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ORIGINAL ARTICLE

Are FIB-4, APRI and GPR Good Predictors for Liver Fibrosis in Hepatitis C Patients According to Virus Genotypes?

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ABSTRACT

AIM: The accurate staging of hepatic fibrosis becomes a clinical priority to better estimate the prognosis and guide management decisions for patients infected with hepatitis C virus (HCV). Noninvasive approaches based on routine and low cost tests to assess liver fibrosis have been used toward increase the possibility of clinical use in the daily practice; the aim of this study is evaluate the accuracy of these tests to predict advanced fibrosis in patients with HCV.

MATERIAL AND METHODS: This study is a convenience cohort where 94 HCV patients were followed-up by 12 weeks during the antiviral therapy. All patients underwent liver biopsy and through laboratory data, the values for noninvasive methods, APRI, FIB-4 and GPR, were calculated to assess the accuracy of the tests in relation to liver biopsy, also considering the viral genotypes.

RESULTS: The concordance of APRI in relation to liver biopsy for advanced fibrosis was AUROC = 0.67 (CI 95% 0.55-0.79). The GPR method represent an AUROC = 0.59 (CI 95% 0.46-0.73) for advanced fibrosis, while FIB-4 represent an AUROC = 0.69 (CI 95% 0.58-0.80) for advanced fibrosis. No significant difference was found when compared the three tests used (p = 0.306). Moreover, when evaluated the tests in relation to the viral genotypes, we found only statistical difference for GPR (p = 0.006), with better accuracy for genotype 2-3.

CONCLUSION: We found association between viral genotypes and advanced fibrosis in the relationship of GPR; however, the results showed no good accuracy for all index evaluated in our population.

Key words: Hepatic fibrosis; Liver biopsy; Hepatitis C

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INTRODUCTION

Estimated global prevalence of chronic Hepatitis C (CHC) ranging between 2-3% and 1.38% in Brazil and CHC is the most common cause of cirrhosis and hepatocellular carcinoma, and the leading indication for liver transplantation in the United States and many Western countries[1-3]. Chronic viral hepatitis and liver cirrhosis are responsible for a significant burden in Brazil affecting mainly men and individuals in their productive years[3].

The prognosis and management of chronic liver diseases depend

on the liver fibrosis degree[4,5]. Therefore, the accurate staging of hepatic fibrosis becomes a clinical priority to better estimate the prognosis and guide management decisions for patients infected with Hepatitis C virus (HCV). Treatment should be indicated for patients with advanced fibrosis (F ≥ 3) because of the risk of evolution to cirrhosis and its associated complications[6,7].

Currently, liver biopsy is the gold standard for this purpose. Unfortunately, as an invasive method, this procedure have some limitations due complications for the patients, variability in pathological interpretation (as high as 20%), and sampling error (up to 25%) that remains a problem in accurate fibrosis staging for individual patients[8]. Nowadays, noninvasive approaches to assess histology in CHC patients have been established; however, none of these tests or markers alone is accurate or reliable in predicting in particular, liver fibrosis[9].

Therefore, many efforts has been focused on the evaluation of noninvasive methods for the assessment of liver fibrosis, particularly, simple, inexpensive and readily available tests, that could be reliable and accurate in predicting liver fibrosis[1]. In this context, the most important tests that have arised are the Fibrosis-4 (FIB-4), aspartate aminotransferase to platelet ratio index (APRI), and the more recently test used for chronic Hepatitis B, the gama-glutamyltransferase to platelet ratio index (GPR)[10]. These models are based on routine and low cost tests and can increase the possibility of clinical use in the daily practice[2,9,10]. The current literature still brings conflicting data regarding these tests, showing positive as well as negative results[9,11-15]. Regarding GPR, there are still few studies evaluating its usefulness in predicting hepatic fibrosis in patients with HCV[10,16,17]. Moreover, the literature is also scarce on the evaluation of these indirect markers of hepatic fibrosis according to viral genotype on hepatic fibrosis, since genotype is related to the severity of the liver condition, being reasonable to speculate that it might also play an important role in liver fibrosis.

Therefore, the aim of this study is evaluate the accuracy of these tests to predict advanced fibrosis in patients with CHC, especially GPR, which has been little studied in this population of patients. Here, we also aim to evaluate the influence of the viral genotype on these markers, increasing or decreasing the chance of a correct patient classification by their degree of fibrosis as the result of these tests.

METHODS

Sample and study design

This is a cross-sectional study nested to a cohort of convenience CHC patients followed-up by 12 weeks during the antiviral therapy. The diagnosis of CHC was established by the presence of HCV antibody on ELISA, and confirmed by the presence of HCV ribonucleic acid HCV RNA (HCV RNA), using qualitative polymerase chain reaction assays.

The study was performed from February 2013 to May 2016, in Gastroenterology Outpatient Clinic - Injectable Medication Monitoring and Application Center - in Medicine Faculty of Federal University of Pelotas (UFPel), Rio Grande do Sul, Brazil. The sample consisted of 94 patients with treatment indication according to the Treatment Protocol of Viral Hepatitis of the Health Ministry (2011-2015)[7,18]. The treatment was based in drugs used for the CHC in Brazil, Peginterferon in association with Ribavirin (mean dose of 13 mg/kg/day) for 24 to 48 weeks depending on the virus genotype, viral load and fibrosis degree. A socio-demographic questionnaire was applied at the baseline, before the beginning of the antiviral therapy.

Inclusion criteria: patients older than 18 years, mono-infected with HCV and liver biopsy evaluated by the Metavir System. Exclusion criteria: patients under 18 years of age, co-infected and patients without biopsy evaluated by the Metavir System.

Laboratorial data

Laboratorial information such as the biochemical analysis, degree of fibrosis, virus genotype and viral load values were obtained from the medical records in UFPel Hospital along the antiviral therapy. The following laboratory variables were studied: aspartate aminotransferase (AST), alanine aminotransferase (ALT), gama-glutamyltransferase (GGT) and platelet count. Taking into account that genotypes 2 and 3 have similar treatment indication for CHC and genotype 1 demonstrates a worse disease prognosis as well as a poorer response to Interferon treatment, all analysis were conducted considering the effects of genotype 2/3 in relation to genotype 1. The liver biopsy, the reference standard for assessing fibrosis, was evaluated using the METAVIR scoring system. Fibrosis was staged on a 0–4 scale: F0 = no fibrosis, F1 = mild fibrosis, F2 = moderate fibrosis, F3 = moderate–severe fibrosis and F4 = cirrhosis, according to the METAVIR scoring system. These definitions represented at least significant fibrosis and influenced the management of the patients in terms of treatment indications. High viral load was defined by values above 600,000 IU/mL and low viral load by less than 600,000 IU/mL.

The formulas for GPR, APRI, and FIB-4 are as follows: (1) FIB-4 = (age (years) × AST (IU/L)) / (platelet count (10^9/L) × (ALT (IU/L))$^{1/2}$); (2) APRI = (AST (IU/L) /ULN of AST) /platelet count (10^9/L) × 100; (3) GPR = (GGT (IU/L) /ULN of GGT) /platelet count (10^9/L) × 100.

The results obtained were used to plot three ROC (Receiver Operating Characteristic) curves to determine the best cutoff points for advanced hepatic fibrosis (F3 and F4). The value used as the upper limit of normality (ULN) for AST was 40 for men and 37 for women and 50 for GGT according to the reference value used at the UFPel Hospital. The cutoff points used by the Ministry of Health protocol in Brazil for the evaluation of advanced fibrosis were 2.0 for APRI and 3.25 for FIB-4.

Statistical Analysis

Socio-demographic and clinical characteristics of CHC patients were described by simple frequencies. Variables are presented as mean ± standard deviation (SD) or number and percentage. ROC and area under the curve (AUROC) were used to analyze the accuracy of the non-invasive tests APRI, FIB-4 and GPR for disease staging. The discriminant ability of each test was obtained calculating the sensitivity and specificity. The comparison between the tests was performed using X^2. The analyses were performed in STATA 14 and p values ≤ 0.05 are considered statistically significant.

Ethical Aspects

All ethical principles established by the National Health Council in Resolution No. 466/12 were respected and in accordance with the 1964 Helsinki declaration and its later amendments. All patients who agree to participate in the research provided a written informed consent. The Catholic University's Ethics Committee (151.642 and 658.087) approved the study.

RESULTS

From 94 patients that participated in the study, the average age of patients was 54.2 (± 11.2) years, 53 (56.4%) were male, 50 (53.2%)

were married, 80 (85.1%) were white, 71 (75.5%) were performing the first treatment for CHC, 56 (59.6%) had genotype 1, 28 (29.8%) had advanced fibrosis (F3-F4), and 12 (12.8%) were cirrhotic as METAVIR system (Table 1 and Table 2). The mean value of platelets was 173516.12 ± 64161.07 mm^3, of GGT was 86.97 ± 75.60 UL/mL, of AST were 80.07 ± 76.20 UL/mL, and ALT was 78.98 ± 61.66 UL/mL. Regarding viral pretreatment, 56 (59.6%) have a high viral load and 34 (36.2%) low.

When evaluated the accuracy of GPR test for liver fibrosis, the value of AUROC was 0.59 (CI 95% 0.46-0.73) with cutoff point of 0.02 (60.61% sensitivity/specificity 61.40%) for advanced fibrosis (Figure 1A). When evaluated GPR according to genotypes of CHC, the genotype 2-3 (n = 38) shows higher accuracy for liver fibrosis with AUROC value of 0.64 (CI 95% 0.42-0.84) when compared to AUROC value of 0.55 (CI 95% 0.37-0.74) for genotype 1 (n = 52), revealig significant difference between genotypes (p = 0.006) (data not shown).

In the analysis of APRI corcondance in relation to Liver Biopsy, we found an AUROC of 0.67 (CI 95% 0.55-0.79) with cutoff point value 1.46 (60.61% sensitivity / specificity 68.42%) for advanced fibrosis (Figure 1B). When evaluated the APRI according to genotypes of HCV, the value of AUROC was 0.60 (CI 95% 0.43-0.78) for genotype 1 (n = 52), and an AUROC of 0.77 (CI 95% 0.62-0.92) for genotype 2-3 (n = 38), without statistically significant difference between the genotypes (p = 0.355) (data not shown).

When evaluated FIB-4 with liver biopsy, the AUROC value was 0.69 (CI 95% 0.58-0.80) with cutoff point value 2.77 (66.67% sensitivity/specificity 64.91%) for advanced fibrosis (Figure 1C). When evaluated FIB-4 according to genotypes of HCV, for genotype 1 (n = 52) the value of AUROC was 0.61 (CI 95% 0.44-0.78), and for genotype 2-3 (n = 38) the AUROC was 0.83 (CI 95% 0.69-0.96), without statistically significant difference between the genotypes (p = 0.099) (data not shown). When compared all the tests analyzed in this study (APRI, FIB4 and GPR), no statistical significant difference was found between the tests (p = 0.306).

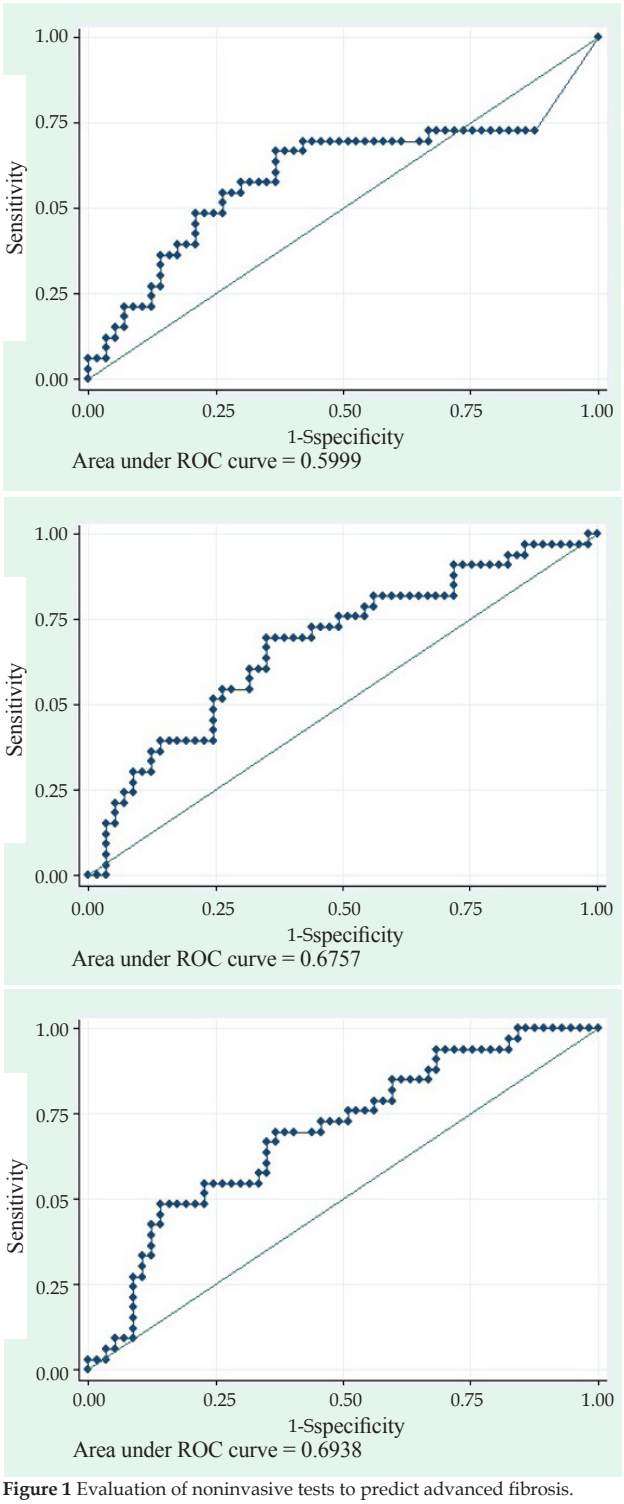

Figure 1 Evaluation of noninvasive tests to predict advanced fibrosis.

Table 1 Sociodemographic characteristics of Hepatitis C patients before treatment.

Variable	N (%) or Mean (± SD) †
Male gender	53 (56.4%)
Caucasian ethnicity	80 (85.1%)
Age (years)	54.27 ± 11.24
Years of study	9.7 ± 5.2
Marital status (% of married)	50 (53.2%)
Currently working	45 (47.9%)
Total	94

† Displayed as mean ± standard deviation (SD) or number (n) and %. Descriptive analysis were made by single frequency.

Table 2 Clinical characteristics of Hepatitis C patients before treatment.

Variable	N (%) †
First treatment	71(75.5%)
Contamination mode	31(33.0%)
Blood transfusion	13 (13.8%)
Drugs	41(43.6%)
Unknow	
Currently working	45 (47.9%)
Type of medication for hepatites C	
Interferon pegylated	85 (90.4%)
Interferon alpha	9 (9.6%)
Genotype	
1	56 (59.6%)
2/ 3	38 (40.4%)
Degree of fibrosis	
Low	66 (70.2%)
High	28 (29.8%)
Total	94

† Displayed number (n) and %. Descriptive analysis was made by single frequency.

DISCUSSION

Considering the limitations and risks of biopsy, there is great interest, in develop and validate the use of quick, safe and accurate method of noninvasive biochemical markers to detect hepatic fibrosis among patients with chronic liver disease, since liver biopsy should no longer be considered mandatory[1,2]. Moreover, we have an interest in determinate and comprehend possible confounding factors such as virus genotypes on the fibrosis progression, to better estimate the method validity.

APRI, a tool with limited expense, is based on routinely performed inexpensive laboratory parameters, and is potentially the pattern tool since most CHC-infected patients reside in regions with limited healthcare resources, where the prevalence of CHC tends to be higher[1,19]. In time in which the number of fibrosis markers is growing readily, many clinicians, patients, researchers, and policy makers are confused about the best measure. The definition of a perfect diagnostic tool is if the AUROC is 1, excellent if the AUROC is greater than 0.90 and good if the AUROC is greater than 0.80[1]. In this study, the APRI for advanced fibrosis and cirrhosis, presented inferior results with AUROC of 0.67 and no differences between the genotypes were demonstrated, although the genotypes 2/3 seems to have a slightly better result (AUROC 0.77). Our results corroborate with previous studies where the AUROC of APRI has inferior values to those considered as a good index (80%), such as the data presented for an Asiatic population where 302 CHC and Chronic hepatitis B patients with advanced hepatic fibrosis were evaluated showing APRI value AUROC = 0.71[13]. Other study evaluating 120 patients with CHC and advanced fibrosis in Turkey obtaining a value of AUROC = 0.67[14]. Furthermore, El Sayed (2011) evaluating 113 patients with CHC in Egypt finding an AUROC for APRI = 0.63 in adults[15].

In the original study of APRI analysis for CHC-related fibrosis, consecutive treatment-naive CHC patients who underwent liver biopsy over a 25-month period were divided into 2 sequential cohorts: training set (n = 192) and validation set (n = 78). The AUROC of APRI for predicting significant fibrosis and cirrhosis were 0.80 and 0.89, respectively, in the training set[9]. However, a systematic review and meta-analysis comparing APRI with liver biopsy showed an AUROC accuracy of 0.77 for the diagnosis of significant fibrosis, less than previously described[1]. Another systematic review, also showed a modest accuracy of APRI for significant fibrosis (AUROC = 0.76)[19]. Based on these major predictive values, Shahenn (2007) concluded that the APRI could be used to prevent the biopsy in approximately half of patients. Subsequently, numerous studies have attempted to externally validate these findings, but results have been yet controversial, with some of them showing lower accuracy of APRI in predicting fibrosis while considering different staging systems (the Scheuer system vs. the Ishak system)[20-22].

Differences in patient populations, including the prevalence of significant fibrosis, and reference ranges for AST, may explain these discrepancies[2,19]. In fact, the AST-ULN variability is highly associated with the variance of metabolic risk factors between the different control groups. This variability induces a spectrum effect, which could cause misleading interpretations of APRI performance for the staging of fibrosis, comparisons of APRI with other non-invasive tests, and estimation of false positive rate[23].

Lemoine *et al*, (2015), identified a new serum fibrosis model based on the GPR, in a cohort of 135 chronic hepatitis B patients in Gambia (West Africa), and then assessed its diagnostic accuracy in two external validation cohorts. The results showed that GPR is more accurate than APRI and FIB-4 in West Africa, but not superior to APRI and FIB-4 in France[10]. Qiang Le (2016), in the large sample size retrospective study, found that GPR does not show advantages than APRI and FIB-4 in identifying significant fibrosis, severe fibrosis, and cirrhosis in Chronic hepatitis B patients in China[17]. In the context that few studies have been evaluated GPR in CHC, and considering the complexity of the pathophysiology of liver cirrhosis, it is of greatly importance the reproduction of these data in different populations, since it is unlikely that a single biomarker will reliably reflect the disease process. In our study, when evaluated for advanced fibrosis and cirrhosis, the GPR presented poor accuracy as a predictor (AUROC = 0.59). However, when stratified by genotypes, individuals with genotype 2/3 presented a slightly better result (AUROC = 0.64) than genotype 1 (AUROC = 0.55). According to the results depicted in this manuscript, GPR cannot be used for clinical practice as a good tool for the confirmation of advanced fibrosis and cirrhosis when other clinical signs and examinations are not decisive. Further studies are required to test this index in other populations with greater sample size. To date, this is the first study to evaluate GPR in CHC patients in the Brazilian population, according to the authors' knowledge.

The FIB-4 was originally described in a study with co-infection HCV/HIV patients using the ISHAK classification, showing an AUROC = 0.71[24]. Further studies evaluating FIB-4 founded AUROCs = 0.81-0.87 to predict advanced fibrosis[2,12,25,26]. Our results corroborate with previous studies, showing an AUROC = 0.69 similar to the results found in Gokcan's work which presented an AUROC = 0.68[14]. When we evaluated the values of FIB-4 index according to genotypes, we found that genotype 1 presented a lower AUROC = 0.61 related to genotypes 2/3 (AUROC = 0.83), suggesting that FIB-4 analysis for genotypes 2/3 can better rated the patients in relation to advanced fibrosis.

In this study, when we evaluated the three tests in the attempt to identify a noninvasive test for the detection of advanced fibrosis and cirrhosis, we verify although with no significant results that the FIB-4 (AUROC = 0.69) presents similar results of APRI (AUROC = 0.67) and slightly better accuracy when compared to GPR (AUROC = 0.59) (p = 0.306). However, none of these indexes has AUROC of 0.80, considered in the literature as the reference value for a good test. Amorin *et al*, 2012 comparing the APRI with the FIB-4 respectively, did not found significant differences regarding the superiority of the methods (0.79 *vs* 0.81, p = 0.57), as well as De Oliveira *et al*, (2016) (APRI = 0.80 and FIB-4 = 0.83)[2,25]. Gokcan (2016) also described no statistical significance between values of the FIB-4 test (AUROC = 0.70-0.68) and APRI (AUROC = 0.67-0.72)[14]. However, a meta-analysis showed lower performances of APRI compared to FIB-4[27].

In conclusion, our study showed for the first time a comparative analysis of these three methods, APRI, GPR and FIB-4, for patients with CHC in Brazil. In addition, due the significant role of the viral genotypes of CHC for treatment decisions, response, and time of treatment, we assess the in this study, the influence of viral genotype in the accuracy of this tests. Here, we found association between viral genotypes and advanced fibrosis in the relationship of GPR. Importantly, the small sample size of our study represents a limitation in the evaluation of these parameters of accuracy for the three methods tested. In this view, future studies including these tests should be consider different populations, higher sample size and clinical characteristics of patients such asviral genotypes, which may allow the refinement of its use in the clinical practice.

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