR were significantly elevated, whereas lower platelet count was associated with advanced fibrosis. As these parameters were used to calculate APRI, FIB4, and GUCI, these scores were significantly elevated with advanced fibrosis and cirrhosis as reported in previous studies [18,19].

Our study showed that FibroScan was the efficient predictor of advanced fibrosis with AUROC 0.9 as reported in other studies [15,16]. FIB4 was the next most efficient predictor with AUROC 0.85, in line with other studies [17,18]. Then APRI and GUCI were

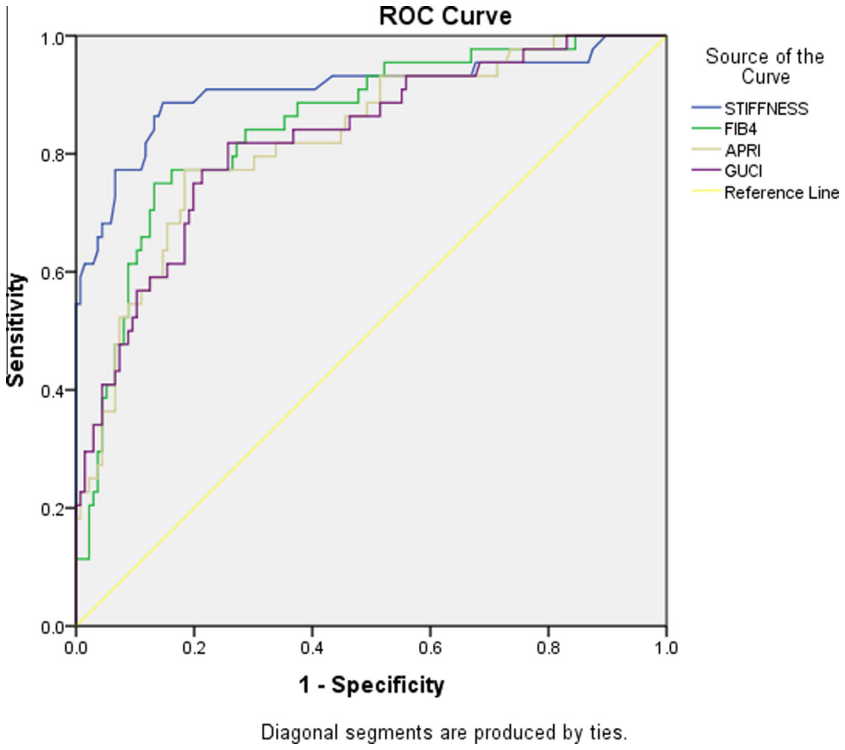

Fig. 1. Receiver–operator curve (ROC) curve of advanced fibrosis and cirrhosis for stiffness. GUCI, aspartate aminotransferase-to-platelet ratio index (APRI) and FIB-4.

Table 2
Clinical characteristics according to virological response in the studied patients.

	Sustained responders (97.53%)	Nonresponders (85.47%)	*p*-Value
Demographics			
Age (years)	40.4 ± 10.48	39.65 ± 10.54	0.629
BMI (kg/m^2)	27.1 ± 4.17	28.19 ± 4.02	0.541
Sex			0.216
Male	73.2% (71)	64.7% (55)	
Female	26.8% (26)	35.3% (30)	
Laboratory			
AST (U/L)	48.68 ± 28.21	63.6 ± 47.23	0.038
ALT (U/L)	56.08 ± 39.43	70.68 ± 56.99	0.145
ALB (gm/L)	4.26 ± 0.49	4.21 ± 0.47	0.486
TBIL (mg/dl)	0.84 ± 0.3	0.89 ± 0.39	0.353
PC (%)	88.06 ± 9.82	87.23 ± 10.03	0.565
INR	1.09 ± 0.12	1.11 ± 0.13	0.137
Creat. (mg/dl)	0.98 ± 0.21	0.93 ± 0.21	0.127
HB (g/dl)	14.15 ± 1.52	14.1 ± 1.71	0.815
TLC	6453 ± 2294	6604 ± 2136	0.605
PLT (10^3/mm^3)	214,371 ± 66,634	211,306 ± 62,417	0.982
AFP (ng/ml)	3.28 ± 2.68	6.06 ± 7.23	0.004
Stiffness	7.99 ± 5.31	11.24 ± 9.47	0.026
FIB4	1.4 ± 0.87	1.68 ± 1.38	0.338
APRI	0.63 ± 0.46	0.92 ± 0.98	0.081
GUCI	0.7 ± 0.57	1.07 ± 1.28	0.103
⩽F2	81.4%	68.7%	0.047
>F2	18.6%	31.3%	

Table 3
Multiregression analysis for prediction of advanced fibrosis.

	p-Value	OR	95% CI for OR	
			Lower	Upper
FIB4	0.000	3.184	1.882	5.384
BMI	0.011	1.170	1.036	1.320
AFP	0.001	1.241	1.087	1.417

efficient in predicting advanced fibrosis as reported in other studies [6,18,20].

Liver stiffness, FIB4, APRI, and GUCI were significant in univariate analysis. However, FIB4 remained the only noninvasive score with a significant role in the prediction of advanced fibrosis by multivariate logistic regression analysis.

Several factors have been identified as predictors of SVR amongst patients receiving PEG-IFN/ribavirin, including HCV genotype, viral load, age, BMI, and baseline ALT and AFP levels [21,22].

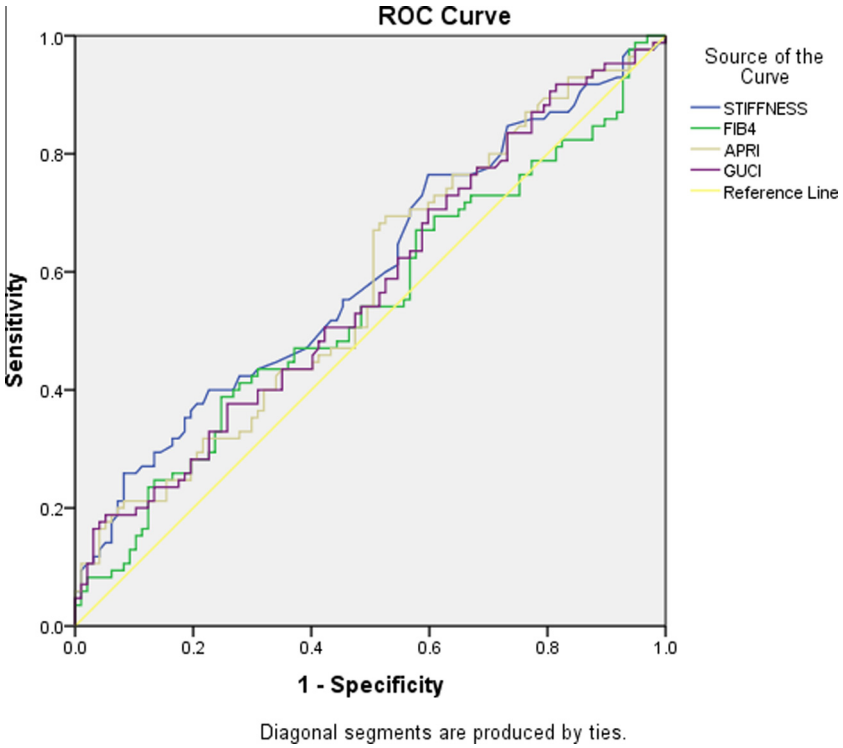

Fig. 2. Receiver–operator curve (ROC) curve of different scores such as stiffness, APRI, FIB4, and GUCI for evaluation as predictors of response.

Table 4
Multiregression analysis for predication of virological response.

	p-Value	OR	95% CI for OR	
			Lower	Upper
AFP	0.002	1.141	1.048	1.242

In our study, the pretreatment AST level was significantly lower amongst patients who achieved SVR than amongst nonresponders. This finding supports the correlation between the progression of histological activity and hepatic fibrosis, as AST is a better predictor of histological activity than ALT [23,24].

The pretreatment AFP level was significantly lower amongst patients who achieved SVR than amongst nonresponders, as reported by Abdo and Sanai in 2009. They concluded that a higher AFP level was associated with a negative treatment outcome in CHC patients of genotype 4 [25] and that AFP significantly predicted the virological response by multivariate logistic regression analysis. This was also reported by Esmat et al.; they concluded that AFP was a good predictor of complete early virological response (cEVR) and hence SVR in CHC patients of genotype 4 [26]. El Raziky et al. performed a similar study, proving AFP to be a significant predictive factor of treatment response [27].

The pretreatment liver stiffness was significantly lower amongst patients who achieved SVR than amongst nonresponders. It is well known that liver fibrosis is a host factor consistently associated with response rates to IFN-based therapies. Thus, patients with fibrosis stages ($\leqslant$F2) have a higher chance of SVR than patients with advanced liver fibrosis (>F2) do, as reported in several studies [27–29]. Based on univariate analysis, liver stiffness was found to be significant. However, the multivariate analysis did not augment this relation, and liver stiffness was not a good predictor of SVR in our study. Our results were in disagreement with previous studies that reported FibroScan as a predictor of virological response [30–32]. The difference between our results and previous findings may be due to the small number of patients in our study with different genotypes.

Although the pretreatment FIB4, APRI, and GUCI values were lower amongst patients who achieved SVR than amongst nonresponders, this relation was not statistically significant. According to both univariate and multivariate analyses, none of these noninvasive scores could be a predictor of virological response. Nevertheless, few studies have explored the use of noninvasive tests for the prediction of viral response in HCV-infected patients receiving PEG-IFN/ribavirin. In their study, Thandassery et al. concluded that APRI, FIB4, GUCI, and other noninvasive liver fibrosis scores had low predicative accuracy to treatment response [33]. Other studies reported that the APRI score was not a strong predictor of virological response [21,30,34]. These indirect scores might have been influenced by the inflammatory activity, as they are usually based on aminotransferase levels. They possibly reflect changes in necroinflammatory activity in the liver, which might have limited these scores as predictors of virological response in our study [35].

However, in a previous study, Ogawa et al. showed that noninvasive fibrosis assessments (FibroScan, APRI, FIB4) are valuable in predicting SVR by prior partial or null responders in telaprevir-based triple therapy [36]. The difference between our results and those of Ogawa et al. may be due to the different therapy regimens, as telaprevir was later added on to the usual PEG-IFN/ribavirin. This difference may also be due to the presence of different types of patients with different genotypes.

All of these results should spur further studies into noninvasive methods for proper use in different clinical aspects.

In conclusion FibroScan and noninvasive scores such as APRI, FIB4, and GUCI can be used as good predictors of liver fibrosis in CHC, which can minimize the need for liver biopsy. However, they are not good predictors of response to PEG-IFN/ribavirin therapy. Further studies including a combined use of these scores with FibroScan or the use of direct markers are needed to enhance the diagnostic reliability of these methods. These methods may be

used to accurately assess liver fibrosis to predict the virological response before initiation of treatment with new anti-HCV treatment (DAAs).

Conflict of interest

The authors declared that there was no conflict of interest.

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