Liver fibrosis staging with combination of APRI and FIB-4 scoring systems in chronic hepatitis C as an alternative to transient elastography

Nikolaos Papadopoulos[a], Sofia Vasileiadi[b], Maria Papavdi[b], Eirini Sveroni[a], Pinelopi Antonakaki[b], Erminia Dellaporta[b], Evangelia Koutli[b], Stavroula Michalea[b], Spilios Manolakopoulos[b,c], John Koskinas[b], Melanie Deutsch[b]

417 Army Share Fund Hospital of Athens; 2nd Academic Department of Internal Medicine, National and Kapodistrian University of Athens; Medical School of National and Kapodistrian University of Athens, Greece

Abstract	**Background** Liver disease severity must be determined before treatment of chronic hepatitis C (CHC). We evaluated the diagnostic performance of the APRI and FIB-4 scores compared to transient elastography liver stiffness (TE-LS) in detecting significant fibrosis (F3) or cirrhosis (F4).

Methods We retrospectively enrolled 575 patients with CHC who underwent TE-LS between May 2014 and September 2018: 365 (63.5%) male, mean age 51.54±12.4 years. APRI and FIB-4 scores were compared to TE-LS.

Results One hundred patients (17.5%) had TE-LS values between 9 and 11.9 kPa, and were classified as F3, while 265 (46%) were classified as F4 (TE-LS ≥12 kPa). APRI and FIB-4 scores predicted F4 patients adequately using cutoff values of 0.65 (sensitivity 85.5%, specificity 77%) and 1.63 (sensitivity 91%, specificity 77%), respectively. Cutoff values of 0.64 for APRI and 1.46 for FIB-4 predicted F3/F4 patients (sensitivity 72% and 81.5%; specificity 83% and 79%, respectively). The use of these cutoff values with APRI and FIB-4 in combination adequately predicted patients with significant fibrosis or cirrhosis (positive predictive value 91.5%), while cutoff values of 0.3 and 0.98, respectively, predicted F1/F2 patients with specificity 94.5% and sensitivity 26.5%, suggesting that in 58.5% of patients TE-LS could possibly be avoided.

Conclusions The APRI/FIB-4 combination performed well in predicting significant fibrosis, while FIB-4 performed well in predicting cirrhosis. These noninvasive biochemical markers could be used as screening tools instead of LS measurement, which is not widely available. Further prospective validation studies are required to confirm this finding.

Keywords Chronic hepatitis C, APRI, FIB-4, APRI-FIB-4-COMBO, transient elastography, fibrosis, cirrhosis

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[a]1st Department of Internal Medicine, 417 Army Share Fund Hospital of Athens (Nikolaos Papadopoulos, Eirini Sveroni); [b]Hippokration General Hospital, Athens, Greece, 2nd Academic Department of Internal Medicine, National and Kapodistrian University of Athens (Sofia Vasileiadi, Maria Papavdi, Pinelopi Antonakaki, Erminia Dellaporta, Evangelia Koutli, Stavroula Michalea, Spilios Manolakopoulos, John Koskinas, Melanie Deutsch); [c]Laiko General Hospital, Athens, Greece, Department of Gastroenterology, Medical School of National and Kapodistrian University of Athens (Spilios Manolakopoulos), Greece

Introduction

Chronic infection with hepatitis C virus (HCV) is a major and growing global public health problem, with more than 71.1 million persons infected worldwide [1]. In the era of new direct acting antivirals (DAAs), more than 95% of patients with chronic hepatitis C (CHC) can now be cured [2]. According to the recommendations of the European Association for the Study of the Liver for the treatment of hepatitis C in 2018, all patients with CHC willing to be treated, and who have no contraindications for treatment, should be treated. Moreover, it is recommended that patients with significant fibrosis (METAVIR F2/F3) or cirrhosis (F4) should be treated without delay [3].

However, an evaluation of liver disease severity is necessary prior to therapy. Patients with cirrhosis or advanced fibrosis

(F3) are of particular importance, as the choice of treatment regimen and the post-treatment prognosis depend on the stage of fibrosis [3]. Liver biopsy has long been considered the gold standard for the assessment of liver fibrosis, but nowadays it has been almost entirely replaced by noninvasive methods that measure liver stiffness (LS), such as transient elastography (TE), or biochemical markers and scoring systems, such as the APRI score and FIB-4 scores [4,5]. The main advantage of biochemical noninvasive scores in evaluating liver fibrosis is that they are generally available at a low cost and are very simple to use. However, TE-LS measurement is not widely available, largely because of technical and practical reasons together with its high cost, while APRI and FIB-4 scores have been proved quite reliable for assessing liver fibrosis. However, validation in different patient populations is still needed [6,7].

In this study, the diagnostic performance of APRI and FIB-4 scores compared to TE-LS in detecting F3/F4 patients was evaluated in a Greek CHC cohort. In addition, we estimated the best cutoff for these scores to predict the likelihood of advanced fibrosis or cirrhosis, in order to reduce the need for TE-LS.

Patients and methods

We reviewed the records of all patients with CHC who sought care and underwent TE-LS evaluation in 2 tertiary liver centers of Athens between May 2014 and August 2018. All patients were evaluated with a Fibroscan (Echosens, Paris, France) in the supine position, with the tip of the transducer placed on the skin between the ribs over the right lobe of the liver. Only the M probe was used for LS measurement, and at least 10 validated measurements with an interquartile range of ≤30% and a success rate of >60% were required for a valid interpretation. While the correlation of TE-LS with METAVIR fibrosis stages has been established by several studies, different cutoffs for each stage of fibrosis have been proposed [6,8]. In our study the following stages of fibrosis were defined: F0-1: <7, F2: 7-8.9, F3: 9-11.9 and F4: ≥12 kPa, as these cutoff values have been adopted by the Greek National Insurance Program [6].

Patients who had coinfection with hepatitis B virus and/or human immunodeficiency virus, invalid TE-LS assessments and laboratory findings of acute hepatitis (alanine aminotransferase [ALT] levels ≥10 upper limit of normal [ULN]) were excluded. The database included patient demographic and epidemiological characteristics, medical history, and clinical and laboratory data. The study was performed in accordance with the World Medical Association Declaration of Helsinki and was approved by the hospital's ethics committee.

Laboratory methods

Hematological and biochemical parameters were determined using commercially available assays. The upper limit of normal for both ALT and aspartate aminotransferase (AST)

was 40 IU/L. For each patient, the APRI score was calculated using the proposed formula: APRI = [(AST level/ULN)/platelet count $(10^9/L)$] × 100. The FIB-4 score was determined using the following formula: FIB-4 = [age × AST/platelet count $(10^9/L)$ × $\sqrt{ALT}$] [9,10].

Statistical analysis

All data were analyzed using the statistical package MedCalc, version 18.11. Continuous variables are represented by their median (min-max) or mean ± standard deviation. Statistical analysis was performed using the *t*-test for comparisons of continuous variables between groups and the corrected chi-squared test for comparisons of qualitative data. Correlation analysis was used to compare the degree of hepatic fibrosis between TE-LS and both APRI and FIB-4 scores. Diagnostic performances for APRI and FIB-4 scores versus TE-LS were analyzed separately, according to sensitivity (Se), specificity (Sp), negative predictive value (NPV), positive predictive value (PPV) and area under the receiver operating characteristic (ROC) curve. The optimal cutoff value for each test was determined by applying the Youden index criterion. A two-tailed P-value <0.05 was considered to be statistically significant.

Results

In total, 575 patients with CHC were evaluated. Their mean age was 51.54±12.4 years and 63.5% of them were male. The vast majority (94%) were Caucasians. The most frequent possible sources of infection were parenteral drug use in 269 (47%), transfusion of blood or blood products before 1992 in 127 (22%), and unknown in the remaining 179 (31%). HCV genotype testing was performed in 551 (96%) patients. Genotype 1a was detected in 20%, genotype 1b in 20%, genotype 2 in 5%, genotype 3 in 38.5% and genotype 4 in 16.5%. The mean TE-LS score was 13.4±8.5 kPa, the median APRI score was 0.68 (0.1-11.6) and the median FIB-4 score was 1.8 (0.2-19.4). Stages of liver fibrosis according to TE-LS were evaluated as F0-1 in 60 (10.5%), F2 in 150 (26%), F3 in 100 (17.5%), and F4 in 265 (46%) patients (Table 1).

Correlation analysis showed a significant positive correlation between TE-LS fibrosis stage and APRI (*r*=0.4515, 95% confidence interval [CI] 0.3839-0.5142; P<0.0001) and FIB-4 (*r*=0.5374, 95%CI 0.4766-0.5930; P<0.0001).

Based on TE-LS fibrosis stage classification we estimated the optimal APRI and FIB-4 scores to predict the presence of liver cirrhosis (F4) and advanced fibrosis/cirrhosis (F3/F4) using ROC curve analysis (Table 2).

The optimal APRI score for F4 patients was calculated as >0.65 (area under the curve [AUC] 0.871, 95%CI 0.84-0.897; P<0.0001), giving Se 85.5%, Sp 77%, PPV 76%, and NPV 86% (Fig. 1). The optimal FIB-4 score for F4 patients was calculated as >1.63 (AUC 0.916, 95%CI 0.89-0.937; P<0.0001), giving Se 91%, Sp 77%, PPV 77%, and NPV 91% (Fig. 2).

The optimal APRI score to predict F3/F4 patients as one group indicating advanced fibrosis or cirrhosis was calculated as >0.64 (AUC 0.82, 95%CI 0.785-0.85; P<0.0001), giving Se 72%, Sp 83%, PPV 88%, and NPV 63% (Fig. 3). The optimal FIB-4 score to predict F3/F4 patients as one group was calculated as >1.46 (AUC 0.854, 95%CI 0.822-0.882; P<0.0001), giving Se 81.5%, Sp 79%, PPV 85.5%, and NPV 71% (Fig. 4).

The combination of optimal values (>0.65 and >1.63, respectively) for APRI and FIB-4 (APRI-FIB-4-COMBO) as one score predicted F4 patients with Se 82%, Sp 89.5%, PPV 87%, and NPV 85% (*r*=0.7164, P<0.0001). Furthermore, this combination with optimal values >0.64 and >1.46, respectively,

predicted F3/F4 patients with Se 67%, Sp 91.5%, PPV 93% and NPV 61.5% (*r*=0.566, P<0.0001); hence, its use would avoid the need for TE assessment in 45.5% of referred patients. Thus,

Table 1 Baseline characteristics of the 575 patients

Characteristics	Value
Male sex, n (%)	365 (63.5)
Age, years	51.54±12.4
Caucasian descent, n (%)	539 (94)
Source of Infection, n (%)	
Parenteral drug use	269 (47)
Transfusion	127 (22)
Unknown	179 (31)
ALT, IU/L	71.8±62
AST, IU/L	62.3±48
PLT, k/μL	195±82
HCV genotypes, n/N (%)	
1a	110/551 (20%)
1b	110/551 (20%)
2	29/551 (5%)
3	211/551 (38.5%)
4	91/551 (16.5%)
TE-LS, kPa	13.4±8.5
Stages of liver fibrosis according to TE-LS, n/N (%)	
F0-1 (<7 kPa)	60/575 (10.5)
F2 (7-8.9 kPa)	150/575 (26)
F3 (9-11.9 kPa)	100/575 (17.5)
F4 (≥2 kPa)	265/575 (46)
APRI score	0.68 (0.1-11.6)
FIB-4 score	1.8 (0.2-19.4)

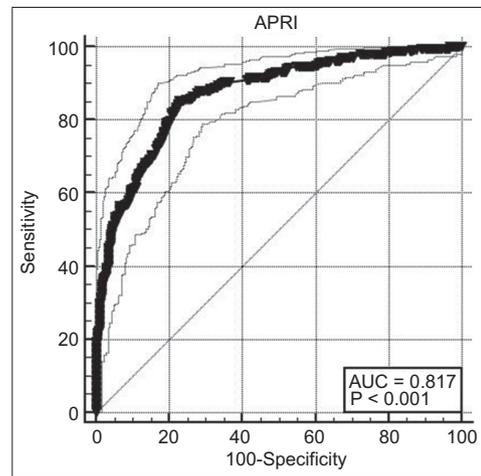*TE, transient elastography; LS, liver stiffness*

Figure 1 Performance of APRI score in the prediction of F4 patients according to TE-LS
TE, transient elastography; LS, liver stiffness; AUC, area under the curve
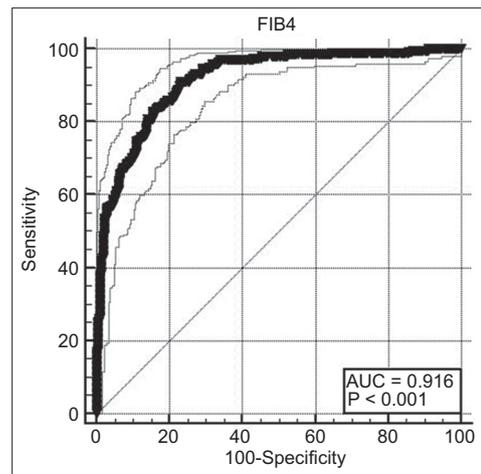

Figure 2 Performance of FIB-4 score in the prediction of F4 patients according to TE-LS
TE, transient elastography; LS, liver stiffness; AUC, area under the curve

Table 2 Performance indicators of APRI, FIB-4 and APRI/FIB-4 combination scores in F3/F4 and F4 patients

Score	APRI		FIB-4		APRI-FIB-4-COMBO	
Fibrosis stage	F3/F4	F4	F3/F4	F4	F3/F4	F4
Cutoff value	>0.64	>0.65	>1.46	>1.63	>0.64/>1.46	>0.65/>1.63
Sensitivity, %	72	85.5	81.5	91	67	82
Specificity, %	83	77	79	77	91.5	89.5
PPV, %	88	76	85.5	77	93	87
NPV, %	63	86	71	91	61.5	85.5

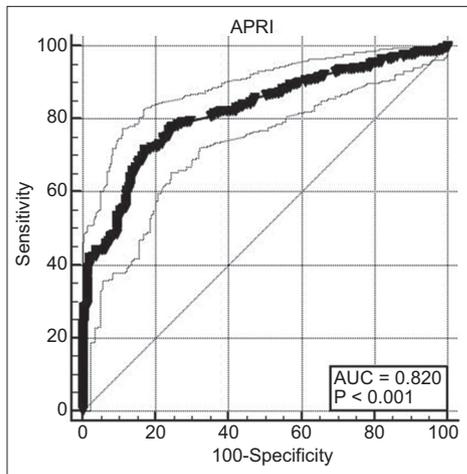*PPV, positive predictive value; NPV, negative predictive value*

Figure 3 Performance of APRI score in the prediction of F3/F4 patients
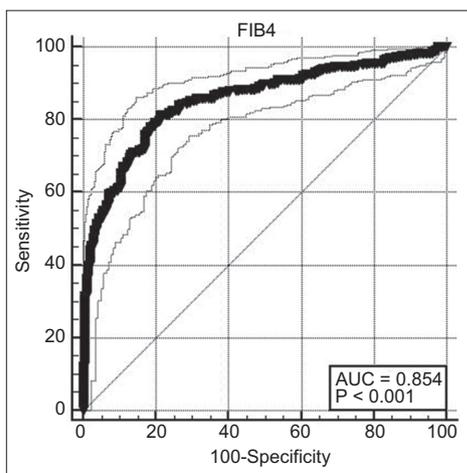*AUC, area under the curve*

Figure 4 Performance of FIB-4 score in the prediction of F3/F4 patients
AUC, area under the curve

it seems that the FIB-4 score is adequate for ruling out non cirrhotic patients, while the APRI/FIB-4 combination has the best predictive ability in determining patients with advanced fibrosis or cirrhosis (F3/F4).

In order to achieve the maximum number of patients who may avoid the need of TE assessment, we performed an additional analysis, trying to define patients with an obviously low fibrosis score. In this context, using a lower cutoff APRI score of 0.3 or less would increase the Sp to 92.5%, but reduce the Se to 34% for F1/F2 patients and would avoid the need for TE assessment in 17.5% of referred patients. Using a lower cutoff FIB-4 score of 0.98 or less would increase the Sp to 91.5%, but reduce the Se to 40.5% for F1/F2 patients and would avoid the need for TE assessment in 20.5% of the referred patients. The APRI-FIB-4-COMBO score using these lower cutoff values (0.3 and 0.98, respectively) predicted F1/F2 patients with a Sp of 94.5% and a Se of 26.5% and would avoid the need for TE assessment in 13% of referred patients (Table 3).

Table 3 Lower APRI, FIB-4 and APRI/FIB-4 combination scores in the detection of patients with low fibrosis (F1/F2)

Score	APRI	FIB-4	APRI-FIB-4-COMBO
Cutoff value	≤0.3	≤0.98	≤03/≤0.98
Sensitivity, %	34	40.5	26.5
Specificity, %	92.5	91.5	94.5
PPV, %	71.5	72.5	74
NPV, %	71	73	69

PPV, positive predictive value; NPV, negative predictive value

Discussion

Nowadays liver biopsy tends to be replaced by noninvasive tests. TE-LS is one of the most reliable methods for the assessment of liver fibrosis in CHC, but because of its high cost its use is not widespread in low- and middle-income countries [4]. On the other hand, APRI and FIB-4 scores are 2 of the most popular scoring systems for liver fibrosis and have been reported to achieve high accuracy for the diagnosis of advanced fibrosis and cirrhosis in CHC patients compared to liver biopsy [11,12]. However, there is a lack of data comparing the diagnostic accuracy of both APRI and FIB-4 scores with that of TE-LS in CHC patients. In everyday practice, and taking into account the DAAs used today in most countries, the only information we need about the fibrosis stage is whether the patient has baseline advanced fibrosis or cirrhosis. This fact dictates the treatment duration (8 or 12 weeks), but is also extremely crucial in defining patients who need further evaluation, even after a successful sustained viral response (SVR), especially with regard to surveillance for hepatocellular carcinoma (HCC).

In the present study, we found that both scores predicted F4 (cirrhotic) patients adequately. The AUROC was 0.871 and 0.916 for the APRI and FIB-4 score, respectively. A threshold of >0.65 for APRI score was 85.5% sensitive and 77% specific in detecting F4 patients. The PPV of this threshold was as high as 76%, with an NPV of 86%. A threshold of >1.63 for FIB-4 score was 91% sensitive and 77% specific in the diagnosis of F4 patients. The PPV of this threshold was 77% and the NPV was 91%, indicating that FIB-4 is a satisfactory tool for ruling out non-cirrhotic patients.

However, while simply classifying CHC patients into cirrhotics and non-cirrhotics could be considered correct in order to decide the duration of the DAA treatment, it is insufficient to distinguish patients who need post-SVR HCC surveillance from those who do not. For this purpose an accurate tool for discriminating between the cohorts of F3 and F4 patients (advanced fibrosis and cirrhosis) is needed.

It is well known that any noninvasive biochemical markers and scores are less effective *per se* at defining intermediate degrees of fibrosis [13]. Thus, we conducted an analysis of F3 and F4 patients as one group, indicating significant fibrosis, in an attempt to define an applicable cutoff for both APRI and FIB-4.

Separately, a threshold of >0.64 for APRI score was 72% sensitive and 83% specific in the diagnosis of this group of

patients, with PPV 88% and NPV 63%, indicating that APRI score was a good tool for ruling-in patients with significant fibrosis. The FIB-4 score with a cutoff value of 1.46 was 81.5% sensitive and 79% specific in the diagnosis of F3/F4 patients, but was less effective than APRI at ruling-in these patients (PPV 85.5%). However, when the 2 scores were considered together, the combination of both APRI and FIB-4 with threshold values of 0.64 and 1.46, respectively, led to a more robust model that could predict patients who had significant fibrosis with a PPV of 93%.

Several optimal APRI cutoff values for prediction of cirrhosis have been proposed in the literature [14]. In a systematic review, the lower recommended threshold cutoff value of 1 was 76% sensitive and 76% specific, with an overall AUROC of 0.76. The PPV of this threshold was 32% while NPV was 94% [15]. The higher recommended threshold cutoff value of 2 was more specific (91%), but less sensitive (49%), with PPV 50% and NPV 91%, indicating its effectiveness in ruling-out cirrhosis. A lower threshold of 0.5 and a higher one of 1.5 have been suggested in the literature as cutoff values for the identification of significant fibrosis. Se and Sp were 81% and 50% for the 0.5 cutoff, 35% and 91% for the 1.5 cutoff. PPV and NPV were calculated to be 59% and 75% for the 0.5 threshold, and 77% and 61% for the 1.5 threshold.

Regarding FIB-4 score, Vallet-Pichard *et al* evaluated its use in 847 patients with CHC in comparison to liver biopsy [16]. FIB-4 with a threshold <1.45 had an NPV of 94.7% to exclude significant fibrosis, with a Se of 74.3%, while a threshold higher than 3.25 had a PPV to confirm the existence of a significant fibrosis of 82.1%, with a Sp of 98.2%.

It is not unusual for threshold values to differ between published data. Differences in patient populations, including the prevalence of significant fibrosis, cirrhosis, and reference ranges used for AST and ALT levels, may explain these discrepancies [17]. Our data included a large number of patients with advanced fibrosis (63.5%) or cirrhosis (46%), quite a high proportion compared to literature data. The most important difference is that, in our study, biochemical markers were compared to TE-LS rather than liver biopsy, which remains the gold standard for liver fibrosis assessment.

In the era of economic crisis, and taking into account the high prices of antiviral drugs together with the need to simplify treatment in terms of HCV elimination, the question arises whether the use of biochemical scores such as APRI and FIB-4 could avoid TE or liver biopsy. Based on our findings, patients with advanced fibrosis could be defined relatively safely using a combination of APRI and FIB-4. But what about the non-cirrhotic patients? In this context we also tried to find a best lower cutoff that could help in directly prescribing DAAs in CHC patients without the use of TE. Using a lower cutoff FIB-4 score of 0.98 or less and an APRI of 0.3 or less we were able to distinguish F1/F2 patients who do not need TE. Taking together the 2 groups of patients (those with severe fibrosis and those with low fibrosis) we could obviate the need for TE assessment in 58.5% of referred patients, leaving TE to be used only in the "grey zone", which seems to contain less than 50% of patients.

There are limitations to our study. The most important limitation was the use of a noninvasive technique such as TE

for liver fibrosis assessment. Traditionally, liver biopsy has been considered as the "gold standard", but nowadays this invasive technique is no longer considered as the first-line method in routine daily practice in patients with viral hepatitis. TE has been evaluated by several studies and is considered as an effective noninvasive tool for liver fibrosis assessment [6,8]. Regarding the cutoff values we propose, they could be considered quite applicable in the group of the patients with severe fibrosis/cirrhosis; however, the limited number of patients in our cohort with F1/F2 make the cutoff we found in this group less relevant for low fibrosis. On the other hand, the retrospective nature of our study is the other main limitation. However, we used only well documented cases from our medical records who fulfilled our inclusion criteria, while the large number of participants allowed us to evaluate the scope of our study correctly.

In conclusion, our study demonstrated that the use of the marker we propose, the APRI-FIB-4-COMBO, namely the combination of APRI/FIB-4 scores, with cutoff thresholds of 0.64 and 1.46, respectively, could potentially be used to predict patients with significant fibrosis, while the use of a FIB-4 score

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Summary Box

What is already known:

- Patients with cirrhosis or advanced fibrosis are of particular importance in chronic hepatitis C (CHC), as the choice of treatment regimen and the post-treatment prognosis depend on the stage of fibrosis
- Noninvasive methods for liver stiffness (LS) assessment include transient elastography (TE) and biochemical scoring systems such as APRI and FIB-4
- The diagnostic performance of APRI and FIB-4 scores compared to TE-LS in the detection of patients with cirrhosis or advanced fibrosis remains unclear

What the new findings are:

- Both scores predicted F4 patients adequately
- A FIB-4 score threshold of 1.63 could predict cirrhotic patients
- The combination of APRI/FIB-4 score thresholds of 0.64 and 1.46, respectively, could potentially be used to predict patients with significant fibrosis, while score thresholds of 0.3 and 0.98, respectively, detect patients with low fibrosis
- The effectiveness of APRI and FIB-4 scores is lower for resolving intermediate degrees of fibrosis
- In about 58% of CHC patients, TE-LS could possibly be avoided if the APRI-FIB-4-COMBO scoring system is used

threshold of 1.63 could predict cirrhotic patients. Moreover, APRI-FIB-4-COMBO score thresholds of 0.3 and 0.98 respectively could potentially be used to define patients with low fibrosis. We believe that these markers could significantly reduce the need for TE-LS in the pretreatment evaluation of patients with CHC. This would allow a more rapid treatment decision for patients with CHC, which is of special significance in the era of a worldwide HCV elimination plan. Larger prospective studies are needed to confirm our findings.

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