Dynamics of APRI and FIB-4 in HCV cirrhotic patients who achieved SVR after DAA therapy

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Abstract. There are limited data available on the regression of fibrosis in hepatitis C virus (HCV) patients who have achieved sustained virologic response (SVR) after interferon-free treatments. Moreover, a perfect method for assessing liver fibrosis and its dynamics has not been established yet. The main objective of this study was to evaluate the dynamics of aspartate aminotransferase to platelet ratio index (APRI) and Fibrosis-4 (FIB-4) scores in patients with HCV who registered SVR. We performed ROC curve analysis to evaluate the diagnostic performance of APRI and FIB-4 scores in determining the presence of cirrhosis in comparison to FibroTest. In total 251 patients were enrolled: 164 cirrhotic and 83 non-cirrhotic patients, and they were evaluated at baseline, at 6 and at 12 months post-end of treatment (EOT). In the cirrhotic group, at baseline, there was a weak but statistically significant correlation between APRI and FibroTest (τ=0.173, P=0.001), as well as between FIB-4 and FibroTest (τ=0.265, P<0.001). At the 6-month follow-up, APRI no longer correlated with FibroTest (τ=0.144, P=0.057), while FIB-4 was correlated (τ=0.256, P=0.001). The same pattern was shown at 12 months post-EOT. Between baseline and the 6-month evaluation, there was a significant decrease in APRI (P<0.001) and FIB-4 (P<0.001) scores, but for the next follow-up period, there was no reduction. In the non-cirrhotic group, APRI and FIB-4 did not correlate with the FibroTest value at any of the evaluation times. There was a significant difference between baseline and the 6-month visit for APRI (P=0.01) and for FIB-4 (P=0.014). The areas under the receiver operating characteristics curve (AUROCs) for the presence of cirrhosis compared with FibroTest for APRI and FIB-4 were 0.682 [95% confidence interval (CI), 0.613-0.752] and 0.693 (95% CI 0.625-0.76). Both APRI and FIB-4 prove to be easy, quick and inexpensive tools for screening HCV cirrhosis, with moderate diagnostic accuracy and FIB-4 can be useful for monitoring patients post-EOT.

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Introduction

Since November 2015, direct-acting antiviral (DAA) based regimens have been used in Romania for treating patients with hepatitis C virus (HCV) infection. The patients with liver cirrhosis were treated during the first year that the protocol was being implemented in Romania (1,2) and in the following years non-cirrhotic patients were also included. The percentage of sustained virologic response (SVR) in patients with HCV genotype 1 (found in 99% of the HCV infected patients in Romania) is known to be over 95% (3). There are limited previous data collected on the regression of fibrosis in patients who have achieved SVR after interferon-free treatments. A perfect method for assessing liver fibrosis and

its dynamics has not been established yet. The gold standard for evaluating the liver fibrosis has been the liver biopsy (LB), but in the recent years, non-invasive methods, especially the FibroTest, have been used instead (4). However, liver biopsy has significant limitations: possible complications during the procedure, sometimes with life-threatening potential (5), difficulties to carry out serial examinations in order to monitor the dynamic of liver fibrosis, some patients may be afraid to do the test, and usually the test is poorly accepted. Small liver samples may not always be sufficient to estimate the structure of such a large organ (sampling errors because it only evaluates 1/50,000 of the liver parenchyma). Moreover, it is considered that fibrosis has a heterogeneous disposition in the liver (6-8). The optimal size of liver fragment at liver biopsy seems to be around 40 mm and the acceptable size is 25 mm. However, it is difficult to obtain optimal size fragments and Poynard *et al* (9) analyzed in 2004 more than 10,000 liver biopsies with 25-35% inadequate sample size.

Histopathological aspects from different fibrosis stages of the liver tissue in patients with chronic hepatitis obtained through liver biopsy are shown in Fig. 1. Using Masson staining of liver tissue, stage 1 Ishak fibrosis score (A) corresponds to fibrous expansion of portal tracts with inflammatory cell infiltration; stage 3 Ishak fibrosis score (B) consists in fibrous septa which form occasional bridges between adjacent vascular structures; stage 5 Ishak fibrosis score (C) appears later in the progression of disease, with numerous bridges and rare parenchymal nodules completely surrounded by fibrosis; the late stage: Stage 6 Ishak score-cirrhosis (D) corresponds to the entire tissue being composed of parenchymal nodules surrounded by fibrosis (Fig. 1).

In Romania, the national guidelines use the FibroTest as a reference. Other non-invasive, cheaper and faster methods for evaluating the liver fibrosis in HCV infected patients have been developed by scientists, among them being the aspartate aminotransferase to platelet ratio index (APRI) (10) and the Fibrosis-4 (FIB-4) score (11), but these are rarely used in daily practice.

A meta-analysis conducted in 2018 by Zubair and Wajid (12) stresses upon the fact that the FibroTest (although not a perfect method), has a better diagnostic accuracy that APRI and FIB-4, but it is more expensive, not as accessible and as simple as calculating the APRI and FIB-4 scores.

The main objective of this study was to evaluate the dynamics of APRI and FIB-4 scores in patients with HCV who registered SVR and to evaluate if they could be useful and less expensive tools for screening HCV patients for cirrhosis and monitoring after DAA treatment. We performed ROC curve analysis to evaluate the diagnostic performance of APRI and FIB-4 scores in determining the presence of cirrhosis in comparison to FibroTest.

Materials and methods

Design and ethics. This study is a prospective observational analysis of HCV patients, both cirrhotic and non-cirrhotic (liver fibrosis determined by FibroTest), treated with DAA therapies and monitored in a tertiary-care infectious disease hospital, 'Prof. Dr. Matei Balş' National Institute for Infectious Diseases (Bucharest, Romania). The study was approved by the Ethics Committee and all patients signed an informed consent before inclusion in the analysis.

Patients were enrolled between November 2015 and January 2020 and included HCV patients who received DAA therapies for 12 weeks and achieved SVR. According to the National Protocol, patients were categorized as cirrhotic by having a result at FibroTest of F3-F4 or F4, each level below and equal to F3 being considered non-cirrhotic. All the patients included in the study were evaluated at baseline (before the start of treatment), at the first visit, at 6-months after the end of treatment (post-EOT), the 2nd visit and at 12-months post-EOT, the 3rd visit. At each visit, FibroTest, APRI and FIB-4 scores were determined for each patient. The main group of study consisted of cirrhotic patients (164 patients), as labeled by the National Protocol using the scores of FibroTest of F3-F4 or F4 (a value of >0.72) and a control group of HCV non-cirrhotic patients (83 patients ≤F3).

APRI was calculated with the formula: [AST (IU/l)/AST (Upper Limit of Normal-IU/l)/Platelet count (10^9/l)] x100 and the patients were distributed according to prior determined cut-offs from the medical literature (<1, 1-2, >2) (13). FIB-4 was determined according to the formula: [Age (years) x AST level (IU/l)]/[(Platelet count (10^9/l)x $\sqrt{ALT}$(IU/l)] and patients were distributed by previously studied cut-offs (<1.45, 1.45-3.25, >3.25) (14).

Information was gathered regarding the demographic parameters (age, gender) and complete medical history for all patients, and at each visit we determined FibroTest and biological parameters: including complete blood count (CBC), complete biochemistry analysis and coagulation parameters.

Statistical analysis. The statistical analysis was performed using IBM SPSS® Statistics version 22 (IBM Corp.). In univariate analysis, the type of variable distribution was assessed by visual inspection of histograms, Q-Q plots and the Shapiro-Wilk test. The central tendency and dispersion for non-Gaussian distributed variables were expressed as median and interquartile range (IQR). In multivariate analysis, associations between continuous non-Gaussian distributed variables were assessed using Kendall's tau-b (τb) correlation coefficient. Paired t-test was used to determine the significance of differences between paired continuous sample data. The Friedman test was also performed for differences between three groups of continuous data that has marked deviations from normality. ROC curve analysis was performed to assess the diagnostic ability of several variables. $P<0.05$ was considered to indicate a statistically significant difference.

Results

A total of 251 patients were enrolled in the study, divided into 2 groups: The cirrhotic patients (164 patients) and the non-cirrhotic patients (83 patients). The median age for the cirrhotic group was 62.5 years (35-80); 92 were females (56.1%) and 72 (43.9%) were males. The median age of the non-cirrhotic group was 63 years (33-85), including 57 (68.7%) females and 26 (31.3%) males.

At baseline, FibroTest, APRI and FIB-4 scores were performed for both groups and the results are shown in Table I.

Table I. Baseline APRI, FIB-4 and FibroTest scores in cirrhosis vs. non-cirrhosis groups.

Variable	Cirrhosis (164 patients) (F3-F4 and F4)	Non-cirrhosis (83 patients) (F0-F3)	P-value
APRI (n, %)			
Median (IQR)	1.14 (0.72-2.3)	0.73 (0.41-1.13)	0.002
<1	67 (40.85)	58 (69.88)	
1-2	47 (28.66)	16 (19.28)	
>2	50 (30.49)	9 (10.84)	
FIB-4 (n, %)			
Median (IQR)	3.32 (2.17-5.32)	2.21 (1.5-2.98)	<0.0001
<1.35	13 (7.93)	11 (13.25)	
1.35-3.25	75 (45.73)	55 (66.27)	
>3.25	86 (52.44)	17 (20.48)	
FibroTest			
Median (IQR)	0.84 (0.78-0.9)	0.63 (0.58-0.68)	<0.0001

APRI, aspartate aminotransferase to platelet ratio index; FIB-4, Fibrosis-4 score; IQR, interquartile range. Results are expressed as median (IQR). The frequencies are expressed as number and percentage (%). Statistical significance of the differences between the cirrhotic patients and non-cirrhotic patients was determined by P<0.05 using the independent samples t-test.
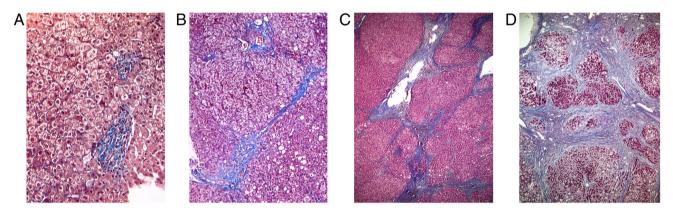

Figure 1. Masson staining of liver tissue with chronic hepatitis. (A) Fibrous expansion of portal tracts with inflammatory cell infiltration; below short spike-like septa (stage 1 Ishak fibrosis score). Magnification, x200. (B) Fibrous septa form occasional bridges between adjacent vascular structures (stage 3 Ishak fibrosis score). Magnification, x100. (C) With progression of disease, numerous bridges are formed and rare parenchymal nodules completely surrounded by fibrosis may form (stage 5 Ishak fibrosis score). Magnification, x40. (D) The entire tissue is composed of parenchymal nodules surrounded by fibrosis (stage 6 Ishak score-cirrhosis). Magnification, x40.

For the second visit (6 months post-EOT) and the third visit (12 months post-EOT), the same evaluations were performed and are described in Table II (for the cirrhotic patients) and Table III (for the non-cirrhotic patients).

In the cirrhotic group, at baseline, correlations were made between the FibroTests, APRI and FIB-4 and the results showed that there was a weak, but statistically significant correlation between APRI and FibroTest (τ=0.173, P=0.001), as well as between FIB-4 and FibroTest (τ=0.265, P<0.001). At the 6 months follow-up, APRI no longer correlated with the FibroTest (τ=0.144, P=0.057), but the FIB-4 score had a weak correlation with the gold standard of the study (τ=0.256, P=0.001). The same pattern was observed at 12 months post-EOT, APRI did not correlate with FibroTest (τ=0.100, P=0.255), but FIB-4 showed significant correlation (τ=0.200, P=0.023).

For the cirrhotic patients group, Friedman tests were performed which showed that there was a statistically signifi-

cant difference between the baseline and the two follow-up visits of APRI values (P<0.001), FIB-4 values (P<0.001) and FibroTest values (P<0.001). The study showed that between baseline and the 6-month evaluation, there was a statistically significant difference for APRI (P<0.001, confidence interval (CI) 95%: 0.982-1.61) and for FIB-4 (P<0.001, 95% CI, 1.43-2.26), but for the next follow-up period (between 6 and 12 months post-EOT) no reduction for these scores (P=0.739 for APRI, P=0.913 for FIB-4) was observed.

On the contrary, in the non-cirrhotic group, APRI and FIB-4 did not correlate with the FibroTest at any of the evaluation times. For APRI the results were: Baseline: τ=0.015, P=0.841, visit 2: τ=0.104, P=0.402, visit 3: τ=0.005, P=0.974; and for FIB-4: Baseline: τ=0.041, P=0.589, visit 2: τ=0.107, P=0.384, visit 3: τ=-0.037, P=0.820.

Friedman tests were performed for this group as well and they showed that there was a statistically significant differ-

Table II. Follow-up FibroTest, APRI and FIB-4 scores for cirrhotic patients.

Variable	Baseline (164 patients)	Baseline vs. 6 months post-EOT		6 months vs. 12 months post-EOT		
		6 months post-EOT (83 patients)	P-value	6 months post-EOT (83 patients)	12 months post-EOT (63 patients)	P-value
APRI (n, %)						
Median (IQR)	1.14 (0.72-2.3)	0.428 (0.289-0.685)	<0.001	0.428 (0.289-0.685)	0.423 (0.28-0.635)	0.739
<1	67 (40.85)	76 (91.57)		76 (91.57)	54 (85.71)	
1-2	47 (28.66)	7 (8.43)		7 (8.43)	9 (14.29)	
>2	50 (30.49)	0 (0)		0 (0)	0 (0)	
FIB-4 (n, %)						
Median (IQR)	3.32 (2.17-5.32)	1.987 (1.459-2.9)	<0.001	1.987 (1.459-2.9)	1.958 (1.44-3.14)	0.913
<1.35	13 (7.93)	20 (24.1)		20 (24.1)	16 (25.4)	
1.35-3.25	75 (45.73)	50 (60.24)		50 (60.24)	32 (50.8)	
>3.25	86 (52.44)	13 (15.66)		13 (15.66)	15 (23.8)	
FibroTest						
Median (IQR)	0.84 (0.78-0.9)	0.68 (0.57-0.79)	<0.001	0.68 (0.57-0.79)	0.72 (0.58-0.78)	0.42

APRI, aspartate aminotransferase to platelet ratio index; EOT, end of treatment; FIB-4, Fibrosis-4 score; IQR, interquartile range. Results are expressed as median (IQR). The frequencies are expressed as number and percentage (%). Statistical significance of the differences between visits was determined by $P<0.05$. The differences between the grades of fibrosis at different visits were evaluated by the paired samples t-test.

Table III. Follow-up FibroTest, APRI and FIB-4 scores for non-cirrhotic patients.

| Variable | Baseline vs. 6 months post-EOT | | | 6 months vs. 12 months post-EOT | | |
	Baseline (83 patients)	6 months post-EOT (37 patients)	P-value	6 months post-EOT (37 patients)	12 months post-EOT (21 patients)	P-value
APRI (n, %)						
Median (IQR)	0.73 (0.41-1.13)	0.343 (0.23-0.58)	0.01	0.343 (0.23-0.58)	0.341 (0.27-0.66)	0.214
<1	58 (69.88)	32 (86.49)		32 (86.49)	18 (85.71)	
1-2	16 (19.28)	5 (13.51)		5 (13.51)	3 (14.29)	
>2	9 (10.84)	0 (0)		0 (0)	0 (0)	
FIB-4 (n, %)						
Median (IQR)	2.21 (1.5-2.98)	1.53 (1.18-2.8)	0.014	1.53 (1.18-2.8)	1.99 (1.48-3.32)	0.441
<1.35	11 (13.25)	13 (35.13)		13 (35.13)	4 (19.05)	
1.35-3.25	55 (66.27)	17 (45.95)		17 (45.95)	12 (57.14)	
>3.25	17 (20.48)	7 (18.92)		7 (18.92)	5 (23.81)	
FibroTest						
Median (IQR)	0.63 (0.58-0.68)	0.53 (0.44-0.62)	<0.001	0.53 (0.44-0.62)	0.6 (0.54-0.69)	0.011[a]

APRI, aspartate aminotransferase to platelet ratio index; EOT, end of treatment; FIB-4, Fibrosis-4 score; IQR, interquartile range. Results are expressed as median (IQR). The frequencies are expressed as number and percentage (%). Statistical significance of the differences between visits was determined by P<0.05. The differences between the grades of fibrosis at different visits were evaluated by the paired samples t-test. [a]P-value shows a statistically significant difference between the 6-month and the 12-month visit, but the FibroTest is in progression, not regression as seen for the first 6 months.
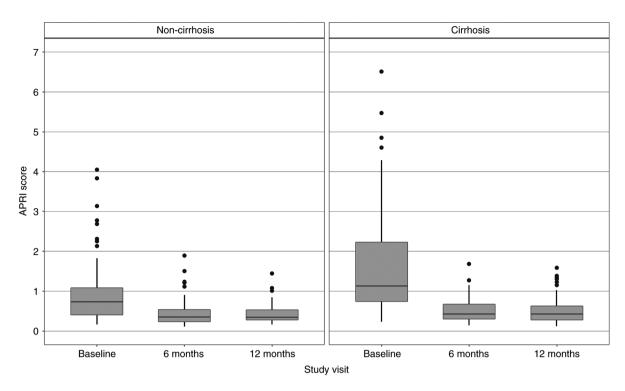
Figure 2. Regression of APRI score between baseline and 6 months and 12 months post-EOT in non-cirrhotic and cirrhotic HCV patients. APRI, aspartate aminotransferase to platelet ratio index; EOT, end of treatment; HCV, hepatitis C virus.
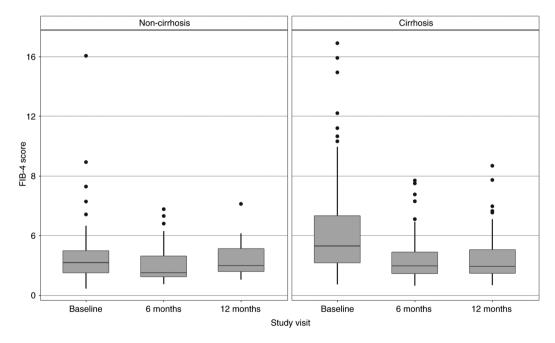

Figure 3. Regression of FIB-4 score between baseline and 6 months and 12 months post-EOT in non-cirrhotic and cirrhotic HCV patients. FIB-4, Fibrosis-4 score; EOT, end of treatment; HCV, hepatitis C virus.

ence between visits in the APRI values (P<0.001), FIB-4 values (P<0.001) and FibroTest values (P=0.02). However, the statistically significant difference was observed between baseline and the 6-month visit (P=0.01 for APRI and P=0.014 for FIB-4), but for the next 6 months no reduction was shown.

The regression of APRI and FIB-4 scores in the cirrhotic and non-cirrhotic groups can also be observed in Fig. 2 (for APRI) and Fig. 3 (for FIB-4).

Additionally to these results, we performed the area under the receiver operating characteristics curve (AUROC), sensitivities, specificities, positive predictive value (PPV) and negative predictive value (NPV) for our data in evaluating the presence of cirrhosis in comparison to the FibroTest for the two scores: APRI and FIB-4 when differentiating F0-F3 vs. F4. The ROC curves for APRI and FIB-4 are presented in Fig. 4, and the AUROC of these 2 scores have
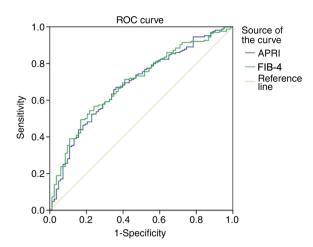
Figure 4. Receiver operating characteristic (ROC) curves for APRI and FIB-4 scores in differentiating F0F1F2F3 vs. F4. APRI, aspartate aminotransferase to platelet ratio index; FIB-4, Fibrosis-4 score.

values of 0.682 (95% CI, 0.613-0.752) for APRI and 0.693 (95% CI, 0.625-0.76) for FIB-4 (Fig. 4).

The calculated optimal cut-off value for APRI was 0.867 and for this value, the score had a sensitivity of 68%, a specificity of 58%, a PPV of 76% and NPV of 48% for predicting cirrhosis (F4) in comparison to F0-F3. For the FIB-4 score, at a cut-off of 2.32, the sensitivity was 71%, the specificity was 58%, the PPV was 76.9% and NPV was 51% for predicting liver cirrhosis in comparison to F0-F3.

In this study, the sensitivity and specificity of APRI and FIB-4 were evaluated at previously studied cut-offs in expressing liver cirrhosis. For APRI, at a cut-off >1, the sensitivity was 59.1%, the specificity was 69% and for APRI >2, the sensitivity was 30.5% and the specificity 89.3% for predicting cirrhosis. At a level of FIB-4 over 3.25, a sensitivity level of 52.4% and a specificity of 78.6% were determined for cirrhosis.

Discussion

Patients with HCV cirrhosis who registered SVR under DAA therapies need further monitoring in the following years as liver decompensation and hepatocellular carcinoma (HCC) could appear despite the viral clearance. In follow-up evaluations of the liver fibrosis, it could be very difficult to perform LB, especially since it has been mostly replaced by FibroTest (nowadays all other tests are being compared to it). Although it is a very useful tool, with no differences compared with LB regarding its prognostic value (15), healthcare workers are trying to find easier and less expensive methods to evaluate the degree of liver fibrosis, and especially cirrhosis.

According to the present study, both APRI and FIB-4 scores proved to be useful tools in predicting the presence of liver cirrhosis before treatment initiation as they can be rapidly calculated by screening and are less expensive than performing FibroTest. At lower levels of fibrosis (the non-cirrhotic group), neither APRI, nor FIB-4 correlated statistically with FibroTest. That is why these two scores cannot be used to differentiate between F0-F1, F1-F2 or

F2-F3. Also, at the follow-up evaluations, APRI no longer statistically correlated to the FibroTest, but FIB-4 continued to correlate with FibroTest, which shows that FIB-4 can be a useful tool for both screening for cirrhosis and for monitoring the patients after treatment with DAA (sometimes the patient is not able to pay for the FibroTest, as it is not mandatory for the patient follow-up after DAA treatment).

In a study published in 2007, Vallet-Pichard et al (14) reported that FIB-4 had an AUROC of 0.91 in identifying cirrhosis when comparing to the LB. They also performed a comparison between FIB-4 and FibroTest which showed a concordance between the two of 92.1% when FIB-4 was <1.45 and 76% when FIB-4 was >3.25, but for the values between 1.45 and 3.25 there was no correlation between these tests.

Another aspect observed in the present study was that between baseline and the 6-month post-EOT evaluation, there was an important decrease in the values of APRI and FIB-4, but no difference regarding the two scores between 6 months post-EOT and 12-month post-EOT could be observed. This decrease may occur as a result of the normal values of transaminases obtained after starting the DAA treatment. Similar results were published in 2017 which described a decrease of APRI and FIB-4 scores, along with decreased transient elastography (TE) results in patients who achieved SVR after DAA therapies (16).

In a study published in 2012, Tamaki et al (17) made a comparison between FIB-4 and repeated liver biopsies in evaluating the progression of liver fibrosis and concluded that using FIB-4 repeatedly, one could predict the changes in liver fibrosis every year, without having to perform LB.

Although there are many studies and systematic reviews in which the AUROCs for APRI and FIB-4 compared with LB were higher than 0.8 (classified as good to excellent) when predicting cirrhosis, we performed the AUROCs, sensitivities and specificities compared with FibroTest. Our results show lower values compared with the systematic review of Chou and Wasson (13), which reported a median AUROC for APRI of 0.84 (range, 0.54-0.97), for which an optimal cut-off of 2 had a median sensitivity of 48% (range, 17-76%) and median specificity of 94% (range, 65-99%). Also, the median AUROC for FIB-4 was 0.87 (range, 0.83-0.92), with an optimal cut-off of 3.25 for which the median sensitivity was 55% and the median specificity was 92%.

Houot et al (18) elaborated a systematic review which concluded that for patients with HCV, information gathered from 18 different studies, APRI had lower AUROC than FibroTest in describing different degrees of fibrosis, but without any difference regarding cirrhosis.

Cepeda et al (19) tested APRI and FIB-4 at previously validated cut-offs (only APRI had a cut-off of >1.5) in estimating severe liver stiffness by using TE. Their results for severe stiffness (≥12.3 kPa) show an AUROC for APRI of 0.77 (cut-off 1.5, sensitivity 61% and specificity 80%) and for FIB-4 of 0.8 (cut-off 3.25, sensitivity 62% and specificity 87%). They also tried to develop new scoring systems that included FIB-4, gamma-glutamyl transferase (GGT), high-density lipoprotein (HDL), homeostatic model assessment insulin resistance (HOMA-IR) and body mass index (BMI), with enhanced accuracy for predicting cirrhosis and a simplified APRI score that added GGT, BMI and age. This new APRI score had

higher accuracy than the classic APRI (AUROC 0.83, cut-off 0.22, sensitivity 82% and specificity of 70%), but all new FIB-4 models outranked APRI (the highest AUROC for FIB-4 best subset model: 0.87, sensitivity 70% specificity 87%).

Overall, the AUROCs for both APRI and FIB-4 determined in our study were lower than the data described in most studies, but the difference is that most studies from literature have evaluated these scores in comparison with LB (20), while our study evaluates them in comparison to FibroTest. Another explanation could be that the non-cirrhotic group might not have been as well represented as the general population of HCV non-cirrhotic patients.

Both APRI and FIB-4 prove to be easy, quick and inexpensive tools for screening HCV cirrhosis, with moderate diagnostic performance and FIB-4 can also be useful for monitoring patients post-EOT. The ideal biomarker (with very high sensitivity, specificity, specific for liver cells, reliable, useful for monitoring liver fibrosis and inexpensive) is yet to be discovered.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

AL, CP, LN, CT and VA contributed in the conception and design of the study, data acquisition, analysis and interpretation of the data, statistical analysis, manuscript drafting, and critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by The Ethics Committee of 'Prof. Dr. Matei Balş' National Institute for Infectious Diseases. All patients enrolled in the study gave written informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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