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Original paper

FIB-4 and APRI scores for predicting severe liver fibrosis in chronic hepatitis HCV patients: a monocentric retrospective study

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Abstract

Aim of the study: Hepatitis C virus (HCV) can cause a chronic liver infection which could then develop into fibrosis, cirrhosis, and hepatocellular carcinoma. Today the diagnosis of liver fibrosis also includes the use of biomarkers. The purpose of our study was to determine the ability of the fibrosis index based on four factors (FIB-4) and aspartate aminotransferase-to-platelet ratio (APRI) to predict the severity of liver fibrosis or cirrhosis.

Material and methods: Medical records of 106 patients with HCV-related liver fibrosis were analyzed. All patients underwent clinical examination, blood tests (complete blood count, total bilirubin, etc.) and transient elastography. FIB-4 and APRI were calculated for each patient.

Results: Twenty-six patients (24.52%) had F4 fibrosis, 80 patients (75.48%) had non-F4 fibrosis (F0-F3). There was a statistically significant difference ($p < 0.05$) between non-F4 fibrosis patients and F4 fibrosis patients in many parameters, including APRI (F4 fibrosis patients had higher values: 2.06 ±3.22 compared to 0.68 ±0.76 of the non-F4 group; $p = 0.044$) and FIB-4 (F4 fibrosis patients had higher values: 4.84 ±4.14 compared to 2.29 ±2.90 of the non-F4 group; $p = 0.006$). Receiver operating characteristic (ROC) curve analysis for APRI and FIB-4 revealed that the area under the curve (AUC) of FIB-4 was 0.855 (CI: 0.813-0.936), while the APRI score had an AUC of 0.767 (CI: 0.79-0.932).

Conclusions: In this study, patients with severe fibrosis or cirrhosis were found to have a higher FIB-4 value than APRI in the context of chronic hepatitis C.

Key words: liver fibrosis, biomarkers, hepatitis C virus, FIB-4, APRI.

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Introduction

Hepatic C virus (HCV) infection can result in both acute and chronic hepatitis. Its severity can range from a mild disease lasting a few weeks to a serious and permanent disease. Chronic disease has a tendency to evolve towards fibrosis, cirrhosis, and therefore hepatocellular carcinoma (HCC) [1]. In addition to liver damage, HCV infection causes a variety of extrahepatic manifestations. These range from the presence of clinically insignificant autoantibodies to the development of diseases that affect a variety of organs and tissues such as mixed cryoglobulinemia, purpura, polyarteritis nodosa, porphyria cutanea tarda, lichen planus, autoimmune disorders, lymphoproliferative disorders, etc. [2, 3]. In the year 2015 the World Health Organization (WHO) estimated that about 70 million people infected with HCV had the chronic form of the disease, with a worldwide prevalence of 1% [4, 5].

Liver fibrosis consists of excessive deposition of extracellular matrix proteins (ECM), including collagen, which results in the destruction of liver architecture. Chronic HCV infection involves the activation of the immune system, which, among other effects, stimulates the proliferation of myofibroblasts and, therefore, increased production of ECM [6]. The development of liver fibrosis and cirrhosis is determined by multiple mechanisms and it can be considered as the scarring process of the liver in response to injury, supported by a continuous pathological process of inflammation, hepatocyte necrosis, and therefore deposition of ECM. The transition into the cirrhotic form of the disease occurs after about 15-20 years of chronic hepatocellular damage [7].

There are several methods available to clinicians to diagnose liver fibrosis. They can be distinguished in invasive and non-invasive approaches. Invasive approaches include liver biopsy. However, this is very expensive and it is not routinely performed in all centers [8, 9].

Therefore, over the years, various imaging methods and biomarkers have been tested for the diagnosis of liver fibrosis [10, 11]. Among the most used biomarkers there are the fibrosis index based on four factors (FIB-4) and the aspartate aminotransferase-to-platelet ratio (APRI). These scores are easy to use; the calculations are simple and quick. They are inexpensive: there are no additional costs, because the constitutive FIB-4 [aspartate aminotransferase (AST), alanine aminotransferase (ALT), platelet (PLT) count] and APRI (AST and PLT count) parameters are included in the routine investigation of any liver disease [12].

The aim of this study was to determine whether FIB-4 and APRI scores were able to predict severe fibrosis or cirrhosis and which of the two fibrosis scores was more accurate. These patients would be re-evaluated at a later time by postponing or avoiding a liver biopsy.

Material and methods

This is a retrospective monocentric study; therefore informed consent was not necessary and its management was notified to the local ethics committee. Our research was conducted in accordance with the principles of the 1975 Declaration of Helsinki (6th revision). For the study we considered the medical records of 106 patients with HCV related liver disease who were suitable for treatment with HCV direct-acting antivirals (DAA). Their age ranged from 24 to 89 years.

Liver fibrosis or cirrhosis was diagnosed using clinical, laboratory, ultrasonographic, and transient elastography results. Exclusion criteria were: non-HCV-related liver disease, coinfection with hepatitis B virus (HBV), coinfection with human immunodeficiency virus (HIV), HCC, decompensated liver cirrhosis.

All 106 patients had undergone an accurate evaluation of anamnesis, clinical examination, blood tests [AST, ALT, γ-glutamyl transferase (GGT), total bilirubin, serum albumin, complete blood count, serum HCV-RNA count done by PCR] and transient elastography.

Blood and biochemical parameters were obtained using the common assays currently available. We considered the following normal ranges: for AST and ALT 0-35 IU/l, for GGT 0-38 IU/l, for total bilirubin 0.3-1.2 mg/dl, for serum albumin 3.5-5.2 g/dl, for platelet count 130-400 × 10^9/l.

Transient elastography was carried out in every patient using FibroScan (Echosens, Paris, France), just before the possible start with DAA therapy. According to Castera's studies on non-invasive diagnosis of liver fibrosis with transient elastography, patients were classified into:

- patients with no fibrosis or mild fibrosis (liver stiffness > 2.5 kPa and ≤ 7 kPa, METAVIR score F0-F1);
- patients with significant fibrosis (liver stiffness > 7 kPa and ≤ 9.5 kPa, METAVIR score F2);
- patients with severe fibrosis (liver stiffness > 9.5 kPa and ≤ 12.5 kPa, METAVIR score F3);
- patients with cirrhosis (liver stiffness > 12.5 kPa, METAVIR score F4) [13].

The study population was then divided into 2 subgroups based on liver stiffness measured by FibroScan: cirrhosis subgroup (F4 fibrosis) and those without cirrhosis (non-F4 fibrosis, including F0-F1, F2 and F3).

The FIB-4 and APRI scores were calculated for each patient and the values obtained were rounded to two decimal places. Based on the available data from the scientific literature, a cut-off value of 3.25 for the FIB-4 and 2.0 for the APRI were used to predict who, among patients, had cirrhosis [14-16]. The formulas used to calculate the scores are shown in Figure 1.

$$\text{APRI} = \frac{\dfrac{\text{AST level of patient (IU/l)}}{\text{AST (upper limit of normal) (IU/l)}}}{\text{PLT count } (10^9/\text{l}) \times 100} \times 100$$

$$\text{FIB-4} = \frac{\text{age (years)} \times \text{AST (IU/l)}}{\text{PLT count } (10^9/\text{l}) \times \sqrt{\text{ALT (IU/l)}}}$$

Fig. 1. Aspartate aminotransferase-to-platelet-ratio index (APRI) and fibrosis index based on four factors (FIB-4). AST – aspartate aminotransferase, PLT – platelets, ALT – alanine aminotransferase

Table 1. Demographic and laboratory characteristics of the entire population, patient subgroups and the differences between distributions of certain variables among the subgroups

Variable	The entire study population	Non-F4 fibrosis	F4 fibrosis	*p*-value
Male (%)	51 (48.11%)	35 (43.75%)	16 (61.54%)	0.120
Female (%)	55 (51.89%)	45 (56.25%)	10 (38.46%)	
Age (years)	46.24 ±15.36	60.35 ±10.63	64.54 ±13.16	0.156
AST (IU/l)	50.11 ±38.74	42.33 ±26.97	74.08 ±56.59	0.010
ALT (IU/l)	59.99 ±63.88	52.36 ±58.01	83.46 ±75.81	0.063
Platelets (× 10^9/l)	184.52 ±66.57	202.40 ±63.02	129.50 ±43.50	< 0.001
GGT (IU/l)	54.72 ±61.10	44.83 ±28.22	85.15 ±109.03	0.073
Total bilirubin (mg/dl)	0.73 ±0.43	0.71 ±0.43	0.77 ±0.43	0.544
Serum albumin (g/dl)	3.90 ±0.76	3.95 ±0.72	3.77 ±0.87	0.350
Glycaemia (mg/dl)	105.66 ±33.89	102.09 ±32.47	116.50 ±36.61	0.080
Liver stiffness (kPa)	10.57 ±9.12	6.68 ±3.36	24.56 ±11.56	< 0.001
APRI	1.01 ±1.78	0.68 ±0.76	2.06 ±3.22	0.044
FIB-4	2.91 ±3.41	2.29 ±2.90	4.84 ±4.14	0.006

AST – aspartate aminotransferase, ALT – alanine aminotransferase, GGT – γ glutamyl transferase, APRI – AST-to-platelet ratio index, FIB-4 – fibrosis index based on four factors

Statistical analysis

Continuous variables are presented as the means (standard deviations); categorical variables are presented as percentages. Pearson's correlation coefficient *r* was calculated. Clinical and hemodynamic variables were compared using the *t* test for continuous variables and chi-squared test for categorical variables. The area under the receiver operating characteristic (ROC) curve, which ranges from 0.50 (no discrimination) to 1.0 (perfect discrimination), was also calculated. Statistical analysis was performed using NCSS 2007 and PASS 11 software (Gerry Hintze, Kaysville, UT, USA). A two-tailed *p*-value < 0.05 was considered statistically significant.

Results

The demographic and laboratory characteristics of the entire study population and the two sub-populations (those with and those without severe fibrosis) are graphically represented in Table 1.

Twenty-six patients had F4 fibrosis and they represent the 24.52% of the total; 80 patients had non-F4 fibrosis (F0-F3) and they represent 75.48% of the total. There were 49 patients with F0-F1 fibrosis and they represent 46.23% of the total; there were 18 and 13 patients with F2 and F3 fibrosis and they represent 16.98% and 12.26%, respectively.

Table 1 reports the demographic and laboratory characteristics of all patients, the patient subgroups, and the differences between the distributions of some

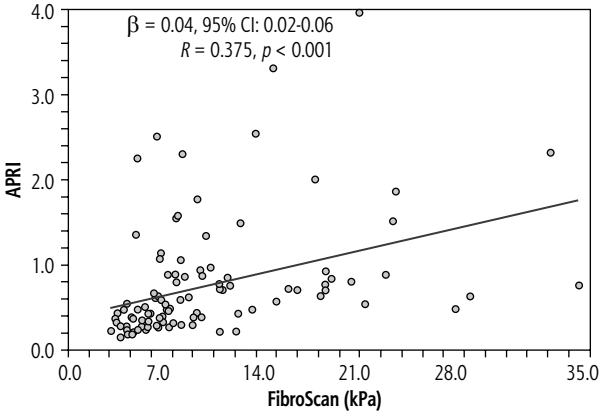

Fig. 2. Association of aspartate aminotransferase-to-platelet-ratio index (APRI) and FibroScan. kPa – kilopascals

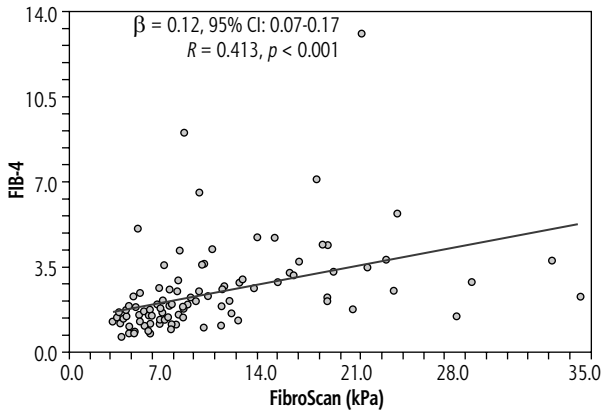

Fig. 3. Association of fibrosis index based on four factors (FIB-4) and FibroScan. kPa – kilopascals

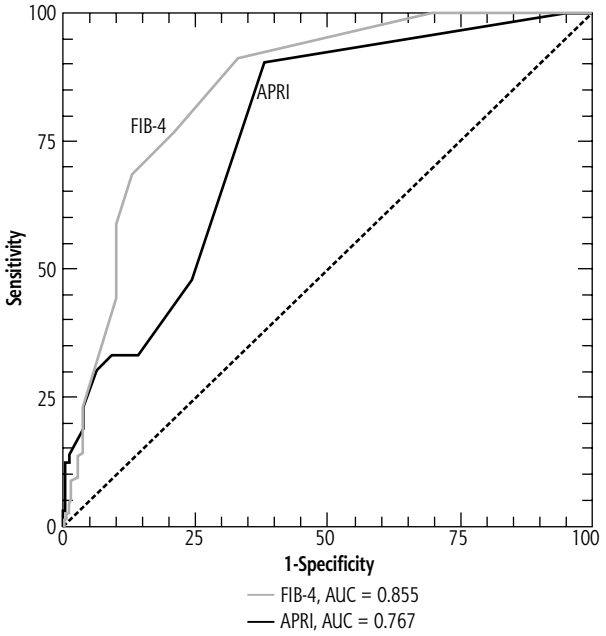

Fig. 4. Receiver operating characteristic curves demonstrating the ability of aspartate aminotransferase-to-platelet-ratio index (APRI) and fibrosis index based on four factors (FIB-4) to predict the presence of severe fibrosis or cirrhosis

variables between the subgroups. There was a statistically significant difference ($p < 0.05$) between patients with non-F4 fibrosis and patients with F4 fibrosis in many parameters. In particular, patients with F4 fibrosis had higher values of AST ($p = 0.01$), APRI ($p = 0.044$), and FIB-4 ($p = 0.006$). However, the platelet levels in these patients were lower ($p < 0.001$). There was not a statistically significant difference ($p > 0.05$) between patients with non-F4 fibrosis and patients with F4 fibrosis in many parameters, such as sex, age, ALT, GGT, etc.

The association of APRI and FIB-4 scores with the stages of fibrosis determined by FibroScan is shown in Figures 2 and 3. Significantly higher APRI and FIB-4 index values were observed among patients with F4 fibrosis.

ROC curve analysis for APRI and FIB-4 scores as predictors of cirrhosis revealed that the FIB-4 had an area under the curve (AUC) of 0.855 (CI: 0.813-0.936) while the APRI score had an AUC of 0.767 (CI: 0.79-0.932). The ROC analysis demonstrated that the FIB-4 and APRI scores were indeed able to predict cirrhosis satisfactorily (AUC = 0.875, $p < 0.001$ for FIB-4 and AUC = 0.076, $p < 0.001$ for APRI) (Fig. 4).

Discussion

As mentioned before, liver fibrosis can develop into more serious and potentially fatal pathological conditions [1]. Therefore an early diagnosis is important, so as to prevent or slow down the evolution of fibrosis. Even today, liver biopsy is the method that allows us to make a diagnosis of liver fibrosis with certainty, as it is based on the histological examination [17]. However, it cannot be exploited in daily clinical practice, so over the years we have tried to exploit more of the non-invasive methods. These include transient elastography, which was used to identify the presence and degree of liver fibrosis in the patients of our study. It is an easy and non-invasive method for measuring the stiffness of the liver through use of elastic waves and low frequency ultrasound (50 Hz). The propagation speed of ultrasound is directly proportional to stiffness: with increasing tissue hardness, the propagation speed of elastic waves increases. Thus, a high result generally indicates the presence of significant liver fibrosis. The final value corresponds to the median of all valid acquisitions, which is considered representative of liver stiffness. This value is expressed in kilopascals (kPa), in a range between 2.5 and 75.0 kPa [8]. However, even in the case of transient elastography there are limits. In fact, false values can occur in the case of obesity, ascites, and restricted intercostal space [18]. Furthermore, false positives can occur during acute viral hepatitis or extrahepatic cholestasis [19, 20]. Moreover, not all hepatological centers have the FibroScan. Therefore, several serum biomarkers able to identify liver fibrosis have been studied over the years. These serum biomarkers can be distinguished into direct and indirect. Direct ones reflect structural changes in the ECM, including indicators of ECM turnover, fibrogenesis and fibrolysis. Indirect biomarkers are expression of liver damage and/or decline in liver function during the development of fibrosis and cirrhosis. These include routine tests combined with other laboratory or clinical parameters and they comprise ALT, AST, GGT, bilirubin, haptoglobin, apolipoprotein A_1, and α2-macroglobulin [14, 21]. APRI and FIB-4 are two of the many scores that can be obtained by combining the various markers, and they have the purpose to increase the diagnostic performance of the markers themselves.

APRI is one of the most studied serum fibrosis indicators in the case of chronic HCV infection. Its calculation derives from the worsening of fibrosis and the portal hypertension that in these patients are associated with the reduction of thrombopoietin production by the hepatocytes, the increase of platelet sequestration by the spleen, and the reduction of AST clearance [15, 21].

FIB-4 is also a non-invasive method to assess liver fibrosis. It is based on simple variables (age, AST, ALT and platelet count). It was initially used by AIDS

researchers of the Pegasys Ribavirin International Coinfection Trial (APRICOT study) to evaluate the presence of liver fibrosis in patients with HIV/HCV co-infection [22]. Then, various other studies showed that FIB-4 had a variable degree of accuracy in HCV infected subjects [23-28].

The results of our study are in line with those obtained by other authors. In accordance with the 2018 WHO guidelines, we considered the value of 2.0 for APRI and 3.25 for FIB-4 as cut-off points for cirrhosis [16]. In patients of the F4 fibrosis group, higher values of APRI and FIB-4 were detected than in the non-F4 fibrosis group. From the analysis of the ROC curve an AUC of FIB-4 of 0.855 (CI: 0.813-0.936) was obtained, while APRI score had an AUC of 0.767 (CI: 0.79-0.932). For both markers these results are statistically significant ($p < 0.001$). However, the observation of the two AUC shows that FIB-4 is a better predictor of severe hepatic fibrosis than APRI. This can be explained by the differences in the laboratory parameters taken into account. In fact, the APRI score depends on the AST value and the platelet count (Fig. 1). Comparing the AST value between the two groups of patients, a significant difference ($p = 0.01$) is observed. In fact, AST is more increased in F4 fibrosis patients than in non-F4 patients (74.08 ±56.59 IU/ml vs. 42.33 ±26.97 IU/ml). In contrast, the platelet count is reduced in the F4 fibrosis group compared to the other group (129.50 ±43.50 × 10^9/l vs. 202.40 ±63.02 × 10^9/l; $p < 0.001$). On the other hand, FIB-4 depends not only on AST and platelet count, but also on ALT and age. Neither ALT nor age showed significant differences between the two groups ($p = 0.063$ and $p = 0.156$, respectively).

In a study conducted on 575 patients, Papadopoulos *et al.* obtained results similar to ours. In this study, both APRI and FIB-4 proved effective in predicting significant fibrosis [24]. Papaluca *et al.* conducted a recent retrospective study based on a cohort of 1007 HCV-positive patients. The authors demonstrated that the use of APRI and FIB-4 scores is a sensitive and reliable non-invasive diagnostic tool and they are good markers to exclude the presence of liver cirrhosis. Furthermore, both APRI and FIB-4 scores reduce the need for transient elastography [29]. In the study of Yen *et al*. FIB-4 proved better than APRI in the evaluation of liver fibrosis in HCV patients. In fact, in patients with F4 fibrosis, the AUC of FIB-4 was 0.73 vs. the AUC of APRI, which was 0.70 [26].

The limitations of our study are the small number of medical records analyzed and the retrospective nature of the study. However, we believe that what our data have shown can represent a valid contribution to encourage the use of a non-invasive and certainly reliable method. In the near future we would like to increase this number or even carry out a prospective study with a large sample of patients.

Conclusions

In conclusion, our study confirms that FIB-4 and APRI scores are both able to predict severe fibrosis and cirrhosis. FIB-4 was superior to APRI in making a distinction between patients with and without cirrhosis in the setting of chronic HCV infection. Since transient elastography is not readily available in low-income countries, FIB-4 may prove very useful in identifying patients without advanced liver disease in which a liver biopsy could be deferred or avoided.

Disclosure

The authors declare no conflict of interest.

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