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Original Article

FIB-4 and APRI scores for predicting severe fibrosis in chronic hepatitis C - a developing country's perspective in DAA era

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Abstract

Introduction: Chronic Hepatitis C Virus (HCV) infection leads to progressive fibrosis making fibrosis staging necessary in the evaluation of such patients. Different fibrosis scores are emerging as possible non-invasive alternatives for liver biopsy. The Fibrosis-4 Index (FIB-4) and AST to Platelet Ratio Index (APRI) scores are the most widely used and the most extensively tested. This study aims to determine if it was possible to accurately use these to identify patients that are unlikely to have severe fibrosis.

Methodology: One hundred and forty-two patients with chronic hepatitis C infection who underwent liver biopsy since January 1st 2014 until May 31st 2017 at the Hospital for Infectious and Tropical Diseases in Belgrade were analyzed. The FIB-4 and APRI scores were calculated for each patient and compared to histologically determined fibrosis stage.

Results: A comprehensive statistical analysis was conducted in order to compare patients with and without severe fibrosis and to evaluate the accuracy of the fibrosis scores. Patients with non-severe fibrosis were younger, had higher platelet counts and lower transaminase levels. FIB-4 had an AUC of 0.875 and the APRI score had an AUC of 0.861. No patients with severe fibrosis or cirrhosis had a FIB-4 lower than 1.08. FIB-4 was superior to APRI in identifying patients with severe fibrosis in the study cohort.

Conclusion: FIB-4 was superior to APRI in the recognition of severe fibrosis. FIB-4 may prove very useful in identifying patients without advanced liver disease, especially if other non-invasive methods are inaccessible.

Key words: FIB-4; APRI score; chronic hepatitis C; liver fibrosis.

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Introduction

Chronic Hepatitis C virus (HCV) infection is a global health problem and it is estimated that it affects 71 million people and is the cause of 399,000 deaths yearly [1]. Chronic HCV leads to progressive liver fibrosis and the development of cirrhosis in 20-30% of untreated patients after about 20 to 30 years [2]. According to various estimates 1-4% of these patients will develop hepatocellular carcinoma each year [2].

A microscopic examination of liver tissue obtained via transcutaneous biopsy used to be considered the gold standard when it comes to assessing the stage of liver fibrosis in those with chronic hepatitis C, but experts have recently started advocating non-invasive methods for determining the stage of fibrosis [3]. According to the latest European Society for the Study of Liver (EASL) guidelines the stage of liver fibrosis can be determined by non-invasive methods during pre-treatment evaluation with a prominent role for liver biopsy in cases where there is uncertainty regarding the stage of fibrosis or in cases in which comorbidities may affect the results of the non-invasive tests [3].

Since liver stiffness measurement is not available in our institution and the FibroMax test is not reimbursed by health insurance, we have thus far performed liver biopsies in order to conduct a pre-treatment assessment of the stage of liver fibrosis. Although liver biopsies are performed by experienced clinicians, they still carry a risk of costly and lethal complications [4]. Additionally, a liver biopsy coupled with a histologic examination of the tissue sample is a relatively costly endeavor and requires significant human and technical resources making this aspect an even more realistic concern in low-income countries. With this in mind, many researchers have tried to find a feasible alternative to the liver biopsy as a means of staging fibrosis. One of

the solutions proposed is the use of fibrosis scores. These scores are calculated using only a few relatively inexpensive laboratory tests performed on peripheral blood sample. Arguably the most widely used and extensively studied fibrosis scores in the setting of chronic HCV infection are the Fibrosis-4 index (FIB-4) and AST to Platelet Ratio Index (APRI). To our knowledge, there are no studies aimed at determining a cut-off value that is selected in order to optimize the sensitivity of these scores.

This study aims to determine which of the two aforementioned fibrosis scores is more accurate and whether it's possible to use any single cut-off value of a fibrosis score to identify patients that are unlikely to have severe fibrosis or cirrhosis. These patients could potentially be safely reevaluated at a later point in time deferring a liver biopsy.

Methodology

In this case series, a search of the paper based medical records of the Hepatitis One Ward of Hospital for Infectious and Tropical Diseases, Clinical Center of Serbia in an effort to identify all patients with chronic hepatitis C that had undergone a liver biopsy from January 1st 2014 until May 31st 2017. The patients analyzed in the study had no histologically proven liver disease other than chronic hepatitis C, i.e. patients with NAFLD/NASH, patients coinfected with HBV or HIV, as well as those with autoimmune, metabolic or alcoholic liver disease etc. were not included in the study. All patients subjected to a liver biopsy gave their written informed consent before undergoing the procedure. None of the patients were receiving antivirals at the time of the biopsy.

Once all the biopsied patients had been identified, data regarding the demographic and laboratory characteristics of this patient group were compiled. A single patient was excluded from the analysis since he had been suspected of having a previously undiagnosed hematologic disease associated with thrombocytosis which could lead to an unrealistically low FIB-4 score even in the setting of severe fibrosis. The laboratory analyses were taken into account only if the blood sample had been drawn in the 3 months before or 3 months after the patient underwent the liver biopsy.

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 former and 2 for the latter were used to predict which patients had severe fibrosis or cirrhosis [5,6]. The scores were calculated by the following formulas:

FIB-4 = (age × AST) ÷ (platelet count × (sqr(ALT))

APRI = (AST÷AST upper limit of normal) ÷ platelet × 100

The METAVIR fibrosis score was determined by a pathologist working at the Institute of Pathology of the Belgrade University Medical School. The study population was then divided into 2 subgroups based on liver histology – those with (the severe fibrosis subgroup) and those without severe fibrosis or cirrhosis (the non-severe fibrosis subgroup).

IBM's SPSS Statistics v11 and MedCalc Software's v17.8.1 were utilized to conduct a statistical analysis and to graph the data. Descriptive statistics were used for categorical and continuous demographic and laboratory variables. The statistical significance of the difference between the variables was computed utilizing a t-test, Mann–Whitney U, chi-squared test and Fisher test. The t-test was used to compare the age distribution between the two patient subgroups (non-severe vs severe fibrosis).

The ability of the FIB-4 score and APRI score to predict severe fibrosis and cirrhosis was appraised using a ROC curve analysis. The more accurate of the two scores was then further analyzed. The cut-off value at which the highest sensitivity for severe fibrosis could be obtained was determined and used to construct a 2×2 contingency table in order to determine the negative and positive predictive values of the test.

Results

One hundred and forty-two patients with chronic hepatitis C that had undergone a liver biopsy in the period evaluated in the study were identified. Liver histology revealed that 22 (15.49%) patients had cirrhosis and 8 (5.63%) had severe fibrosis (Figure 1).

Figure 1. Pathohistologic stage of liver fibrosis (METAVIR stage).

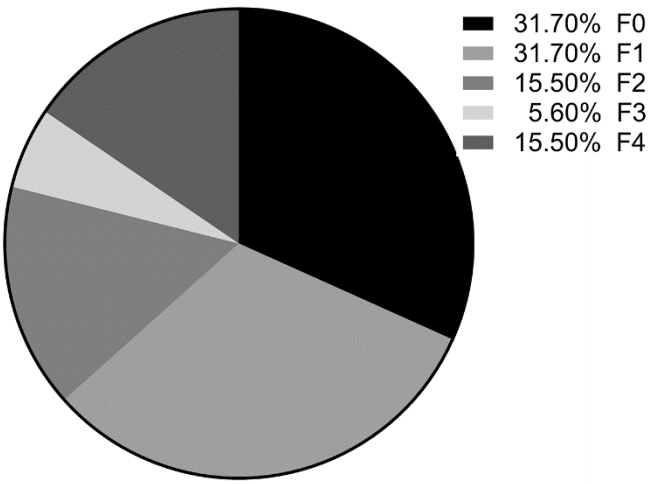
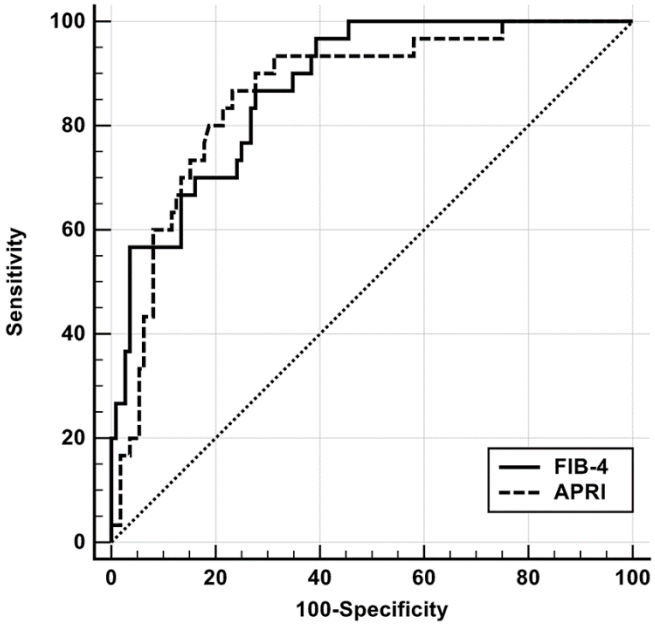


Figure 2. ROC curves demonstrating the ability of APRI and FIB-4 to predict the presence of severe fibrosis or cirrhosis.

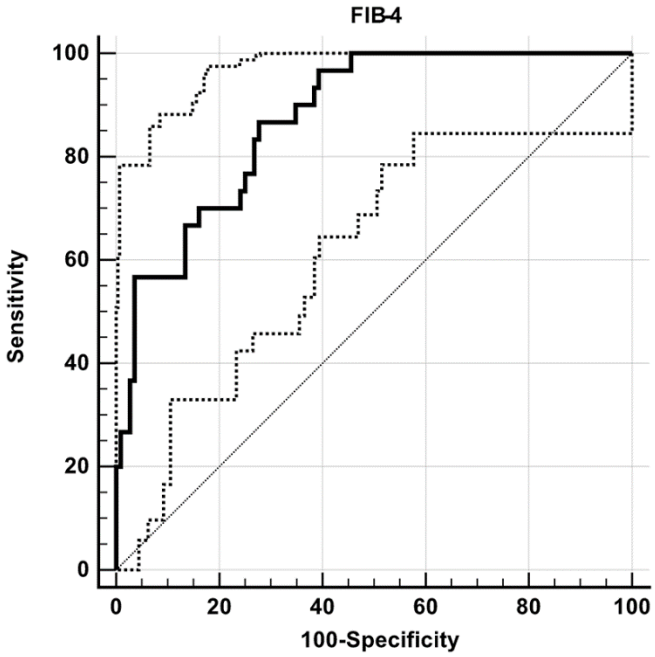


Put another way, 112 (78.9%) patients had no severe fibrosis.

The demographic and laboratory characteristics of the entire study population and the two subpopulations (those with and those without severe fibrosis) are graphically represented in Table 1. Men made up about 2/3 of the study population and this ratio held in both of the two subpopulations. Fifty-seven patients (40.1%) had normal AST levels, 51 (35.9%) had normal ALT levels and 40 patients (28.2%) had normal serum levels of both transaminases. Twenty-one patients (15.5%) had platelet counts lower than 150×10^6 platelets/mL.

There were significant differences between platelet counts, AST and ALT levels between patients in the two subgroups. The patient subgroup with severe fibrosis was significantly older, but the patients in that subgroup had not been aware of their HCV positivity for a longer time period compared to those with less advanced fibrosis.

Figure 3. ROC analysis of the ability of FIB-4 to predict severe fibrosis or cirrhosis (95% CI represented by dash-dot lines).



ROC curves analysis for APRI and FIB-4 scores as predictors of severe fibrosis or cirrhosis revealed that the FIB-4 had an AUC of 0.875 (CI 0.813 – 0.936) while the APRI score had an AUC of 0.861 (CI 0.79 – 0.932) (Figure 2).

Additional testing was performed on the FIB-4 scores. These ranged from 0.1 to 3.48 in patients with non-severe fibrosis and form 1.09 to 5.66 in patients with severe fibrosis. The ROC analysis demonstrated that the FIB-4 score was indeed able to predict severe fibrosis in a satisfying manner (AUC = 0.875, $p < 0.001$) (Figure 3). The optimal cut-off point for the best balance between sensitivity and specificity was determined to be 1.39 with a sensitivity of 86.67% and

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

Variable (unit)	The entire study population	Fibrosis		p
		F < 3	F ≥ 3	
Gender				
Men	93 (65.5%)	73 (65.2%)	20 (66.7%)	0.879
Women	49 (34.5%)	39 (34.8%)	10 (33.3%)	
Age (year)	44.14 ± 11.46	42.53 ± 11.24	50.23 ± 10.32	**0.001**
Time since diagnosis (year)	4.92 ± 5.7	4.5 ± 4.88	6.47 ± 7.96	0.339
AST (IU/mL)	57.1 ± 42.34	49.01 ± 39.24	87 ± 40.64	**< 0.001**
ALT (IU/mL)	103.97 ± 110.66	98.34 ± 119.94	124.97 ± 62.42	**< 0.001**
Platelets (10^6/mL)	197.62 ± 51.2	206.54 ± 50.56	164.33 ± 38.84	**< 0.001**
FIB-4	1.44 ± 0.97	1.15 ± 0.59	2.54 ± 1.3	**< 0.001**
APRI	0.85 ± 0.69	0.68 ± 0.54	1.49 ± 0.79	**< 0.001**

F: fibrosis stage; p: significance level.

Table 2. Contingency table obtained using a FIB-4 cut-off of 1.08.

	FIB-4		Total
METAVIR	**< 1.08**	**≥ 1.08**	
< F3	61	51	112
≥ F3	0	30	30
Total	61	81	142

F: fibrosis stage.

a specificity of 72.32% at that point. The ROC analysis also confirmed that there was indeed a FIB-4 score associated with a sensitivity of 100% (95% CI = 88.4% - 100%) and that the cut-off value was 1.08 (Table 2). The Fisher test demonstrated that the patient classification obtained using this cut-off point was statistically significantly different from a random one ($p < 0.001$). At this cut-off value the specificity was determined to be 54.46%.

Discussion

The subjects in our study cohort were older on average (50.2 ± 10.3 years old) than those from cohorts analyzed by other authors in similar settings [5-10]. There was also a less prominent predomination of males in this study compared to other studies (65% men in this study) [5,9]. Studies differ widely by the proportion of patients with severe and non-severe fibrosis (17-39%) [5-10].

This study confirms that time since the diagnosis of HCV infection is not a predictor of severe fibrosis, while patient age is. This is in concordance with published data that showed that the age is considered a predictor of advanced fibrosis [10].

Patients with at least severe fibrosis had higher ALT and AST levels and lower platelet counts than those with non-severe fibrosis (87 IU/mL vs 49 IU/mL for AST, 125 IU/mL vs 98 IU/mL for ALT, and 164×10^6 platelets/mL vs 207×10^6 platelets/mL). Others have also found this to be the case [5]. This effect was more pronounced with AST than ALT which is to be expected with fibrosis progression since this has been associated with a reversal of the AST/ALT ratio [11]. It is only logical that the subpopulation with severe fibrosis had higher FIB-4 (2.54 vs 1.3) and APRI scores (1.49 vs 0.68). This corroborates the conclusions of studies conducted by other researchers [5].

In this study FIB-4 was shown to be superior to APRI in identifying patients with severe fibrosis or cirrhosis in a setting of chronic hepatitis C (an AUC of 0.875 for FIB-4 vs an AUC of 0.861 for APRI). Other studies have come to a similar realization [12-14].

The ROC curve and contingency table analyses of FIB-4 pointed to a conclusion that there was a cut-off point that could potentially be utilized to identify all patients with severe fibrosis or cirrhosis thus achieving a near 100% sensitivity – determined to be 1.08 in this study. Simply put, no patients with severe fibrosis or cirrhosis had a FIB-4 score lower than 1.08. Interestingly, upon reviewing the figures presented in a landmark study by Sterling et al. we can conclude that there indeed seems to be a FIB-4 score cut-off value that is associated with near 100% sensitivity in the validation set of that study even though the authors themselves do not comment on this. Others have put forth results very similar to these [7,10].

A possible added benefit associated with using FIB-4 in this context is the cost reduction of treating patients with chronic hepatitis C, achieved by avoiding liver biopsies in patients with a low probability of severe fibrosis or cirrhosis.

It could be possible that there was some selection bias in this study since not all patients are motivated to undergo a liver biopsy. The worst case scenario at the 95% CI is that a little less than 90% of patients with severe fibrosis or cirrhosis would be successfully identified using the proposed cut-off. As a precaution, patients should probably be reevaluated with FIB-4 at a later time to minimize the chance of misclassification. Of course, it is still unclear whether reevaluating such patients using the same fibrosis score would indeed increase the overall sensitivity of the tests. Lastly, we could speculate that FIB-4 underperforms in patients with diseases that cause thrombocytosis and an inverse AST/ALT ratio (e.g. muscle breakdown, alcohol abuse etc.).

Conclusion

FIB-4 was superior to APRI when it comes to making a distinction between patients with and without severe fibrosis and cirrhosis in the setting of chronic HCV infection. Since transient elastography and magnetic resonance elastography are 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 safely.

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