Aspartate Aminotransferase-to-Platelet Ratio Index for Fibrosis and Cirrhosis Prediction in Chronic Hepatitis C Patients

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In chronic hepatitis C (CHC), liver biopsy is the gold standard method for assessing liver histology, however it is invasive and can have complications. Non-invasive markers have been proposed and aspartate aminotransferase (AST)-to-platelet ratio index (APRI) has been shown as an easy and inexpensive marker of liver fibrosis. This study evaluated the diagnostic performance of APRI for significant fibrosis and cirrhosis prediction in CHC patients. This study included treatment-naive CHC patients who had undergone liver biopsy from January 2000 to August 2006. All histological slides were reviewed according to the METAVIR system. APRI was calculated based on laboratory results performed within four months from the biopsy. Twenty-eight (56%) patients had significant fibrosis (F2-F4) and 13 (26%) had cirrhosis (F4). The area under ROC curves of APRI for predicting significant fibrosis and cirrhosis were 0.92 (0.83-1.00) and 0.92 (0.85-1.00), respectively. Using cut-off values recommended by prior studies, significant fibrosis could be identified, in accordance with liver biopsy, in 44% and cirrhosis in 66% of patients. APRI could identify significant fibrosis and cirrhosis at a high degree of accuracy in studied patients.

Key-Words: Chronic hepatitis C, fibrosis, cirrhosis, liver biopsy, APRI.

The hepatitis C virus (HCV) was identified in 1989 by Choo et al. [1] and nowadays is considered the greater responsible for the chronic hepatitis and the main cause of cirrhosis and hepatocellular carcinoma in Western World [2]. It is suggested that approximately 170 million people have chronic HCV infection in World [3] and at least four million have been infected by the virus in Brazil [4].

The knowledge of the stage of liver fibrosis is essential for prognostication and for deciding on antiviral treatment [5,6]. Therapy is not mandatory in chronic hepatitis C (CHC) patients with no or minimal fibrosis at presentation. In opposite, patients with significant fibrosis, excluding contraindications, must be treated to avoid almost invariably progression to cirrhosis over a 10 to 20 years period.

Liver biopsy remains the gold standard method for assessing liver histology [7], although it is costly, invasive and has risk of complications with morbidity between 0.3 and 0.6% and mortality of 0.05% [8]. Moreover, liver biopsy requires hospitalization of at least 6–18h [9]. In addition, only 1/50,000 of the organ is removed and this could lead to underestimation of fibrosis stage [10,11]. It has also been reported inter- and intraobserver discrepancies of 10% to 20% [12,13]. For all these reasons, there is a need to develop noninvasive, simple, inexpensive and accurate tests to evaluate hepatic fibrosis.

It has been studied the use of some tests based on indirect markers to predict significant fibrosis or cirrhosis in CHC patients and promising results have already been reported [14-16].

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The FibroTest score is computed with the patient's age, sex and results of analyses of serum haptoglobin, á2-macroglobulin, apolipoprotein A1, ã-glutamyl transpeptidase (GGT) and bilirubin levels. Investigators reported a 91% positive predictive value (PPV) and a 100% negative predictive value (NPV) for the presence of significant fibrosis [14].

Forns et al. [15] developed the Forns score which is an algorithm including platelet count, GGT, age and cholesterol level. They demonstrated a 66% PPV and a 96% NPV for the presence of significant fibrosis.

In 2003, Wai et al. [16] proposed to use aspartate aminotransferase (AST)-to-platelet ratio index (APRI) for fibrosis and cirrhosis prediction. They reported an 88% PPV and an 86% NPV for the presence of significant fibrosis, a 57% PPV and a 98% NPV for the presence of cirrhosis.

These different methods have been applied individually in the different validation studies. All of them have limitations. The diagnostic accuracy has not exceeded 80%-85% [17]. The attractiveness of the APRI is its simplicity and low cost. Our study aimed to evaluate the diagnostic performance of APRI for significant fibrosis and cirrhosis prediction in CHC patients.

Material and Methods

A retrospective analysis was made of medical records of patients with CHC who had undergone percutaneous liver biopsy at University Hospital / Federal University of Sergipe from January 2000 to August 2006. The diagnosis of CHC was established by the presence of HCV-RNA using qualitative polymerase chain reaction.

Patients with the following conditions were excluded from the study: presence of other liver diseases, hepatocellular carcinoma, prior liver transplantation, prior interferon therapy, immunosuppressive therapy, human immunodeficiency virus co-infection, hepatitis B virus co-infection and insufficient liver tissue for staging of fibrosis.

Men who had been drinking more than 30 g of alcohol per day and women who had been drinking more than 20 g of alcohol per day were considered current drinkers. Patients who had stopped drinking completely for more than six months before the biopsy were considered ex-drinkers [17].

Histological slides of all eligible patients were retrieved. All liver biopsies were reviewed by one pathologist in a period of two months. The pathologist was unaware of clinical data, except for HCV-RNA positivity. Fibrosis was scored according to the METAVIR system [18]. Significant fibrosis was defined by METAVIR fibrosis stage F2–F4 and cirrhosis as stage F4.

The following data were collected: AST, alanine aminotransferase (ALT), platelet count and HCV genotype. Except for genotype, only laboratory results performed within four months from the date of the liver biopsy were used for this study. The more recent results were preferred.

Results of serum AST and ALT levels were expressed as ratios of the upper limit of normal (ULN). The index was calculated based on formula proposed by original study of Wai at al. [16]: APRI = [(AST level/ULN)/platelet counts (10^9/L)] × 100. All these variables were compared between the groups F0-F1 (no or minimal fibrosis) *vs*. F2-F4 (significant fibrosis) and F0-F3 (no cirrhosis) *vs*. F4 (cirrhosis).

Statistical analysis was performed by Analyse-it software for Microsoft Excel. Descriptive results were expressed as mean ± standard deviation (SD) or number (percentage) of patients with a condition. The ANOVA one-way test followed by Dunnett test was used to compare quantitative data. P-values less than 0.05 were considered significant. The diagnostic performance of APRI for significant fibrosis and cirrhosis prediction was measured according to sensitivity, specificity, PPV and NPV parameters. They were expressed as percentage. The diagnostic value of the method was assessed by calculating the area under the curve ROC (AUROC) and their corresponding 95% confidence intervals (CI).

This research was approved by Ethics Committee from University Hospital / Federal University of Sergipe. It had been consented the free access to investigators on medical records and pathology department.

Results

This study included 50 patients with CHC, 34 (68%) men and 16 (32%) women. The mean age (± SD) was 49.6 ± 1.7 years. Patients ranged from 21 to 78 years old. The main demographic, laboratory and histological features of patients are summarized in Table 1. AST value was normal in 11 patients (22%) and the AST/ULN mean was 1.81 ± 0.16, ALT value was normal in nine cases (18%) and the ALT/ULN mean was 2.16 ± 0.20. According to METAVIR liver fibrosis staging [18], 28 (56%) patients had significant fibrosis (F2–F4) and 13 (26%) had cirrhosis (F4).

Comparing the groups F0-F1 *vs*. F2-F4 and F0-F3 *vs*. F4 (Table 2), we found significant difference between higher AST and ALT levels and greater fibrosis or presence of cirrhosis and also between lower platelet count value and greater fibrosis or presence of cirrhosis. The APRI has showed higher results in presence of significant fibrosis and cirrhosis (Figure 1).

ROC curve of APRI for predicting significant fibrosis was plotted in Figure 2 with AUROC of 0.92 (95% CI: 0.83-1.00). The cut-off point with higher diagnostic value that has been identified was 0.93, it had a 92.9% sensitivity, a 95.5% specificity, a 96.2% PPV and a 91.3% NPV. Based on prior studies [16,19,20], the cut-off points 0.50 and 1.50 were evaluated to predict the absence or presence of significant fibrosis, respectively (table 3). For patients with APRI of 0.50 or less, 10 of 12 (83.3%) would not have significant fibrosis. Among the 28 patients who had significant fibrosis, only 2 (7%) would have APRI of 0.50 or less, both had a METAVIR stage F2. For patients with APRI greater than 1.50, 14 (100%) would have significant fibrosis. Together, using APRI below the lower cut-off value (0.50) and above the higher cut-off value (1.50), 26 (52%) and 24 (44%) patients in accordance with liver biopsy could be classified as either without or with significant fibrosis, respectively.

ROC curve of APRI for predicting cirrhosis was plotted in Figure 3 with AUROC of 0.92 (95% CI: 0.85-1.00). The cut-off point with higher diagnostic value that has been identified was 1.73, it had a 77% sensitivity, a 97.3% specificity, a 91% PPV and a 92.3% NPV. Similarly, based on prior studies [16,19,20], the cut-off points 1.00 and 2.00 were evaluated to predict the absence or presence of cirrhosis, respectively (Table 3). For patients with APRI of 1.00 or less, 26 of 27 (96.2%) would not have cirrhosis. Among the 13 patients who had cirrhosis, only one (7.6%) would have APRI of 1.00 or less. For patients with APRI greater than 2.00, 7 of 8 (87.5%) would have cirrhosis. Together, using APRI below the lower cut-off value (1.00) and above the higher cut-off value (2.00), 35 (70%) and 33 (66%) patients in accordance with liver biopsy could be classified as either without or with cirrhosis, respectively.

Discussion

Over the last two decades, there has been a proliferation of serum markers of fibrosis with the ultimate goal to replace liver biopsies. Thus far, it has been generally agreed that liver biopsies are the gold standard method for the diagnosis of liver disease. However, because of their invasive nature, they can be contraindicated by a variety of reasons including their complications. The APRI test becomes particularly attractive because of the simplicity of its two measurements (AST and platelets), generally available in clinical settings, and low cost. Moreover, the APRI allows clinicians to use one formula to predict significant fibrosis as well as cirrhosis.

Numerous studies [16,21,22], including ours, have shown the reciprocal relation between decreased platelet count and increased AST level with progression of liver fibrosis. It has been reported [23] that with increasing fibrosis and worsening portal hypertension, there is increased sequestration and destruction of platelets in the enlarged spleen. Hypersplenism seems to be the most frequent cause of decreased platelet

Table 1. Demographic, laboratory and histological characteristics of 50 patients with chronic hepatitis C

Variable	Mean ± SD
Age (years)	49,6 ± 1,7
Male gender, n (%)	34 (68%)
Drinking history, n (%)	
Current drinker	04 (8%)
Ex-drinker	06 (12%)
Genotype 1, n (%)	27 (54%)
AST / ULN	1.81 ± 0.16
ALT / ULN	2.16 ± 0.20
Platelets (10^9/L)	177.3 ± 8
Stage of fibrosis, n (%)	
F0	16 (32%)
F1	06 (12%)
F2	10 (20%)
F3	05 (10%)
F4	13 (26%)

Figure 1. Box plot of APRI in relation to the METAVIR fibrosis score. The box represents the interquartile range. The symbols (o,+) represent outliers. The line across the box indicates the median value. There was significant difference in comparison of groups F0 *vs*. F2, F0 *vs*. F4, F2 *vs*. F4, F3 *vs*. F4.

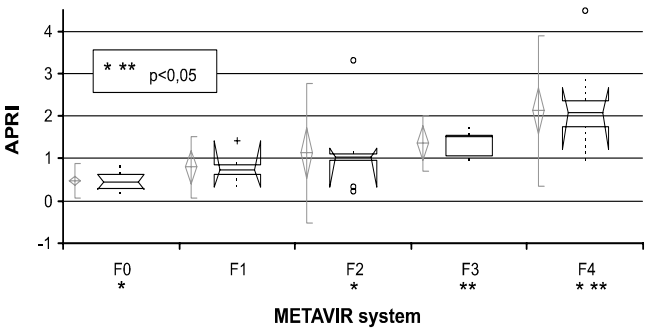


Table 2. Comparison of variables associated with the presence of significant fibrosis and cirrhosis

	F0-F1	F2-F4	p	F0-F3	F4	p
		Mean ± SD			Mean ± SD	
AST / ULN	1.09 ± 0.09	2.37 ± 0.2	<0.0001	1.47 ± 0.15	2.77± 0.33	0.0003
ALT / ULN	1.47 ± 0.15	2.70 ± 0.31	0.002	1.84 ± 0.22	3.08 ± 0.39	0.007
Platelets (10^9/L)	214 ± 12	148.4 ± 7	<0.0001	192.9 ± 9	132.8 ± 8	0.001
APRI	0.56 ± 0.06	1.63 ± 0.17	<0.0001	0.83 ± 0.09	2.12± 0.25	<0.0001
Population, n (%)	22 (44%)	28 (56%)		37 (74%)	13 (26%)	

Table 3. Performance of the APRI in detecting significant fibrosis and cirrhosis (n = 50)

	F0-F1/APRI ≤ 0.5	F2-F4/APRI ≥ 1.50
Sensitivity (%)	92.9	46.4
Specificity (%)	50	100
PPV (%)	70.3	100
PNV (%)	84.6	59.5
Classified patients (%)	52	
Accuracy (%)	92	
	F0-F3/APRI ≤ 1.0	**F4/APRI ≥ 2.0**
Sensitivity (%)	92.3	46.2
Specificity (%)	73	97.3
PPV (%)	54.5	85.7
NPV (%)	96.4	83.7
Classified patients (%)	70	
Accuracy (%)	94.2	

Figure 2. ROC curves of APRI in the prediction of significant fibrosis (^{3}F2). AUROC= 0,92 (95% CI: 0,83-1,0)

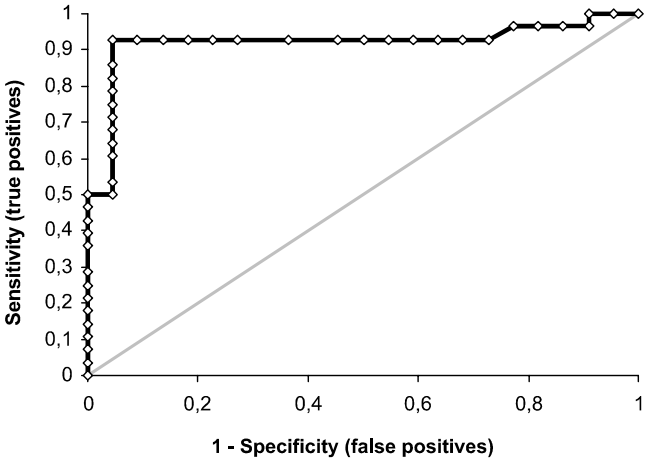
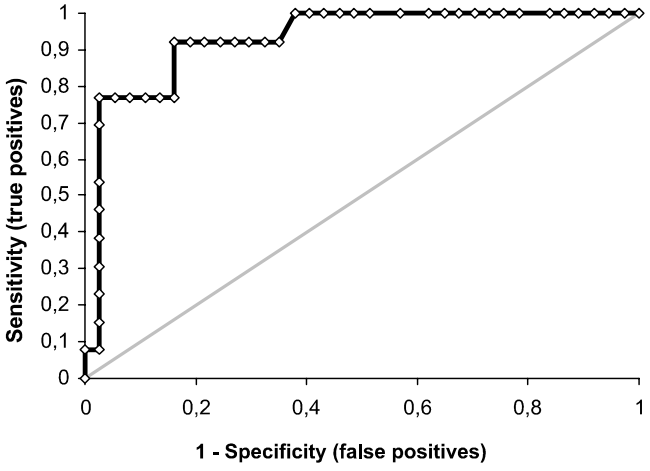


Figure 3. ROC curves of APRI in the prediction of cirrhosis (F4). AUROC=0,92 (95%CI: 0,85-1,0)



count related with cirrhosis and portal hypertension [24]. Studies have already demonstrated that progression of liver fibrosis is associated with decreased production of thrombopoietin by hepatocytes, and hence reduced platelet production [25,26]. The increased AST level had been justified by mitochondrial injury which may be associated with the HCV infection [27]. In addition, progression of liver fibrosis may reduce the clearance of AST, leading to increased serum AST levels [28].

The AUROC of APRI score for significant fibrosis and cirrhosis prediction was comparable to that of the original study [16], 0.92 (0.83-1.00) *vs*. 0.88 (0.80-0.96) for diagnosis of significant fibrosis, in the present study and in the original, respectively, and 0.92 (0.85-1.00) *vs*. 0.94 (0.89-1.00) for diagnosis of cirrhosis. Recent prospective studies have shown lower accuracy rates than our data [19,20,29-31].

In our population, using the respective cut-off values recommended by the original study [16], significant fibrosis could be classified correctly according to liver biopsy in 44% and cirrhosis in 66% of patients. Wai et al. [16] had also found similar results, 44% for significant fibrosis and 72% for cirrhosis. Our findings were lower than those reported in prospective studies [19,20,29-31].

The discrepancy with prospective studies may be due to the 22% of patients who had normal AST value in our research and to the distribution of liver fibrosis in the study, with 56% of patients with significant fibrosis. Bourliere et al. [19] reported that noninvasive markers of fibrosis may have different diagnostic accuracy depending on the prevalence of significant fibrosis in the studied population and that normal AST value can lead to APRI failure.

This study demonstrated some weaknesses of the index that had already been shown in literature [16,19,20]. The APRI can not identify individual stages of fibrosis and many patients remain unclassified after using the respective cut-off values recommended. Moreover, the appropriate definition of the upper limit of for AST remains uncertain. Each laboratory establishes a different value of the ULN. This problem may explain the limitation of the test and the lower diagnostic power of this test as compared with Fibro test in the literature [32]. In conclusion, we have shown that APRI could identify significant fibrosis and cirrhosis at a high degree of accuracy in studied patients compared with liver biopsy. Significant fibrosis and cirrhosis could be correctly predicted in 44% and 66% of treatment-naive CHC patients, respectively.

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